Physiological evidence of hypermasculinization in boys with the inattentive type of attention-deficit/hyperactivity disorder (ADHD)

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is more common in boys than in girls, suggesting that prenatal androgen exposure may play a role in etiology. Click-evoked otoacoustic emissions (CEOAEs) and relative finger length are measures known to exhibit sex differences early in life, also suggesting that prenatal androgen exposure plays a contributing role. CEOAEs and the lengths of the fingers were measured in boys and girls aged 7–15 who were diagnosed as having different types of ADHD. All six possible pairwise length ratios were calculated for the four fingers of each hand. The CEOAEs measured in boys diagnosed as ADHD/Inattentive were substantially smaller than those of either the boys diagnosed as ADHD/Combined or the Control boys, whose mean CEOAEs were alike. Similarly, most of the finger-length ratios (FLRs) were smaller for boys diagnosed as ADHD/Inattentive than for either ADHD/Combined or Control boys. Both of these outcomes represent a hypermasculinization of the boys diagnosed as ADHD/Inattentive. Thus, two quite different physiological measures suggest that these boys diagnosed as ADHD/Inattentive may have been exposed to higher-than-normal levels of androgens at some stage early in development. In accord with both Cantwell’s proposal for validating psychiatric disorders and previous suggestions in the literature, these findings support the hypothesis that the Combined and Inattentive groups represent different disorders, not versions of a single disorder.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) affects 3–7\% of school-aged children, and for about two-thirds of these individuals, some symptoms persist through adolescence into adulthood [1]. The most recent version of the Diagnostic and Statistical Manual for Mental Disorders [2] addressed the ongoing debate about the diagnosis of ADHD by establishing three types that delineate among those children showing predominantly inattentive symptoms (ADHD/Inattentive Type), predominantly hyperactive/impulsive symptoms (ADHD/Impulsive-Hyperactive Type), or both inattention and hyperactive-impulsive symptoms (ADHD/Combined Type). The ADHD/Impulsive-Hyperactive-impulsive type has a low prevalence and has been studied the least, and its status as a discrete manifestation of ADHD remains controversial [3]; that type will not be considered here.

The current study is relevant to the integrating theme of this special issue because it addresses the validity of the distinction between the ADHD/Inattentive and ADHD/Combined types. The Cantwell criteria from 1990 as well as modern criteria (e.g. see Willcutt et al., this issue) provide a framework for evaluation of diagnostic classes. Cantwell [4] proposed the systematic evaluation of the following domains of clinical evaluation: (1) clinical phenomenology, (2) psychosocial factors, (3) demographic factors, (4) biological and other laboratory studies, (5) family genetic studies, (6) family interaction studies, (7) outcome studies, and (8) intervention studies. The existing research supporting the distinction between the diagnoses of ADHD/Combined Type and ADHD/Inattentive Type.
consists largely of data showing differences in the 1st and 3rd of Cantwell’s domains, such as prevalence in the two sexes, comorbidity with other conditions, degree of academic and social impairment, and age of onset [5]. The findings have led to the contention that the ADHD/Inattentive group may best be considered a separate disorder rather than a version of a general ADHD category (for reviews see [1,5]). What remains lacking, however, is evidence for distinct etiological pathways underlying the ADHD/Inattentive and ADHD/Combined types, Cantwell’s 4th area of evaluation. For example, despite speculation that different attentional mechanisms may underlie the different types, studies of neurocognitive correlates have found few differences between the two groups [6–8], and existing neuropsychological tests are poor at discriminating between them [9–11]. If physiological measures could be found that distinguished between these two types, those measures could have value both for individual diagnoses and for the ongoing discussion about the appropriate nosology. Information about the underlying pathophysiological mechanisms also might provide clues to etiology, treatment, and prevention.

ADHD is more prevalent in males than in females, with the estimates ranging from about 2:1 for community-based samples to 9:1 for clinic-based samples [2]. This greater prevalence in males is true for both the ADHD/Inattentive and ADHD/Combined types, but the disparity between the sexes appears to be less extreme in the ADHD/Inattentive group. Because of the marked sex difference in prevalence of ADHD, and because precursors to ADHD are present early in life, it appears reasonable to presume that some androgenic mechanism operating prenatally or perinatally contributes to the expression of ADHD.

