



Research Paper

Sex differences in subcortical auditory processing only partially explain higher prevalence of language disorders in males

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ABSTRACT

Males and females differ in their subcortical evoked responses to sound. For many evoked response measures, the sex difference is driven by a faster developmental decline of auditory processing in males. Using the frequency-following response (FFR), an evoked potential that reflects predominately midbrain processing of stimulus features, sex differences were identified in the response to the temporal envelope of speech. The pattern of later and smaller responses in males versus females is consistent with two of the three response features that track with language development and reading abilities. Therefore, here we analyzed subcortical response consistency, the third distinguishing feature of language ability. Furthermore, though the envelope is primarily a low-frequency response, the greatest sex differences were observed in harmonics encoding. To better understand these sex differences, we extended these findings to the temporal fine structure response, which is biased to high-frequency information. Using the same 516 participants as previously reported (Krizman et al., 2019), we analyzed the effect of sex across development on response consistency and the encoding of temporal fine structure, as indexed by the subtracted frequency-following response. We found that while males and females did not differ on response consistency, there was an effect of age on this measure. Moreover, while males still showed a faster decline in harmonic encoding, the magnitude and breadth of the sex differences were smaller (accounting for 2% variance) in the temporal fine structure response compared to the envelope response. These results suggest that sex differences are distinct, at least in part, from the differences that underlie language abilities and that developmental sex differences reflect subcortical auditory processing differences of both the temporal envelope and fine structure of sounds.

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1. Introduction

In humans, the auditory system is functionally and structurally different in males and females (McFadden, 1998; Shuster et al., 2019). Functionally, evoked response potentials, collected by playing a sound to the ear and recording activity arising from various regions along the auditory pathway, are later and smaller in males than females (Jerger and Hall, 1980; Krizman et al., 2012; Sato et al., 1991). These functional differences were presumed to be byproducts of structural differences, namely the longer cochlea and neural tracts of males relative to females (Aoyagi et al., 1990;

Don et al., 1993). Structural sex differences are present from birth. Consequently, if functional differences have solely structural origins, males and females should differ in their evoked response at every point in the lifespan.

However, we recently found this was not the case (Krizman et al., 2019). Using the frequency-following response (FFR) to the speech sound 'da', we found that some differences in the evoked response, such as neural timing, are evident early in development, coinciding with the neonatal onset of tract and cochlear differences (Moore and Linthicum Jr, 2007; Sato et al., 1991). Others, such as the magnitude of frequency encoding, emerge during adolescence, a period of sexual differentiation (Giedd et al., 1997). Still others, such as non-stimulus neural noise, do not differ between the sexes at any point in development. Not only do these findings suggest that some sex differences originate beyond the cochlea, but that the FFR indexes multiple aspects of auditory processing that are distinctly influenced by sex across de-

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velopment. These findings led us to ask two follow-up questions: (1) can sex differences in subcortical auditory processing account for the higher prevalence of language disorders in males; and, (2) are the sex differences in harmonic encoding evident in the temporal fine structure response?

1.1. Do subcortical auditory processing sex differences account for differences in language disorder prevalence between males and females?

Our initial findings established that males and females differ on two metrics that distinguish children based on their language abilities, namely peak timing and harmonic encoding (Banai et al., 2009; Krizman et al., 2012, 2019; White-Schwoch et al., 2015). For both of these measures, the male response was smaller and later than the female response, similar to differences observed for children with poor, relative to those with good, language skills (Banai et al., 2009; Hornickel and Kraus, 2013; Hornickel et al., 2012; White-Schwoch et al., 2015). Response consistency is the third component of the neural signature distinguishing good from poor readers (Hornickel and Kraus, 2013; White-Schwoch et al., 2015). Given that males are at a greater risk of having a language or reading disorder (Flannery et al., 2000; Quinn and Wagner, 2015; Wheldall and Limbrick, 2020), we wanted to determine whether this metric also differed between the sexes and could help explain the differences in language disability prevalence observed in males and females.

