Published in final edited form as:

Hear Res. 2009 June ; 252(1-2): 37–48. doi:10.1016/j.heares.2009.01.002.

Masculinization of the Mammalian Cochlea

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Abstract

Otoacoustic emissions (OAEs) differ between the sexes in humans, rhesus and marmoset monkeys, and sheep. OAEs also are different in a number of special populations of humans. Those basic findings are reviewed and discussed in the context of possible prenatal androgen effects on the auditory system. A parsimonious explanation for several outcomes is that prenatal exposure to high levels of androgens can weaken the cochlear amplifiers and thereby weaken otoacoustic emissions (OAEs). Prenatal androgen exposure apparently also can alter auditory evoked potentials (AEPs). Some non-hormonal factors possibly capable of producing sex and group differences are discussed, and some speculations are offered about specific cochlear structures that might differ between the two sexes.

Keywords

Otoacoustic emissions; Auditory evoked potentials; Sex differences; Prenatal development; Masculinization; Testosterone; Estradiol

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¹In science, the words sex and gender have distinctly separate meanings and should not be used as synonyms (e.g., Wizemann and Pardue, 2001, p. 176). Sex alludes to a person's body morphology, and gender alludes to a person's self-image as belonging to one (or neither) of the two sexes. Assessing gender requires substantially different procedures from assessing morphological sex. Many investigators who have used the term gender actually did not measure it.

²Pairwise comparisons like sex differences are commonly characterized using effect size, a d' -like measure that expresses the difference between means in standard-deviation units. We calculate effect size as the difference between the means of the two groups of interest divided by the square root of the weighted mean of the two variances. By convention, effect sizes of 0.2, 0.5, and 0.8 are viewed as small, medium and large differences, respectively (Cohen, 1992). I have provided effect sizes in the figure captions.

³One possible reason for this inconsistency in the sex differences for DPOAEs and CEOAEs is the effective level of the stimuli used to elicit the two forms of OAE. DPOAEs typically are measured with primary tones of 50 dB SPL or greater, whereas CEOAEs typically are measured with clicks of 60 – 80 dB peSPL (peak-equivalent sound-pressure level). This means that the spectrum level of the clicks is quite weak at each of the successive locations along the length of the cochlea contributing to the reflection-based component of the CEOAE, while the energy in the primary tones used to evoke DPOAEs is relatively more concentrated. Accordingly, sex differences typically are measured using locally weak stimuli for CEOAEs and locally strong stimuli for DPOAEs, and this difference eventually may prove relevant.

⁴Sometimes it is worthwhile to say the obvious. Having a masculinized cochlea appears not to be especially desirable. At the least, those with weak OAEs are likely to have poorer hearing sensitivity than those with strong OAEs (e.g., McFadden and Mishra, 1993), and it is likely that there are other negative consequences of weak OAEs.

⁵An anonymous reviewer pointed out that female chinchillas also are larger and more aggressive than males, suggesting that the absence of a sex difference in chinchilla DPOAEs (S.L. McFadden et al., 1999) eventually may prove attributable to mechanisms similar to those operating to reduce the OAEs in female spotted hyenas.

Introduction

Thirty years now have passed since David Kemp first reported the existence of otoacoustic emissions or OAEs (Kemp, 1978, 1979). In that time thousands of research papers have been published on the basic facts of OAEs as well as on their use clinically. Much already has been learned, and OAEs continue to offer promise as a valuable tool both for basic auditory research and audiological practice for the foreseeable future.

The purpose of this invited article is to review some research from my lab inhabiting the suburbs of mainstream OAE research. This work has been summarized elsewhere (McFadden, 1998, 2002, 2008), but the target audiences there were not the community of auditory scientists reached by this journal, so some points that were omitted there are discussed here. This review covers data collected from several special populations of humans and some data from certain animal species. The organization is conceptual rather than chronological because this work, like much of science, did not proceed in an especially orderly manner.

Some Background Facts

A number of early studies on OAEs revealed the existence of sex and ear differences in humans (Bilger et al., 1990; Talmadge et al., 1993; McFadden, 1993a; McFadden and Loehlin, 1995; McFadden et al., 1996; McFadden and Pasanen, 1998, 1999; McFadden and Shubel, 2003). Some also revealed that the sex and ear differences seen in adults are evident in newborns as well (Strickland et al., 1985; Burns et al., 1992, 1994; Morlet et al., 1995, 1996). These differences are in the direction of human females having stronger, and more numerous, spontaneous OAEs (SOAEs) and stronger click-evoked OAEs (CEOAEs) than do males; also, human right ears have stronger and more numerous SOAEs and stronger CEOAEs than do left ears. Some representative data are shown in Figure 1. Human-like sex differences also are seen in the CEOAEs of rhesus monkeys (McFadden et al., 2006a) and sheep (McFadden et al., 2008a, 2008b).

By comparison, distortion-product OAEs (DPOAEs) have shown less consistency across studies and species. It appears that DPOAEs are only slightly stronger in females than in males, at least for humans (McFadden et al., 2008c) and rhesus monkeys (Torre and Fowler, 2000; McFadden et al., 2006a). However, the DPOAEs of marmoset monkeys exhibit an extremely large sex difference favoring the females (see Valero et al., 2008; nothing yet is known about their CEOAEs), and the DPOAEs of sheep exhibit a sex difference that favors the males, not the females (McFadden et al., 2008b). Finally, Guimaraes et al. (2004) did find a sex difference favoring the females in the DPOAEs of mice, but only in the older animals, and S.L. McFadden et al., (1999) found no sex difference in the DPOAEs of chinchillas. Shera and Guinan (1999) have argued convincingly that DPOAEs are dependent on different underlying cochlear mechanisms from SOAEs or CEOAEs, so perhaps dissociations of this sort are to be expected (for other dissociations in OAEs see Wier et al., 1988; McFadden and Pasanen, 1994; Whitehead et al., 1996; McFadden et al., 2008b). In part because of these inconsistencies between DPOAEs, SOAEs, and CEOAEs, this review will concentrate on SOAEs and CEOAEs.