Otoacoustic emissions (OAEs) are weak sounds produced by the cochlea that propagate back through the middle-ear system into the external ear canal where they can be measured using small microphone systems [12]. There are several types of otoacoustic emission, but of interest here will be two forms of the click-evoked OAE, or CEOAE. CEOAEs are echo-like responses emitted by the cochlea in response to a brief click stimulus and detected using response-averaging techniques. CEOAEs, like other types of OAE, are substantially stronger in females than in males [13,14], and that sex difference exists in newborns as well as in adults [15]. Certain special populations of subjects [14,16,17] also exhibit CEOAEs that differ from those in control subjects, and sex differences exist in the OAEs of other mammals [18]. Thus, several lines of evidence suggest that the active cochlear elements involved in the production of OAEs (commonly called the cochlear amplifiers) can be affected permanently by exposure to high levels of androgens early in development (for a review see [19]).

Human fingers differ between the sexes not only in absolute length but also in relative length. For example, the ratio of the lengths of the index and ring fingers (called the 2D:4D ratio) is smaller in males than in females (for a summary see [20]). This sex difference exists at least as early as two years of age [20, p. 15], and the 2D:4D ratio has been linked with various medical conditions such as congenital adrenal hyperplasia ([21,22], but compare [23]), heart disease, breast cancer, and autism [20]. Several lines of evidence suggest that the 2D:4D ratio is diminished by exposure to high levels of androgens early in development, presumably during prenatal development (e.g. [20–22]). Other finger-length ratios (FLRs), especially 2D:5D and 3D:4D, also exhibit large sex differences in humans [24], and sex differences in length ratios also have been demonstrated in the mouse [25,26], baboon [27,28], gorilla and chimpanzee [29], and zebra finch [30]. Although FLRs and OAEs both appear to be affected by prenatal exposure to androgens, FLRs correlate only weakly with OAEs [31], which suggests that they are two reliable, but unrelated, measures of a similar etiological sequence. Because hands develop earlier than ears prenatally, studies of group and individual differences in these measures eventually may point to ‘windows’ of different androgenic effects and/or to periods of protracted androgenic influence.

Because the large sex difference in the prevalence of ADHD suggests the possible involvement of androgenic mechanisms operating early in development, and because androgenic mechanisms also appear to affect CEOAEs and FLRs, we measured both CEOAEs and finger lengths in a sample of children diagnosed with ADHD. The expectation was that OAEs, FLRs, or both, would be either hypomasculinized or hypermasculinized in children with ADHD compared to control subjects, as an aftereffect of an anomaly of androgenization occurring at some point in development. We had no a priori expectation that our measures would discriminate between the types of ADHD. A preliminary version of this work was reported by McFadden et al. [32].

2. Methods

The CEOAE measures were added late to a large ongoing study of the neurocognitive correlates of ADHD that already included FLRs as a supplementary measure. Accordingly, OAE data were obtained from fewer subjects than finger-length data.

3. Recruitment and screening

The ADHD participants were recruited from a clinical neuropsychology practice. Control participants were recruited from friends and relatives of the ADHD participants and by word-of-mouth among parents associated with the Psychology Department of The University of Texas at Austin.
To maximize the differentiation between types, more stringent diagnostic standards were used than those described in the DSM-IV-TR [2]. Namely, to be classified as ADHD/Inattentive, children were required to have four or fewer symptoms of hyperactivity/impulsivity instead of fewer than six of the nine symptoms listed in this domain, as well as six or more of the nine symptoms listed for the Inattentive domain. Of the children diagnosed with either type of ADHD in the OAE study, 20 met the diagnostic criteria in ratings from both a parent and a teacher. An additional 10 children met diagnostic criteria based on one source and missed the criteria by only one symptom for the other source. Of the children diagnosed with ADHD in the FLR study, 30 met the diagnostic criteria in ratings from both a parent and a teacher. An additional 16 children met diagnostic criteria based on one source and missed the criteria by only one symptom for the other source. Exclusion criteria included evidence of a neurological disorder such as epilepsy, a history of psychosis, an estimated full-scale IQ of less than 80, history of head injury, or the use of psychoactive medications other than those used to treat symptoms of ADHD. Also, no children qualifying as ADHD/Hyperactive-Impulsive were included in this study.

Table 1
Demographic information and ratings of ADHD symptoms (Sxs) for participants in the OAE and FLR studies