1.2. Are harmonic encoding sex differences evident in the temporal fine structure response?

The previously reported sex differences were found in the FFR generated by adding responses to a stimulus presented in two opposing polarities. This “added” FFR tends to bias lower-frequency information, specifically the fundamental frequency and lower harmonics (Aiken and Picton, 2008; Krizman and Kraus, 2019). Despite this low-frequency bias, the largest developmental sex effects were observed in higher harmonic encoding (Krizman et al., 2019). An alternative method of looking at this response is to subtract the FFRs to the stimulus polarities, a response that is dominated by high frequencies comprising the speech formants. Therefore, we wanted to determine whether these sex differences were also present in the subtracted response. Similar to the previous findings, we hypothesized that sex differences in auditory processing emerge or are strengthened over development. Thus FFR measures would be more distinct between the sexes in young adulthood than in early childhood.

2. Methods

2.1. Participants

The dataset was the same as (Krizman et al., 2019) and consisted of 171 (80 female) children aged 3–5 years, 169 (83 female) adolescents aged 14–15, and 176 (87 female) young adults aged 22–26 years.

2.2. Stimulus and recording parameters

Detailed stimulus and recording parameters can be found in (Krizman et al., 2019). Briefly, 6000 frequency following responses (3000 of each polarity) were elicited to a 40-ms speech syllable ‘da’ presented in alternating polarity at a rate of 10.9 Hz to the right ear using the Bio-logic Navigator Pro System (Natus Medical Incorporated, San Carlos, California). ‘Da’, contains

higher frequency formants modulated by a lower, fundamental, frequency, thus each FFR contains temporal fine structure modulated by a temporal envelope. Spectral energy from the formants make up the temporal fine structure while the fundamental and some lower-frequencies, which result from cochlear rectification distortion, comprise the temporal envelope (Aiken and Picton, 2008; Krizman and Kraus, 2019). Adding or subtracting alternating polarity responses semi-isolates the brain’s response to the temporal envelope and fine structure, respectively (Aiken and Picton, 2008; Krizman and Kraus, 2019; Ruggles et al., 2012). This is because the temporal envelope is relatively phase invariant while the temporal fine structure is phase dependent (Krishnan, 2002; Krizman and Kraus, 2019). The previous paper examined effects of sex and maturation on added FFR measures, except response consistency (Krizman et al., 2019). Here we focus on the effects of sex and maturation on added and subtracted response consistency to determine whether males and females differ on all three components of the reading signature. And, we are examining sex and developmental differences on the subtracted FFR to determine whether the effects observed for the envelope response are similarly evident in the response to the temporal fine structure.

2.3. Data analysis

2.3.1. Magnitude

Consistent with our initial report (Krizman et al., 2019), we calculated the root-mean-square (RMS) amplitude during the pre-stimulus (–15.8 to 0 ms relative to stimulus onset) and the 19.5 ms to 44.2 ms region of the response to generate measures of non-stimulus activity and broadband response magnitude, respectively.

2.3.2. Spectral encoding

The same time region (19.5–44.2 ms) and frequency bins (F0: 75–175 Hz; F1: 175–750 Hz; HF: 750–1050 Hz) were used to examine spectral encoding of the subtracted response as was used to examine spectral encoding of the added response (Krizman et al., 2019).

2.3.3. Response consistency

During data collection, two 3000-sweep (1500 of each polarity) responses were averaged online. Response consistency was calculated by comparing the two averages via a Pearson product-moment correlation. An r-value closer to 1 represents a response that is more consistent and an r-value nearer to zero reflects a less consistent response. To normalize these data, all data points were Fisher z-transformed prior to statistical analyses. For graphing purposes, values are reported as r-values. Response consistency was calculated for both added and subtracted responses.

2.3.4. Statistical analysis

A 2 (Sex: female, male) by 3 (Age: child, adolescent, adult) multivariate analysis of variance (MANOVA) was performed for the seven measures of subcortical auditory processing to determine main effects of age and sex as well as their interaction. To characterize these effects for individual measures, a MANOVA was performed to look at differences between the three age groups separately for each sex. Planned comparisons of males and females at each age were performed using independent-samples t-tests.