In the process of doing a study on the heritability of OAEs using twins, we discovered an interesting fact about females having male co-twins (opposite-sex dizygotic, or OSDZ, twin pairs). As a group, OSDZ females have SOAEs and CEOAEs that are shifted in the male direction (McFadden, 1993b; McFadden and Loehlin, 1995; McFadden et al., 1996); the data are shown in Figure 2. (By the way, our estimates of heritability were about 0.75, which is quite high.)

Various studies (Kemp et al., 1986; Franklin et al., 1992; Burns et al., 1993, 1994; Prieve et al., 1993; Engdahl et al., 1994) have suggested that OAEs are reasonably constant through life, at least prior to the onset of hearing loss. An implication of this apparent constancy early in life is that the group differences seen in the OAEs of OSDZ females as young adults likely were present at birth as well, just as were the sex and ear differences in OAEs (McFadden, 2008). If this reasoning is correct, then we have two facts to explain: why sex differences exist in the OAEs of newborn humans and why OSDZ females have masculinized OAEs (as adults and possibly at birth).

A Working Hypothesis

One obvious explanation for the sex difference in newborns appeals to the same mechanisms and processes that are responsible for so many other sex differences in body, brain, and behavior in humans: the differential prenatal exposure to androgens experienced by the two sexes (Nelson, 2005). Early in the course of prenatal development, male humans, and indeed all male mammals, develop embryonic testes that begin producing the androgens that are responsible for masculinizing the prenatal body and brain. Female mammals do not experience this prenatal androgen exposure and their bodies and brains develop in the female-typical pattern. Thus, a cliché for mammalian development is that female is the default condition; without androgen exposure prenatally, the result is a female body and brain. Accordingly, the explanation for the sex difference in OAEs in newborns may be that the prenatal androgen exposure somehow weakens the cochlear amplifiers (Davis, 1983) and thereby weakens SOAEs and CEOAEs (and perhaps DPOAEs less markedly). Let's call this the prenatal-androgen-exposure explanation (see McFadden, 2002, 2008).

Parsimony argues for as few explanations of a collection of facts as possible. Accordingly, might prenatal androgen exposure explain the weak OAEs in OSDZ females as well? Quite possibly. There is a substantial literature in mammals showing that female fetuses developing next to male fetuses can be masculinized on a large number of physiological and behavioral characteristics (e.g., Clemens et al., 1978; vom Saal, 1989). The apparent mechanism is that some of the androgens being produced by the male fetuses diffuse out of their bodies into the intrauterine fluids, through which they pass to the adjacent female fetuses, where they have masculinizing effects just as they do for male fetuses. That is, in various non-human mammalian species, developing female fetuses can be masculinized prenatally by virtue of their being exposed to the androgens produced by their male litter mates--an instance of unwanted brotherly presence. Might a similar mechanism be operating when human twins share a uterus? And might the masculinized OAEs seen in OSDZ females be the result of such a process? Human OSDZ twins are not well-studied, but there is evidence that OSDZ females do have masculinized dentition (Boklage, 1985; Dempsey et al., 1999), are heavier ("masculinized") at birth (Glinianaia et al. 1998), and have reduced lifetime reproductive success (Lummaa et al., 2007) compared to non-twins. So it is not implausible that these features plus the masculinized OAEs shown in Figure 2 all are attributable to human OSDZ females being exposed to higher-than-normal levels of androgens during prenatal development. At the very least, this is worthy of being a plausible working hypothesis, and it is parsimonious.

Tests of the Working Hypothesis

Humans

Actual tests of the prenatal-androgen-exposure explanation are difficult to implement in humans. One obviously cannot administer, or block, androgens in developing human fetuses just to test this idea, no matter how interesting it might be to some deranged auditory scientist. However, there are some naturally occurring medical conditions in humans that have the potential to serve as tests of the idea that the cochlear amplifiers can be masculinized by

exposure to androgens during prenatal development. Perhaps congenital adrenal hyperplasia (CAH) is the most obvious (Collaer and Hines, 1995).

In CAH, the adrenal glands produce higher-than-normal levels of androgens during prenatal development, and if the fetus is female, it can be masculinized in body and brain. CAH females typically are born with masculinized genitalia, they show an early preference for boys' toys, their finger-length ratios are masculinized (Brown et al., 2002), and they have irregular menstrual periods later in life, among other after-effects of the anomalous androgen exposure (see Collaer and Hines, 1995). The prenatal-androgen-exposure explanation leads to a clear prediction that the OAEs of CAH females ought to be masculinized. Unfortunately, OAEs have yet to be measured in CAH females, so I sand-bagged you on that one. However, I do have hopes of making those measurements someday.

Another interesting medical condition is androgen-insensitivity syndrome (see Collaer and Hines, 1995), in which an XY fetus does develop embryonic testes, and does begin to produce androgens as part of the normal process of masculinizing itself, but it has defective androgen receptors, meaning that the androgens produced by that developing fetus are ineffective at masculinizing its body, brain, and behavior. (There are complete and partial forms of AIS; for simplicity here, I will consider only complete androgen-insensitivity syndrome or CAIS.) As a consequence of the fact that female is the default condition in mammalian development, many individuals having AIS are categorized as female at birth, are raised female, and do not discover that their chromosomal sex is male until puberty, when they fail to menstruate (the internal sex organs are an immature mix of female and male, so these folks are sterile). Most people with CAIS are perfectly content with a female gender identity, they often marry males, adopt children, and never feel a need to reveal to family or friends that they carry a Y chromosome. Clearly, if prenatal exposure to androgens does masculinize the cochlear amplifiers and does lead to the sex difference in the OAEs of newborns, among other auditory effects, then people with CAIS ought to exhibit female-typical (i.e., strong) OAEs. However, if some mechanism driven by the genes is responsible for the sex difference in the OAEs of newborns, then people with CAIS ought to exhibit male-typical OAEs. To my great disappointment, OAEs also have yet to be systematically measured in people having complete or partial AIS.