<table>
<thead>
<tr>
<th></th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OAE study</td>
<td>FLR study</td>
</tr>
<tr>
<td>Number of participants</td>
<td>Inattentive</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>15</td>
</tr>
<tr>
<td>Age in months (mean/SD)</td>
<td>Inattentive</td>
<td>120 (24)</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>114 (24)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>130 (29)</td>
</tr>
<tr>
<td>Parent-endorsed ADHD Sxs (mean/SD)</td>
<td>Inattentive</td>
<td>6.9 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Hyperactive/impulsive Sxs</td>
<td>1.5 (1.5)</td>
</tr>
<tr>
<td></td>
<td>Inattentive</td>
<td>7.8 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Hyperactive/impulsive Sxs</td>
<td>6.9 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Inattentive</td>
<td>0.1 (0.5)</td>
</tr>
<tr>
<td></td>
<td>Hyperactive/impulsive Sxs</td>
<td>0.0 (0.3)</td>
</tr>
<tr>
<td>WRAT reading score (mean/SD)</td>
<td>Inattentive</td>
<td>104 (9.4)</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>99 (10.0)</td>
</tr>
<tr>
<td>WISC-III IQ score (prorated) (mean/SD)</td>
<td>Inattentive</td>
<td>111 (9.2)</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>108 (17.1)</td>
</tr>
<tr>
<td>Caucasian (number/percent)</td>
<td>Inattentive</td>
<td>12 (92)</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Right handed (number/percent)</td>
<td>Inattentive</td>
<td>13 (87)</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>9 (100)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>79 (78)</td>
</tr>
</tbody>
</table>

Children included in the Control groups were required not to have a previous diagnosis of ADHD or a learning disorder, and were required to have fewer than four of the nine symptoms in the inattention and/or hyperactivity/impulsivity domains specified in the DSM-IV manual. For 21 of the 31 Control participants in the OAE study, and for 19 of the 33 Control participants in the FLR study, this information was obtained only from parent ratings; for the remainder of the participants, ratings were obtained from a parent and a teacher.

4. Sample description

Of the 61 participants contributing OAE measurements, 13 boys and 5 girls met the criteria for ADHD/Inattentive, 9 boys and 3 girls met the criteria for ADHD/Combined, and 15 boys and 16 girls served as Controls. Of the 79 participants contributing finger-length measurements, 20 boys and 9 girls met the criteria for ADHD/Inattentive, 14 boys and 3 girls met the criteria for ADHD/Combined, and 17 boys and 16 girls served as Control subjects. Because FLRs vary across ethnic groups [20, p. 19], we omitted all...
participants not identified as White or Caucasian (our most numerous group) from our analyses of FLRs in order to eliminate ethnicity as a source of variability here. This led to the exclusion of 11 boys and 4 girls from finger-length analyses, of which 5 boys and 2 girls had provided OAE data. Although there is no evidence that CEOAEs vary with ethnicity, the CEOAE data were analyzed with and without non-Caucasians included. Thus, some, but not all of the participants included in the OAE study also contributed data to the FLR study.

Demographic information (see Table 1) is provided separately for the children contributing to each of the two studies. ANOVAs evaluating age, IQ, and Wide Range Achievement Test (WRAT-III) [33] were conducted using two independent variables (Sex and Diagnostic Group). In calculating WISC-III IQ [34] scores, a Full Scale IQ score was used for all ADHD groups, and for those controls for whom it was available. For those controls without a Full Scale IQ score, a prorated IQ score based on the Vocabulary and Block Design subtests was used to obtain an estimate of intellectual functioning [35]. For all comparisons, no significant differences were noted for either age or IQ. Among boys in the OAE study, a marginally significant effect \((P = .052)\) that became significant in the FLR study \((P = .023)\) was detected for the ADHD/Combined group to have lower reading scores than Controls. Additional analyses revealed that these group differences in IQ and reading did not influence the primary findings (see Section 10).

For both studies, participants were classified as having a reading disability if the child demonstrated below-average achievement on the WRAT-III Reading subtest (a standardized score of < 85) and a discrepancy of greater than one standard deviation (i.e., > 15 points) between prorated Full Scale IQ on the WISC-III and the WRAT-III reading subtest. In the FLR study, one boy in the ADHD/Combined group was classified as having a reading disability using these criteria, but with this subject excluded, the pattern of results was the same. Overall, these analyses indicate that our results are not attributable to group differences in IQ, reading, or reading-disability status.

For some control participants, handedness was taken as the hand used for writing; for all other participants, handedness was determined by hand preference on three fine-motor tasks [36].

5. Procedure: general

All testing for an individual took place during a three-hour session conducted on a weekend day at the neuropsychology clinic. The neuropsychological testing required about 2.75 h, and the auditory portion required about 15 min. For all subjects participating in the full 3-h session, OAE testing occurred after about 30 min of other activities. Some children recruited as controls participated only in finger-length and OAE measurements, and some ADHD children were called back only for OAE measurements. Parents of children in this second group were given the opportunity to sit with their child during testing, and approximately 60% did so. For these subjects, OAE testing occurred within about 10–30 min of arrival. The OAE testing room was a small office with no special sound-deadening treatment. Because the clinic was not in operation on the weekend, and because the room’s air conditioning and fluorescent lights were turned off, the test room was acceptably quiet. Illumination was provided by a single 60-W bulb.