3. Results

There were no sex differences in response consistency in either the added or subtracted responses. Only harmonic encoding showed a sex difference across development. Harmonic encoding was equivalent in males and females during early childhood and became more dissimilar with age, due to greater developmental

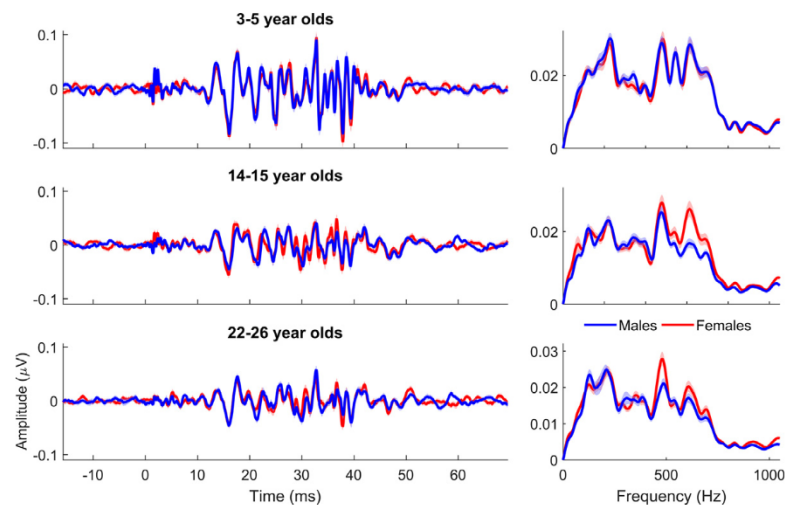


Fig. 1. Grand average subtracted waveforms (left) and FFTs (right) for children (top), adolescents (middle), and young adults (bottom). Males are in blue and females are in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

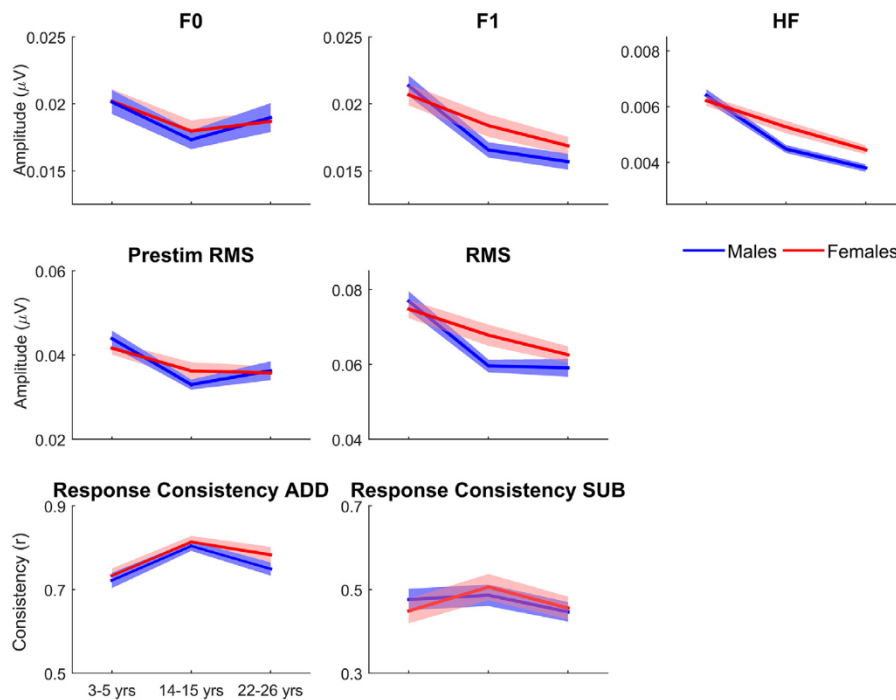


Fig. 2. Line plots showing changes in FFR measures across age in males (blue) and females (red) for children (left point on each plot), adolescents (middle point) and young adults (right point). The top row shows, from left to right, changes in males and females across development for F0, F1, and HF amplitude, the middle row shows changes in prestimulus amplitude (Prestim RMS, left) and response amplitude (RMS, right) and the bottom row shows changes in added (left) and subtracted (right) response consistency. Solid lines represent means and shaded bars represent ± 1 standard error. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

declines in male harmonic amplitude (Figs 1, 2). For the remaining measures, except subtracted response consistency, an effect of age was observed, with males and females increasing on added response consistency and declining on all remaining measures over development (Fig 2).