Non-Humans

Theoretically, tests of the prenatal-androgen-exposure explanation should be possible using animal models, but unfortunately many of the animals commonly used in auditory research do not exhibit SOAEs or CEOAEs. Those species do exhibit DPOAEs, but as noted above, DPOAEs show only small sex differences in humans (McFadden et al., 2008c), so those species may not be of much help in this context. (I do not know if stimulus-frequency OAEs show sex differences in any species, but the recent paper by Kalluri and Shera, 2007, suggests they might.) Fortunately, we were extremely lucky and found some laboratories housing species that did provide experimental tests of the prenatal-androgen-exposure explanation. CEOAEs were measured in spotted hyenas living at the University of California, Berkeley (McFadden et al., 2006b), rhesus monkeys living at the Yerkes National Primate Research Center (McFadden et al., 2006a), and sheep living at the University of Michigan (McFadden et al., 2008a, 2008b). We are deeply in debt to our various collaborators for helping us obtain those measurements. (All of the animal studies described here were conducted after approval by the relevant university committees on animal care and experimentation.)

Spotted hyenas—This species is interesting in the current context because the females are larger than the males, they dominate the males, they have an elaborated clitoris that is similar in appearance to a penis, including being erectile, and these male characteristics all are the result of female spotted hyenas being exposed to high levels of androgens during prenatal

development (Frank et al., 1991; Glickman et al., 1992). The obvious prediction is that the OAEs of female spotted hyenas should not be stronger than the OAEs of the males, and that prediction was confirmed. The left side of Figure 3 shows that not only were the CEOAEs of female spotted hyenas not stronger than those of males, they were slightly weaker (although not significantly so). (No SOAEs were measurable in this species.) So, this appears to be evidence supporting the idea that the cochlear mechanisms underlying CEOAEs are indeed weakened by exposure to high levels of androgens prenatally. An important caveat, however, is that nothing is known about the OAEs of any of the other three existing species of hyenas (where female masculinization does not exist), so we do not know yet if female hyenas not exposed to high levels of androgens exhibit a human-like sex difference in CEOAE strength.

Caveats aside for the moment, the data in the middle of Figure 3 also provide support for the prenatal-androgen-exposure suggestion. These data were obtained from spotted hyenas who were exposed prenatally to one drug that blocked the androgen receptors (flutamide) and another drug that blocked the breakdown of testosterone into dihydrotestosterone (finasteride). The effect of these two anti-androgen agents was to strengthen the CEOAEs in both sexes, and the implication is that the cochlear amplifiers were weakened less than in untreated spotted hyenas because of these drugs. This is the direction of effect predicted by the prenatal-androgen-exposure explanation.

The data at the right in Figure 3 were obtained from spotted hyenas that experienced normal prenatal development and then were ovariectomized or castrated after birth. Accordingly, the cochleas of these animals did not experience whatever changes normally occur during the course of puberty in this species; yet their CEOAEs were indistinguishable from those of untreated spotted hyenas. Thus, it appears that the hormonal exposures important to normal cochlear development occur prenatally, not during puberty.

All of these conclusions about spotted hyenas need to be tempered by the small Ns involved, but in our defense, we did measure all of the animals available at the time, and in the case of some of the treated hyenas, we measured all the animals of that sort on Earth.

Rhesus monkeys—When we measured CEOAEs in rhesus monkeys, we found a human-like sex difference (McFadden et al., 2006a); namely, the CEOAEs of female rhesus monkeys were stronger than those of males. Figure 4 shows the data. Additional measurements revealed that this sex difference fluctuated seasonally in accord with the annual fluctuations in male rhesus testosterone levels. That is, the CEOAEs of male rhesus monkeys were weaker in the breeding season (when male androgen levels are high) than in the birthing season (when male androgen levels fall), and the sex difference varied accordingly (McFadden et al., 2006a, Fig. 1). If this fluctuation in CEOAEs does prove to be related to androgen levels, it will be an instance of an activational effect of hormones (Nelson, 2005) in distinction to the permanent, organizational effects that occur prenatally. Androgen levels also fluctuate seasonally in human males (reviewed by van Anders et al., 2006), but to my knowledge, no one has ever reported a seasonal fluctuation in the OAEs of human males.

Some of the rhesus monkeys in this colony also had been treated with an anti-androgenic agent or with additional androgens during prenatal development. The outcomes were more complex than those for spotted hyenas, in part because some monkeys received treatment only early in gestation and other monkeys only late in gestation. The outcomes already have been discussed in detail (McFadden et al., 2006a), but what can be said here is that male monkeys receiving the anti-androgenic agent flutamide either early or late in gestation did have slightly stronger CEOAEs than untreated monkeys, which is in accord with prediction from the prenatal-androgen-exposure idea and with the results from spotted hyenas. But for some reason, treatment with flutamide did not strengthen the CEOAEs of the females (see McFadden et al.,

2006a, for a discussion). Also in accord with prediction, the CEOAEs of monkeys treated with additional androgens late in gestation were weaker than those of untreated monkeys, and that was true for both sexes. Again, the implication is that the cochlear mechanisms responsible for CEOAEs were weakened by exposure to high levels of androgens. The CEOAEs of female monkeys treated early in gestation with additional androgens also were slightly weaker than in untreated females, but not for the males treated early with additional androgens. These various results are likely to be especially informative in the long run because rhesus monkeys are commonly viewed as an excellent model system for humans.

Note that, unlike humans, no consistent ear difference was seen either for spotted hyenas or rhesus monkeys. If this asymmetry in the auditory periphery proves to be unique to humans, it eventually may become interesting to our colleagues interested in the origins of speech perception, speech production, and lateralization of other functions.

Sheep—Recent measurements of OAEs in sheep revealed a small sex difference like that seen in humans; namely, females had slightly stronger CEOAEs than males (McFadden et al., 2008a). Furthermore, female sheep treated with androgens during prenatal development had CEOAEs weaker than those of untreated females, which is in accord with prediction from the prenatal-androgen-exposure idea. However, the CEOAEs of male sheep treated with additional androgens were not different from those of untreated males, perhaps because of a systemic down-regulation of androgen production. A fact of interest when trying to establish the exact mechanisms underlying these effects on the cochlear amplifiers is that female sheep receiving additional estradiol during prenatal development also had weaker CEOAEs than untreated females. If this outcome were to hold up, it would suggest that the agent ultimately responsible for reducing the strength of the cochlear amplifiers may not be testosterone itself but its derivative estradiol (testosterone is routinely transformed into estradiol in the bodies and brains of mammals through the action of the enzyme aromatase—see Nelson, 2005).