All procedures were approved in advance by the UT Institutional Review Board. Consent forms were signed by the parents and Assent forms were signed by the children prior to the test session. Subjects were paid $15–$25 depending upon how many neurocognitive measurements other than OAEs were made. The same experimenter (author JGW) measured the OAEs of all subjects, and was responsible for informing the subjects and parents about the nature and purpose of this aspect of the larger study.

Those children normally receiving medication for their ADHD symptoms underwent a washout period of 18 h or greater prior to the weekend test session.

Because our samples were small, and the number of possible pairwise comparisons was large, here we will emphasize effect sizes [37] rather than level of statistical significance. Effect size was calculated as the difference between the means of the two conditions being compared divided by the square root of the weighted mean of their variances. For pairwise comparisons of this sort, Cohen [37] has suggested that effect sizes of 0.2, 0.5, and 0.8 should be considered small, medium, and large, respectively. Unpaired \(t\)-tests and Pearson correlations also are reported. A resampling procedure was used to put the obtained data into an overall perspective statistically.

6. Procedure: OAE measurements

All included subjects passed a hearing screening test administered prior to OAE testing. Typically, the screening test occurred immediately before OAE testing, but for about one-third of the ADHD children, the hearing test had been conducted previously. To pass the screening test, a child had to hear test frequencies of 500, 1000, 2000, and 4000 Hz at 25 dB Hearing Level or better in both ears. Only one child, a Control male, was excluded due to an inability to detect a tone at 4000 Hz at 60 dB.

For the OAE measurements, the participant reclined in an upholstered arm chair with the feet supported by a footstool. A hollow, foam-padded eartip was inserted securely into the external ear canal. The click stimuli were presented using an Etymotics ER-2 earphone that was connected to a small plastic tube that passed through the hollow ear tip. An
Stimulus presentation and data collection were implemented using an Apple Powerbook G3 laptop computer running LabView software. The click stimuli were generated using the built-in sound system of the computer (sampling rate of 44.1 kHz, 16-bit resolution), amplified, and delivered to the ER-2 earphone. The output of the microphone was delivered to its preamplifier and then to a custom-built low-noise amplifier/filter device that amplified the waveform by about 14 dB and high-passed it at about 400 Hz (in order to minimize extraneous body noises). The output of the filter was digitized (with 16-bit precision) at a sampling rate of 50,000 sample points per second using a National Instruments PCMCIA card plugged into the computer.

To collect CEOAEs, a series of electrical pulses about 91 μs in duration were delivered to the earphone. Beginning 2 ms after each click, 40 ms of the echo-like response was collected and summed with the responses from previous clicks. Having a 2-ms delay before initiating data collection eliminates the click stimulus itself and much of the ringing in the ear canal and middle-ear system that is not part of the cochlear response to the click.

Clicks were presented in sets of 10 at a nominal rate of 10/s, with approximately 500 ms between sets. The noise level in the ear canal was monitored continually and whenever it exceeded a predetermined criterion value, the presentation of the next set of 10 clicks was postponed until the noise level again fell below the criterion value. Similarly, responses to individual clicks that were too large were not included in the averaging procedure on the presumption that they contained extraneous body noise. The procedure for determining the criterion value for each ear was described in McFadden and Shubel [31]. Data collection was complete once cochlear responses had been obtained for at least 250 individual clicks. The resulting averaged waveform was analyzed off-line.

Measures of two types were extracted from the averaged echo-like waveform. To obtain typical CEOAE data, the initial 4 ms of the averaged waveform was deleted (for a total delay of 6 ms from click onset) as a further precaution against including mechanical ringing of the middle-ear system. The next 20.5 ms of the waveform was bandpass-filtered between 1.0 and 5.0 kHz. The rms level of the resulting waveform was calculated and transformed into decibels sound-pressure level (dB SPL). Here, we call the result ‘CEOAE Level’. Our standard analysis bandwidth for adults is 1–5 kHz, but other bandwidths also were examined, as reported below.

A second type of CEOAE was obtained by deleting the initial 18 ms of the waveform (for a total delay of 20 ms from click onset), and then processing the subsequent 20.5 ms in the manner described above. After a delay of 20 ms, much of the immediate echo-like response has died away, and much of what remains is often attributable to spontaneous OAEs (SOAEs) that were synchronized by the click stimulus [38]. Accordingly, the response measured after a long delay is called the synchronized spontaneous OAE (SSOAE). Here, we call this measure ‘SSOAE Level’.