3.1. Group comparisons

Across all measures, a MANOVA revealed an effect of sex ($F_{(7, 503)} = 2.104$, $p = 0.042$, $\eta^2 = 0.028$), and age ($F_{(14, 1008)} = 13.051$, $p < 0.0005$, $\eta^2 = 0.153$), but no interaction of the two ($F_{(14, 1008)} = 1.233$, $p = 0.245$, $\eta^2 = 0.017$).

Harmonic encoding showed an effect of sex ($p = 0.005$) and an age by sex interaction ($p = 0.013$). While harmonic encoding in both males and females declined over development, the decline was greater for males. With respect to the effect of age on individual measures, all measures, except subtracted response consistency, changed over development (Table 1). All magnitude measures decreased with age, and added response consistency increased with age, similar to what has been reported previously (Skoe et al., 2015). Interestingly, the magnitude of the sex effect and age by sex interaction were greater for the previously reported differences observed in the added response (Krizman et al., 2019).

When looking at development effects separately for males and females, both sexes showed age effects on all measures except F0

Table 1
MANOVA results for individual measures. Significant effects are bolded.

Component		F(df)	p	η^2	η^2 ADD
Prestimulus magnitude (Prestim RMS)	Age	11.884 (2515)	<0.0005	0.045	0.074
	Sex	0.011 (1515)	0.916	0	0
	Age x Sex	1.230 (2515)	0.293	0.005	0
Response magnitude (RMS)	Age	22.699	<0.0005	0.082	0.021
	Sex	2.803	0.095	0.005	0.025
	Age x Sex	2.344	0.097	0.009	0.008
Fundamental frequency amplitude (F0)	Age	4.126	0.017	0.016	0.011
	Sex	0.046	0.830	0	0.012
	Age x Sex	0.133	0.875	0.001	0.003
First formant amplitude (F1)	Age	24.605	<0.0005	0.088	0.129
	Sex	1.851	0.174	0.004	0.035
	Age x Sex	1.687	0.186	0.007	0.015
High frequency amplitude (HF)	Age	78.168	<0.0005	0.235	0.140
	Sex	8.277	0.004	0.016	0.041
	Age x Sex	4.458	0.012	0.017	0.030
Response consistency SUB (RC SUB)	Age	1.438	0.238	0.006	
	Sex	0.001	0.970	0	
	Age x Sex	0.358	0.699	0.001	
Response consistency ADD (RC ADD)	Age	12.425	<0.0005	0.046	
	Sex	1.322	0.251	0.003	
	Age x Sex	0.161	0.851	0.001	

Table 2
Age effects for males and females. Significant differences are bolded.

Component		F(df)	p	η^2	η^2 ADD
Prestim RMS	Female	3.551	0.03	0.028	0.085
	Male	9.371	<0.0005	0.067	0.065
RMS	Female	6.025	0.003	0.047	0.003
	Male	20.566	<0.0005	0.135	0.058
F0	Female	1.792	0.169	0.014	0.003
	Male	2.446	0.089	0.018	0.025
F1	Female	6.306	0.002	0.049	0.060
	Male	22.582	<0.0005	0.147	0.228
HF	Female	21.694	<0.0005	0.149	0.042
	Male	66.361	<0.0005	0.335	0.287
RC SUB	Female	1.124	0.327	0.009	
	Male	0.565	0.569	0.004	
RC ADD	Female	5.43	0.005	0.042	
	Male	7.239	0.001	0.052	

amplitude and subtracted response consistency (Table 2). This is different from the added response, where males showed declines on almost all added FFR measures while females declined on relatively few (Krizman et al., 2019). Nevertheless, for almost all subtracted FFR measures, the magnitude of the developmental decrease was larger for males than females.