Marmoset monkeys—A recent finding in marmosets is interesting, in part because it runs counter to results in several other species. Valero et al. (2008) reported a substantial sex difference favoring the females in marmosets. The surprising part is that this large sex difference was for DPOAEs, the form of OAE that shows only small sex differences in humans and rhesus monkeys (McFadden et al., 2008c). As yet there is no information available about the existence or size of a sex difference in CEOAEs in marmosets, but work proceeds on this question.

Additional Findings that Might be Relevant

Sexual Orientation

When we measured OAEs in people having different sexual orientations, we found that homosexual and bisexual females had SOAEs and CEOAEs that were shifted in the male direction (McFadden and Pasanen, 1998, 1999). The data are shown in Figure 5. Note that the OAEs of homosexual males were not noticeably different from those of the heterosexual males (there were too few bisexual males to support trustworthy conclusions).

One possible explanation for the non-heterosexual women having weaker OAEs than heterosexual women is that their cochleas were masculinized somehow—perhaps during early development. To understand the reasoning, note that if female is the default condition in humans, then the default choice of sex partner is male; the typical female chooses males for sex partners. The fact that males typically choose females for sex partners suggests that some time during development some neural switch gets thrown from the default state to its alternative. Because so many other aspects of body, brain, and behavior in males are altered by masculinization processes operating during prenatal development, it is not implausible that

this neural switch is set then, too, and it also is not implausible that androgen exposure plays a role in this process.

In this context, how do we interpret the fact that non-heterosexual women exhibit the male-typical choice for sex partner? Perhaps that neural switch determining choice of sex partner was moved from its default state to the alternative state at some time early in development. How might that happen? Perhaps for some short period of time, in some localized regions of the brain, some sex-atypical masculinization process occurs, the neural switch is thrown, and for some mysterious reason, that masculinization process also affects the cochlea in a way that weakens the cochlear amplifiers and thus the OAEs. In addition, perhaps that masculinization process involves exposure to higher-than-normal levels of androgens. Note that this surely-too-simplistic account of lesbianism does have the virtue of being parsimonious in the current context of outcomes. This account is bolstered by the fact that we saw similar masculinization effects in the auditory evoked potentials (AEPs) of homosexual and bisexual women.

McFadden and Champlin (2000) measured auditory brainstem responses (ABRs), middle-latency responses (MLRs), and long-latency responses (LLRs) (see Hall, 1992) in people of differing sexual orientations. This led to 19 measures of latency and amplitude. On five of those measures, non-heterosexual women differed from heterosexual women. Curiously, some of those five measures did not exhibit a basic sex difference, but for all of those that did, the AEPs of the non-heterosexual women were shifted in the direction of the heterosexual males (see Figure 6)—they were masculinized just as were the OAEs in our previous study (Figure 5).

There surely are a number of possible explanations for this outcome, but one parsimonious explanation is that the auditory brains, as well as the cochleas, of these women were masculinized at some time in development, perhaps by exposure to higher-than-normal levels of androgens. Unfortunately, the OAE and AEP measures were obtained from different samples of homosexual and heterosexual subjects, so nothing yet is known about how those different types of measures covary.)

ADHD Children

Some symptoms of attention-deficit/hyperactivity disorder (ADHD) are evident quite early in life. This suggests that an early developmental anomaly plays a role in this disorder. The fact that ADHD is at least twice as prevalent in males as in females (American Psychiatric Association, 2000) suggests that this developmental anomaly may have something to do with the physiological processes of masculinization. Accordingly, my lab was interested in the OAEs of children diagnosed with ADHD.

ADHD currently is recognized as having multiple subtypes. When a child has symptoms of hyperactivity/impulsivity and symptoms of inattention, the diagnosis is ADHD/Combined subtype. When a child only has symptoms of inattention, the diagnosis is ADHD/Inattentive subtype. We measured CEOAEs in boys from both subtypes as well as in control boys (McFadden et al., 2005). The results are shown in Figure 7.

As can be seen, the CEOAEs of the ADHD/Combined boys were not significantly different from those of the control boys, but the CEOAEs of the ADHD/Inattentive boys were substantially weaker (hypermasculinized). By implication, the cochlear amplifiers also were weaker in ADHD/Inattentive boys. There surely are a large number of ways that this could have come about, but one parsimonious explanation is that these boys were exposed to unusually high levels of androgens early in development, perhaps during prenatal development. Supporting that interpretation is the fact that the finger-length ratios of those same ADHD/Inattentive boys also were hypermasculinized (McFadden et al., 2005; also see Martel et al.,

2008). Our Ns for ADHD girls were small and not reliable, but the CEOAEs of the ADHD/Inattentive group were masculinized as well. These ADHD children took no drugs on the day their OAEs were measured.

Other Possible Causal or Contributing Factors

In summary, there exists a body of findings that can be interpreted as supporting the prenatal-androgen-exposure explanation for the sex difference in the OAEs of newborns. But, if we are honest, we have to acknowledge that much of the evidence is circumstantial, many of the findings are “just” correlations, and some of the reasoning involves inferences that have not been tested directly. Clearly, we need to be cautious with our conclusions, and that requires our considering factors other than hormonal effects that might have contributed to some of these outcomes.

Hearing Loss and Drug Use

It is logically possible that some lifestyle differences may be responsible for some or all of the OAE differences noted above for our various special populations of humans. While OAEs do appear to be reasonably stable through life, they are not immutable. Any experience or agent that produces a hearing loss also can produce a weakening of the OAEs (because the cochlear amplifiers apparently contribute to both). So it may be that females, or females with male co-twins, or non-heterosexual females, or all three, are exposed to some lifestyle factor(s) that weakens their OAEs. We were aware of this possibility at the time those various studies were conducted, so we screened the hearing sensitivity of all our subjects and eliminated those not having nominally normal hearing. Also, we asked about such issues as recent and past noise exposure and recent and past drug use, and we eliminated subjects whose answers led to concern about possible incipient hearing loss. So all the data shown above are for samples that were reasonably carefully vetted for possible incipient cochlear damage. Fortunately, a more direct test of undetected hearing loss also was possible.

For nearly every common form of cochlear damage, the hearing loss proceeds progressively from high to low frequencies. Thus, if non-heterosexual women, for example, had incipient cochlear damage in the high-frequency regions of their cochleas (even though they passed our hearing screening test), that damage could have led them to possess fewer SOAEs and weaker CEOAEs overall. But if that were the origin of the group differences shown in Figure 5, then those group differences ought to diminish or disappear if we were to consider only emissions from the lower-frequency region of the cochlea. Yet when we re-analyzed the SOAE data, eliminating all SOAEs above 3.0 kHz, we got exactly the same pattern of outcomes as shown in Figure 5 above (see McFadden and Pasanen, 1999). Those results are shown in Figure 8. Thus, an undetected, high-frequency hearing loss, of whatever origin, appears not to be the basis for the masculinization of the OAEs of non-heterosexual women.

One potentially worrisome difference between heterosexual and non-heterosexual women is that the former might be more likely to use oral contraceptives than the latter, and if those drugs altered the cochlea, that might be the basis for the group differences shown in Figures 5 and 8 above. Because our extensive questionnaire provided information about drug use, including oral contraceptives, we also were able to test this possibility. As the data in Figure 9 reveal, oral contraceptives masculinize OAEs slightly and AEPs substantially (McFadden, 2000). However, that is the wrong direction of effect to account for the results in Figures 5 and 8; the non-heterosexual females showing masculinized OAEs are less likely to be using oral contraceptives than are the heterosexual females. Even so, all users of oral contraceptives were eliminated from the AEP study (McFadden and Champlin, 2000) and, thus, did not contribute to the data shown in Figure 6 here. (Presumably these auditory side-effects of oral contraceptives are temporary, activational effects that dissipate when drug use ends.)

So, although we cannot definitely rule out the possibility of some lifestyle difference, or other factor, contributing to the OAE and AEP differences seen in the various special populations of humans we have studied, we have tried to eliminate confounding factors. We are especially confident that the OAE differences seen for heterosexual and non-heterosexual women are not likely to be attributable either to a differential, high-frequency hearing loss or to a differential use of oral contraceptives, and we routinely have screened potential subjects for nominally normal hearing.

Outer- or Middle-Ear Factors

There are sex differences in the anatomy of the outer and middle ears (e.g., Chan and Geisler, 1990), and these unquestionably can produce differences in the acoustics, both when presenting stimuli to evoke OAEs and when recording OAEs. The question is how major a role these differences in acoustics play. Are outer- and middle-ear acoustics solely or primarily responsible for the sex, ear, and group differences observed in human OAEs? I believe that the answer is no, and the reasoning is as follows.

Sex differences have been reported for various middle-ear measures (see Johansson and Arlinger, 2003, for a review). For example, middle-ear compliance sometimes has been reported to be higher in males than in females. Contradicting that previous finding, however, Johansson and Arlinger (2003) themselves did not observe sex differences either in middle-ear compliance or middle-ear pressure when they pooled their data across the nearly 500 subjects and seven age groups they studied. Much more important for this discussion, however, is the fact that Johansson and Arlinger did observe more SOAEs and stronger TEOAEs (transient-evoked OAEs) in their female subjects than in their male subjects, the typical direction of effect. This implies that middle-ear factors are not playing a major role in sex, ear, and group differences in OAEs. That implication was strengthened by Johansson and Arlinger's additional finding that middle-ear compliance did not change significantly with age whereas the strength of both TEOAEs and DPOAEs did decline with age.

Margolis et al. (1999) reported small, but significant, sex differences in measures of wideband reflectance measured in humans; however, those differences were primarily at frequencies below 1.0 kHz (their Fig. 5c), and none of our findings about sex, ear, or group differences in OAEs depend critically upon measurements from below 1.0 kHz. Keefe et al. (2005) reported that ear differences in vLo (the equivalent middle-ear volume averaged from 0.25 to 1.0 kHz) and rHi (energy reflectance averaged from 2.0 to 8.0 kHz) do exist in infants, but those ear differences did not explain the ear differences observed in the TEOAEs or DPOAEs of those same infants.

Naeve et al. (1992) manipulated the air pressure in the ear canal and found that CEOAE strength decreased with both increases and decreases in air pressure. This suggests that the smaller ear-canal volume in human females might not be a decisive factor for the existence of sex differences in OAE strength.

One strong counter-argument against outer- or middle-ear differences being major contributors to the sex, ear, and group differences we have observed in OAEs is that we, and many other investigators, always adjust the levels of the sounds used for evoking CEOAEs and DPOAEs in each ear canal immediately prior to collection of the data. This means that at least the stimuli are reasonably comparable even if the acoustics of the canal do contain sex, ear, or group differences that can affect the outward-propagating waves.

Another counter-argument relies on a fact mentioned previously. The sex difference for DPOAEs is much smaller (Gaskill and Brown, 1990; Moulin et al., 1993; Cacace et al., 1996; Bowman et al., 2000) than the sex differences for SOAEs and CEOAEs (Bilger et al.,

1990; Talmadge et al., 1993; Burns et al., 1992; McFadden and Pasanen, 1998, 1999), and this is true even when the DPOAEs and CEOAEs were measured on the same subjects (McFadden et al., 2008c). For me at least, this partial dissociation among different types of OAE is much easier to understand in terms of sex differences in various cochlear mechanisms (see Shera and Guinan, 1999, 2003) than in terms of sex differences in some outer- or middle-ear characteristic. Even within sex, DPOAEs exhibit large individual differences, but Lonsbury-Martin et al. (1990) were unable to find any middle-ear measure that accounted for the individual differences they observed in DPOAEs.

Finally, the CEOAEs of male rhesus monkeys were weaker when their androgen levels were known to be high (breeding season) than when they were low (birthing season) (McFadden et al., 2006a, Fig. 1). Although it is possible to imagine aspects of the outer- or middle-ear systems being altered by androgen levels to produce this seasonal fluctuation, it is far simpler (for me, at least) to imagine changes in certain cochlear mechanisms in response to those seasonal variations in androgen levels.

So, although anatomical differences in the outer and middle ears undoubtedly do contribute to individual differences, and perhaps even to some group differences, in OAEs, I believe it is safe to conclude that these pre-cochlear differences are not the primary factor producing those sex, ear, and group differences in OAEs that are the topic of this review. A long-term goal of auditory science ought to be determining what fraction of these various OAE effects can be attributed to pre-cochlear, cochlear, and possibly post-cochlear mechanisms, but in my opinion, work on the latter two need not await the final word on the first.