Consistent with the MANOVA results, group comparisons within each age group showed a limited number of sex effects (Table 3). Specifically, males and females differed in response magnitude (RMS) during adolescence, driven by a faster decline in RMS for males relative to females. They also differed in harmonic encoding during adolescence and young adulthood, again, driven by a steeper rate of decline with age, for males compared to females.

4. Discussion

We find that over development, males and females do not differ in the consistency of their response, a response feature that does vary based on language skill (De Vos et al., 2020; Hornickel and Kraus, 2013). This is true for both the envelope and fine structure response. We also find that the temporal fine structure response undergoes a number of developmental changes; however, only harmonic encoding changes differently for males and females during this time. This is in contrast to the response to the temporal envelope, which showed male and female developmental differences on many measures of magnitude and timing (Krizman et al., 2012,

2019; Liu et al., 2017). Consistent with our previous findings, magnitude of the response, both broadband and frequency-specific, decreased with age (Krizman et al., 2019).

4.1. Sex differences do not wholly account for greater prevalence of language disability in males

An important finding to emerge from this study is that males and females do not differ in response consistency at any age. However, males and females do differ on harmonic encoding and peak timing, with males having later and smaller responses (Krizman et al., 2012, 2019; Liu et al., 2017). Response inconsistency, timing delays, and reduced harmonic encoding comprise the neural signature for language disability (Arya, 2019; Banai et al., 2009; Centanni et al., 2013; De Vos et al., 2020; Hornickel and Kraus, 2013; White-Schwoch et al., 2015). While differences in some aspects of auditory processing between males and females may partly explain the greater prevalence of language disorders in males (Flannery et al., 2000), there appear to be unique facets of auditory processing disrupted in individuals with a learning disability that cannot be explained by sex. In support of this, the neural signature of language disability was identified with a cohort of male and female children with a diagnosis of a learning disability (Hornickel et al., 2012). An important next step for understanding the interplay between sex and disability would be to investigate whether the manifestation of sex differences differs for males and females diagnosed with a reading or language disorder compared to sex differences observed in typically developing males and females.

4.2. Sex differences, though evident, are less pronounced in fine structure versus envelope encoding

Sex differences are less pronounced in the fine structure response and this may be due to magnitude differences between added and subtracted FFRs. The magnitude of subtracted responses are about half the size of added responses, which may reduce the overall range over which responses can occur. The developmental decline, together with the smaller subtracted response magnitude may be obscuring sex differences, given that the greatest sex difference occurs when the responses are the smallest (i.e., in young adulthood). Nevertheless, we still observed a greater decline in harmonic encoding in the subtracted response of males, relative

Table 3

Group comparisons across development. Within-age sex effects for individual measures.