Temperature Differences

There are small differences in body temperature between males and females, and temperature has been shown to affect OAEs (e.g., Seifert et al., 1998). Might this physiological difference be responsible for producing some of the sex and group differences reported above? I don't think so, for reasons discussed by Don et al. (1993) and Bergevin et al. (2008) in other contexts.

Differences in Outer Hair Cells

The outer hair cells (OHCs) are widely regarded as playing an important role in the production of OAEs. Thus, it is difficult to resist speculating how differences in the OHCs might contribute to sex, ear, and group differences in OAE strength. The electromotility (Brownell et al., 1985) that makes OHCs unique in the cochlea is known to be dependent on the prestin molecules contained in the walls of the OHCs (Liberman et al., 2002), so any sex, ear, or group differences in prestin could be a major contributor to the OAE differences of interest here. Perhaps, for some reason, females have, on average, more prestin molecules per OHC than do males, or perhaps the prestin molecules in female OHCs are more co-linearly aligned along the cell's axis of contraction. In either case, female OHCs ought to be capable of greater electromotility than male OHCs. Alternatively, perhaps female OHCs are less spherical than male OHCs, meaning that the conformational changes in the prestin molecules produce greater changes in OHC length than in the more spherical male OHCs. Electromotility also might be affected if female OHCs had more stereocilia, more K⁺ channels, or more efferent synapses per OHC than male OHCs. Finally, if any of those "randomly and densely distributed perturbations in impedance" that Shera (2003) argues are crucial to the reflection-based mechanism in OAE production are created in part by structural differences in OHCs, then perhaps their number, size, or density differ either in the two sexes or in some of the special populations sampled in our studies. While we are speculating, other structural possibilities include differences in the tectorial membrane or the supporting cells, differences that perhaps affect the retrograde propagation of energy in the cochlea. While speculation of this sort can

be intriguing and entertaining, what clearly is needed is experiments testing possibilities like these.

Efferent Effects

The OHCs, which are believed to be crucial elements to the functioning of the cochlear amplifier system (Davis, 1983), are known to be affected by the efferent system (Guinan, 2006). Namely, activation of the MOC efferent system can reduce both the strength of the cochlear amplifier system (Brown et al., 1983) and the strength of OAEs (Guinan, 2006). An early suggestion (McFadden, 1993a) was that the sex and ear differences seen in OAEs might be attributable to sex and ear differences in the strength of the resting efferent inhibition. Unfortunately, tests of this appealing idea (appealing to me, at least) have not been especially supportive of it (Khalfa and Collet, 1996). Nonetheless, the efferent system is sufficiently complex that the possibility still remains that sex differences in some aspects of the medial or lateral efferent systems might be responsible for some of the effects reported here.

Endocochlear Potential

There is a potential difference of about 80 mV between the perilymph-filled canals of the cochlea and the endolymph-filled scala media, meaning that the shearing of the cochlear hair cells shunts a larger voltage than just the intracellular potential established in the hair cells by the differential distribution of ions across their individual membranes. The cochlear amplifier system is dependent upon the integrity of this endocochlear potential (e.g., Zwicker and Manley, 1981), so it is plausible that the sex differences in OAEs may be directly attributable to a sex difference in the magnitude of the endocochlear potential.

Androgen or Estrogen Receptors in the Cochlea

A common question from audiences listening to this story about possible androgenic effects on the cochlear-amplifier system is: What is known about the existence of androgen receptors in the cochlea? A sophisticated version of the question includes estrogen receptors as well because androgen can be aromatized into estradiol (a form of estrogen) in the brain, and estradiol is known to have strongly masculinizing effects in the brains of some mammals (e.g., Zuloaga et al., 2008), although apparently not in humans (see Wallen and Baum, 2002). My answer is that I know of no reports of androgen receptors being found in mammalian cochleas, although estrogen receptors do exist in the spiral ganglion and stria vascularis (Stenberg et al., 2001). However, this answer is close to meaningless in the present context because it comes from measurements of adult cochleas, and the argument I have tried to make is that some masculinization process apparently is occurring during prenatal life. It is easily possible that androgen or estrogen receptors are expressed (perhaps quite briefly) in some cochlear cells during prenatal development but then cease to be expressed, and this could be very difficult to detect experimentally.

What kinds of sex differences might one expect to see in androgen or estrogen receptors in embryonic cochleas? One logical possibility is presence of some type of receptor in one sex and its absence in the other. More likely, however, receptor density might differ in one of the sexes in some cells crucial to the cochlear amplifiers, and this difference might exist only for a short period of time in development. In this context, it needs to be noted that androgens and estrogens also can have indirect effects on structures of the body; they do not have to act directly themselves (see review by Jordan and DonCarlos, 2008).

Cochlear Length

A fact that may prove relevant to the sex and group differences in OAEs is that the cochleas of human females apparently are about 8 – 13% shorter than those of males (Don et al.,

1993; Sato et al., 1991; Kimberley et al., 1993; Bowman et al., 2000; but compare Miller, 2007). If those random, distributed perturbations in impedance that are thought to be important for the reflection-based component of OAEs (Shera, 2003) were more densely packed in shorter cochleas than in longer cochleas, then the greater density might lead to stronger reflections, meaning stronger SOAEs and CEOAEs in female cochleas. If cochlear length is relevant to some of the differences discussed here, the prediction is that the cochleas of males, females with male co-twins, non-heterosexual females, boys diagnosed as ADHD/Inattentive, female spotted hyenas, and/or rhesus monkeys and sheep treated with androgens prenatally, should be longer than the relevant comparison cochleas, and the cochleas of monozygotic females should be significantly shorter than those of non-twin females.

Discussion

So, that is the story. The big question is whether these various findings are in fact related or instead represent separate phenomena with differing underlying causes. Many of the findings have yet to be replicated and most of the *Ns* were small, so the uncertainty is high. On the other hand, the corpus of findings is compelling (to me at least). Personally, I find the prenatal-androgen-exposure explanation to be plausible and parsimonious, but only future research can determine its correctness.

To be candid, I expect progress to be slow on the question of exactly what cochlear differences contribute to sex differences in OAEs. One reason is the seemingly large number of possibilities needing to be tested. A second reason is the absence of an appropriate animal model. As noted, the small mammals that are commonly used for auditory physiology typically have no SOAEs, and either have no CEOAEs or their CEOAEs echo back with such short latency that most of the reflections are masked by the click stimulus. That leaves DPOAEs and SFOAEs; DPOAEs do not exhibit large sex differences in humans (McFadden et al., 2008c) and, to my knowledge, no one yet has studied whether SFOAEs exhibit sex differences in humans or any other species. Rhesus monkeys and sheep do show human-like sex differences in CEOAEs (McFadden et al., 2006b, 2008b), but these species are not suitable for routine auditory research. Marmoset monkeys are intriguing in this context because they do show a large sex difference in their DPOAEs (Valero et al., 2008), but their CEOAEs have yet to be studied. If they were to show large sex differences in CEOAEs, then that would be an attractive species for work of this sort (they are primates, they are small, they mature quickly, females can give birth multiple times a year, and births are typically twins or triplets).

One hope I have is that this review will encourage some readers to begin to consider the issues of sex differences and hormonal effects on the auditory system in the course of doing their own auditory research. If I succeed in this goal, as a fringe benefit, we ought to acquire additional information on the big-picture question of whether the basic mammalian model of cochlear structure includes sex differences or not. At this point, we know that rhesus monkeys and sheep do show weaker versions of the human sex difference in CEOAEs—females stronger than males—but most of the species commonly used for auditory research either do not have CEOAEs or we don't know how to measure them. The human sex difference for DPOAEs is smaller than that for CEOAEs and SOAEs, and we know next to nothing about sex differences in DPOAEs in most of the other species commonly used for auditory research. SOAEs have been observed only occasionally in non-human species, so the question of sex differences in SOAEs of non-humans appears moot. There is reason to expect SFOAEs to show sex differences like those of CEOAEs and SOAEs (Kalluri and Shera, 2007), both in humans and non-humans, but that expectation has yet to be tested. In contrast to my pessimism about our being able to make rapid progress on the cochlear mechanisms underlying sex differences in OAEs, it should be relatively easy to determine how many other species commonly studied by auditory physiologists exhibit sex differences in their OAEs.

While thinking about possible underlying mechanisms and alternative explanations for the various individual outcomes reviewed here, it is easy to lose track of another big-picture question. What is it about the auditory system that apparently makes it so susceptible to masculinizing mechanisms operating early in development? Whatever the differences in exposure to masculinizing agents that, say, opposite-sex dizygotic females experience, they unquestionably are subtle. As children and adults, these females are not morphologically different from non-twin females or same-sex dizygotic females. They are not larger, markedly more aggressive, nor uniformly non-heterosexual. The most overwhelmingly obvious characteristic of these females is how similar they are to all other females. Yet, if our data are right, their cochleas are noticeably masculinized. The same point can be made about non-heterosexual women and ADHD/Inattentive boys. Why should the cochleas of these people be so sensitive to whatever masculinizing mechanisms are operating? Why should a cochlea be like a canary in a coal mine? Answering this question is likely to bring the answerer some recognition.

One final question that can be asked about these various findings is: So what? If there are sex and group differences in OAEs, what exactly does that mean for everyday listening? What aspects of auditory performance might females be better at, or worse at, than males because of their stronger OAEs? OAE strength is known to be correlated with hearing sensitivity (e.g., McFadden and Mishra, 1993), but beyond that we know very little about how OAEs (or AEPs) are related to auditory ability. Accordingly, we have little basis for predicting how females, or other groups with stronger OAEs, ought to differ from males, or from other groups with weaker OAEs, on standard psychoacoustical tasks. This is a curious state of affairs given that OAEs were discovered 30 years ago. There clearly is plenty left to be done.

Acknowledgments

Supported by research grant DC 00153 awarded by the National Institute on Deafness and other Communication Disorders (NIDCD). E.G. Pasanen was instrumental to the implementation and completion of all of our studies, and he made numerous valuable comments about early drafts of this paper. R.H. Margolis kindly provided helpful, and much appreciated, comments about the paper. M.M. Maloney assisted with the figures.

List of Abbreviations

ABRs	auditory brainstem responses
ADHD	attention-deficit/hyperactivity disorder
AEPs	auditory evoked potentials
AIS	androgen-insensitivity syndrome
CAH	congenital adrenal hyperplasia
Castr	castrated
CEOAEs	click-evoked otoacoustic emissions
CAIS	

	complete androgen-insensitivity syndrome
* dB	decibel
DPOAEs	distortion-product otoacoustic emissions
* Hz	Hertz
K+	potassium
* kHz	kilohertz
LLRs	long-latency responses
MLRs	middle-latency responses
MOC	medial olivocochlear
* mV	millivolt
Ns	sample size
* nV	nanovolt
OAEs	otoacoustic emissions
OC	oral contraception
OHCs	outer hair cells
OSDZ	opposite-sex dizygotic
Ovx	ovariectomized
peSPL	peak-equivalent sound-pressure level
rHi	energy reflectance

* author recommends deleting these because all readers of Hearing Research will know them.

* rms	root-mean-square
* SPL	sound-pressure level
SOAEs	spontaneous otoacoustic emissions
SFOAEs	single-frequency otoacoustic emissions
TEOAEs	transient-evoked otoacoustic emissions
vLo	equivalent middle-ear volume

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Figure 1.

Sex and ear differences in human otoacoustic emissions. For both SOAEs (left) and CEOAEs (right), females have more or stronger OAEs than males, and right ears have more or stronger OAEs than left ears. The effect sizes for the sex differences are 0.98 and 0.76 for SOAEs and CEOAEs, respectively (using two-ear averages). The effect sizes for the ear differences are 0.16 and 0.24 for SOAEs and CEOAEs, respectively (averaged across sex). In one study, the correlation between SOAE number and CEOAE strength was 0.76 (McFadden and Pasanen, 1999). In this and all subsequent figures, the flags designate standard errors of the mean. [Based on Figure 3 of McFadden (2008) and reproduced with permission from Wiley-Blackwell Publishing.]

Figure 2.