Component	Age Group	Males	Females	t (df)	p	d	d ADD
Prestim RMS	3–5 yrs	0.044(0.018)	0.042 (0.014)	.913 (169)	0.363	0.12	0
	14–15 yrs	0.033 (0.011)	0.036 (0.018)	1.389 (167)	0.167	0.20	0
	22–26 yrs	0.036 (0.021)	0.036 (0.014)	0.193 (174)	0.847	0	0
RMS	3–5 yrs	0.077 (0.025)	0.075 (0.022)	0.592	0.554	0.09	0.12
	14–15 yrs	0.059 (0.016)	0.068 (0.026)	2.509	0.013	0.37	0.32
	22–26 yrs	0.058 (0.022)	0.062 (0.020)	1.134	0.259	0.19	0.52
F0	3–5 yrs	0.020 (0.008)	0.020 (0.008)	0.050	0.960	0	0.11
	14–15 yrs	0.016(0.005)	0.018 (0.007)	0.608	0.544	0.33	0.16
	22–26 yrs	0.019 (0.01)	0.018 (0.007)	0.182	0.856	0.12	0.36
F1	3–5 yrs	0.021 (0.007)	0.021 (0.007)	0.618	0.537	0.14	0.22
	14–15 yrs	0.016 (0.0045)	0.018 (0.007)	1.809	0.072	0.34	0.66
	22–26 yrs	0.016 (0.005)	0.017 (0.006)	1.375	0.171	0.18	0.59
HF	3–5 yrs	0.006 (0.002)	0.006 (0.002)	0.686	0.494	0	0
	14–15 yrs	0.004 (0.001)	0.005 (0.002)	2.996	0.003	0.64	0.63
	22–26 yrs	0.0037 (0.001)	0.0044 (0.001)	3.199	0.002	0.70	0.63
RC SUB	3–5 yrs	0.476 (0.243)	0.451 (0.262)	0.659	0.511	0.10	
	14–15 yrs	0.486 (0.236)	0.506 (0.285)	0.490	0.625	0.08	
	22–26 yrs	0.45 (0.215)	0.454 (0.250)	0.094	0.925	0.02	
RC ADD	3–5 yrs	0.722 (0.173)	0.734 (0.150)	0.483	0.630	0.07	
	14–15 yrs	0.805 (0.109)	0.813 (0.132)	0.432	0.666	0.07	
	22–26 yrs	0.754 (0.148)	0.780 (0.176)	1.045	0.298	0.16	

to females, in line with what we observed in the envelope-biased added response (Krizman et al., 2019), suggesting that the extent of this particular sex difference is quite large. It is also possible that the enhanced temporal fine structure response of the harmonic frequencies underlies the envelope differences, given that envelope can be extracted from fine structure (Ghitza, 2001). Interestingly, in line with the observed harmonic encoding enhancement in females, females also show heightened harmonic encoding in the FFR to an infant's cry (Dhatri et al., 2018), suggesting a possible biological relevance for these sex differences.

All FFR sex differences that emerge in adolescence and young adulthood are driven by an accelerated decline and delay in males, relative to a maintenance in females, of the larger, earlier responses seen early in development. Hormonal differences, namely differences in estradiol levels, are one possible explanation for these auditory processing differences, as higher levels of estradiol have been linked to enhanced auditory function. For example, in women, heightened auditory perception and processing align with points of increased estradiol concentration during the menstrual cycle (da Silva Souza et al., 2017; Haggard and Gaston, 1978; Walpurger et al., 2004) and a rise in estrogen concentration in rodents corresponds with heightened recognition of pup calls (Frisina, 2012). Additionally, age-related hearing loss is more prevalent and profound in males relative to females (Hultcrantz et al., 2006; Liu et al., 2017; Shuster et al., 2019), and hormone replacement therapy studies in humans and noise-exposure studies in mice support the role of estrogen in mitigating these hearing-loss effects (Kilicdag et al., 2004; Milon et al., 2018). From these observations, estrogen has been presumed to have an otoprotective effect. Future studies should investigate whether the auditory processing sex differences observed in the FFR can account for any of the differences in hearing and perception found in older adult males and females.

4.3. Conclusions

In conclusion, because males and females differ on only two of the three markers of reading and language disabilities, sex differences cannot fully account for the difference in prevalence of these disorders between males and females. Additionally, the temporal fine structure response undergoes a number of developmental changes between early childhood and young adulthood. However, only harmonic encoding in the subtracted FFR changes differ-

ently for males and females during this time. In contrast, many sex differences in the magnitude and timing of the temporal envelope response arise across development (Krizman et al., 2012, 2019; Liu et al., 2017). Consistent with previous findings, both broadband and frequency-specific response magnitude decreased with age (Krizman et al., 2019).

CRedit authorship contribution statement

Jennifer Krizman: Conceptualization, Software, Formal analysis, Data curation, Writing - original draft, Visualization, Project administration. **Silvia Bonacina:** Conceptualization, Formal analysis, Data curation, Writing - original draft. **Nina Kraus:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.heares.2020.108075.

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