SOAEs (top) and CEOAEs (bottom) collected from human twins and non-twins (two-ear averages are shown). Note that females with male co-twins (opposite-sex dizygotic females) had OAEs that were more like those of males than those of females from any other group. The most appropriate comparison is between opposite-sex dizygotic females and same-sex dizygotic females because both were twins, only the sex of the co-twin was different. The effect sizes for the difference between opposite-sex and same-sex dizygotic females were 0.49 and 0.43 for SOAEs and CEOAEs, respectively (using two-ear averages). The average numbers of SOAEs shown in Figure 1 are larger than here because of improvements made in our measurement techniques between studies (see Pasanen and McFadden, 2000). The especially strong OAEs seen in the monozygotic females have neither been explained nor further studied to my knowledge. [Based on Figure 2 in McFadden (2002) and Figure 6 in McFadden (2008), adapted from McFadden et al. (1996), and reproduced with permission from Springer Science and Business Media and Wiley-Blackwell Publishing.]

Figure 3.

CEOAEs measured in spotted hyenas. At the left are two-ear averages from untreated females and untreated males. Unlike humans, rhesus monkeys, and sheep, female hyenas did not have stronger CEOAEs than males. The effect size for this sex difference was -0.36 . In the middle are two-ear averages from spotted hyenas treated with two anti-androgen agents during prenatal development (flutamide and finasteride); as predicted, the CEOAEs in both sexes were strengthened. The effect sizes were -0.35 and -0.54 for females and males, respectively. At the right are two-ear averages for spotted hyenas that were untreated during prenatal development but then were ovariectomized (Ovx) or castrated (Castr) after birth; their CEOAEs were similar to those for the untreated hyenas, suggesting that prenatal events have more effect on cochlear structures than do current, circulating levels of hormones. [Based on Figure 3 in McFadden et al. (2006b) and Figure 5 in McFadden (2008) and reproduced with permission of Elsevier Limited and Wiley-Blackwell Publishing.]

Figure 4.

CEOAE strength in prenatally untreated rhesus monkeys. All data were collected in the breeding season, when the sex difference was largest. The effect sizes for sex difference were 1.26 and 1.03 for the left and right ears, respectively. Note that CEOAEs were stronger in the left ear than in the right, which is opposite to the findings for humans. Rhesus monkeys of both sexes who were treated with additional androgens late in gestation had weaker (masculinized) CEOAEs than untreated monkeys. [Based on Figure 3 in McFadden et al. (2006a) and reproduced with permission of Elsevier Limited.]

Figure 5.

SOAE number (top panel) and CEOAE strength (bottom panel) for people of differing sexual orientations. Note that the data for the homosexual and bisexual women are intermediate to those for heterosexual females (far left) and heterosexual males (far right); their SOAEs and CEOAEs have been masculinized in some way. The effect sizes for the differences between the heterosexual and non-heterosexual females were approximately 0.57 and 0.41 for SOAEs and CEOAEs, respectively. The data for homosexual males did not differ from those for heterosexual males (too few bisexual males were tested for safe conclusions). The SOAE data for the heterosexual females and heterosexual males are the same as shown in Figure 1. [Based

on Figure 3 in McFadden (2002) and Figure 8 in McFadden (2008) and reproduced with permission of Springer Science and Business Media and Wiley-Blackwell Publishing.]

Figure 6.

Amplitude of wave 5 of the auditory evoked potential (AEP) for people of differing sexual orientations. The data for heterosexual females (far left) and heterosexual males (far right) exhibited a significant sex difference; that effect size was approximately 0.51 for this measure. As was true for the OAE data shown in Figure 5, the data for homosexual and bisexual women were shifted in the direction of the heterosexual males; this AEP measure was masculinized. (The subjects here are different from those in Figure 5.) Unlike the OAE results, this AEP measure was even smaller in homosexual males than in heterosexual males; that is, this measure was hypermasculinized in the homosexual males. The effect size for the two-ear difference between the heterosexual and non-heterosexual females was approximately 0.24, and the effect size for the two-ear difference between the heterosexual and non-heterosexual males was approximately 0.54. Other AEP measures showed similar shifts for both sexes (see McFadden and Champlin, 2000). Data from women using oral contraceptives were excluded here (see McFadden, 2000). [Based on Figure 9 in McFadden (2008) and reproduced with permission of Wiley-Blackwell Publishing.]

Mean rms Amplitude of CEOAE from 1-5 kHz (dB SPL)

Figure 7.

CEOAE strength in boys diagnosed with ADHD and in control boys, all aged 7 – 12 years. The results were similar in both ears; the CEOAEs of the ADHD/Inattentive boys were weaker than those of the ADHD/Combined boys or the control boys, and the latter two groups did not differ statistically. That is, the CEOAEs of the ADHD/Inattentive boys were hypermasculinized. The effect sizes for the differences between the ADHD/Inattentive boys and the control boys were about 0.97 and 0.95 for the left and right ears, respectively. Similar directions, and magnitudes, of effect were seen for finger-length ratios in these same subjects. [Based on Figure 1 in McFadden et al. (2005) and Figure 7 in McFadden (2008) and reproduced with permission of Elsevier Limited and Wiley-Blackwell Publishing.]

Figure 8.

The data from the top panel of Figure 5 after deletion of all SOAEs higher than 3.0 kHz in frequency. The goal was to test whether a small, undetected, high-frequency hearing loss might be responsible for the pattern of results seen for SOAEs in Figure 5 (top panel). The answer was no; the results with and without the high-frequency SOAEs were essentially identical. The effect size for the sex difference was 0.95, and the effect size for the difference between the heterosexual and non-heterosexual females was 0.50 (both calculated using two-ear averages).

Figure 9.

OAEs (left panel) and AEPs (right panel) for non-users and users of oral contraceptives (OC). Two-ear averages are shown throughout. SOAEs and CEOAEs were slightly weaker (masculinized) in subjects using oral contraceptives. The effect sizes (non-users minus users) were 0.31 and 0.10 for SOAEs and CEOAEs, respectively. Similarly, various AEP measures were masculinized in subjects using oral contraceptives. The effect sizes (non-users minus users) for the two AEP amplitude measures shown in the right panel were 0.47 and 0.31. The direction of effect for both OAEs and AEPs suggests that differential use of oral contraception by the heterosexual and non-heterosexual women is not likely to have contributed to the pattern of results in Figures 5 and 8; this factor unquestionably could not contribute to the results in Figure 6 because all users of oral contraceptives were excluded from that analysis. Similar OC effects for additional OAE and AEP measures were reported in McFadden (2000).