After the measurements of the individual waveforms were complete, they were examined further, and some ears were excluded from the data analyses because the averaged responses were so weak they could not be distinguished from the background noise of the recording system. The procedure was as follows: CEOAE levels were calculated for 20.5-ms samples having total delays of 7 and 20 ms, those levels were transformed into powers, the second was subtracted from the first, and the difference was transformed back into decibels. When the difference was 0 dB or smaller, that ear was excluded from all further data analyses. Using this exclusion rule, both ears were excluded for one boy from each of the three subject groups. In addition, one right ear was excluded for a boy diagnosed as ADHD/Inattentive, one left ear was excluded for a boy diagnosed as ADHD/Combined, and five left ears and one right ear were excluded for Control boys. For the girls, both ears were excluded for two Control subjects. In addition, one left ear was excluded for a Control girl, and one left ear and one right ear were excluded for girls diagnosed as ADHD/Inattentive.

Because of the time limitations, cochlear responses were collected for only one level of the click for each ear. The peak-equivalent sound-pressure level (peSPL re 20 μPa) of each click was approximately 75 dB. The right ear was always tested first. The collection of OAE data required approximately 2.5 min for each ear of a subject.

7. Procedure: finger-length measurements

Images were obtained of the two hands placed side by side, using either a photocopier or a digital scanner. The palms of the hands were pressed lightly onto the glass bed of the photocopier or scanner with the fingers evenly spaced and with a white towel covering the hands and forearms. The photocopied images were scanned into Photoshop 5.0 LE, and all the scans were imported into Canvas 7.0.2 where finger lengths were measured. The measurement procedures were basically the same as those described in McFadden and Shubel [24]. Briefly, two experienced judges independently drew lines through the crease at the base of each finger and then drew another line connecting the midpoint of the first line to the tip of the finger. Canvas displayed the length of the second line accurate to fractions of a millimeter. The two judges were blind to the sex and classification of the subjects and were unable to see the lines drawn by the other judge. For each finger, the average of the lengths estimated by the two judges was used to calculate all of the six possible length ratios for each hand, and those ratios were used for our analyses. Correlations were calculated between the lengths estimated by the two judges for each finger of
each hand. Those correlations ranged from 0.953 to 0.983 with an average of 0.968 across fingers and hands. On those rare occasions when the quality of the image did not permit an estimate for a finger, all the possible ratios using the other three fingers were calculated and used in the analyses.

Making the measurements using Photoshop and Canvas has several advantages over the use of photocopies. For example, it is possible to adjust the contrast of the image in Photoshop in order to maximize the visibility of the relevant landmarks (the basal crease and the tip of the finger). Further, those landmarks can be viewed under high magnification in Canvas, which can greatly increase the accuracy of the length measurements. Our judges mark the tip of the finger to the nearest pixel. Also, Canvas itself calculates the lengths of the line segments fitted to the individual fingers, which eliminates a source of human error; plus, those lengths are many times more precise than is possible by eye. Finally, this procedure yields a permanent record (in Canvas) of the lines actually fitted to each finger of each participant by each judge, which can be helpful in resolving the rare discrepancy between judges. A pilot study comparing finger-length measurements made from scans with measurements made directly from photocopies of the same hands (data not shown) revealed that the correlations between judges were higher for the measurements obtained from direct scans (and from scanned photocopies) than for the measurements obtained directly from photocopies.

Although the ADHD/Combined boys were younger than, and their finger lengths shorter than, those of the boys in the other groups, this should not have affected FLRs. Lippa showed that the 2D:4D ratio does not vary with body size.

8. Results: OAE data

The results will be discussed separately for boys and girls. For both the short-delay (CEOAE) and long-delay (SSOAE) conditions, the responses from the boys diagnosed as ADHD/Inattentive were considerably weaker than those from either the Control boys or the boys diagnosed as ADHD/Combined, whose means were generally similar. Because males typically exhibit weaker OAEs than females, the even-weaker OAEs in the boys diagnosed as ADHD/Inattentive can be thought of as a hypermasculinization. The average OAE data for the three groups of boys are shown in Fig. 1 for both CEOAEs and SSOAEs, and for the two ears separately. For boys, the effect sizes and significance levels for the various comparisons are shown in the top part of Table 2. All four of the effect sizes for the comparisons between the boys diagnosed as ADHD/Inattentive and the Control boys were substantial. When the left and right ear data were averaged for each subject, the effect sizes were 1.34 and 1.13 for CEOAEs and SSOAEs, respectively, for the comparison between ADHD/Inattentive and Control boys.

For an effect size of 1.34 (1.13), a sample size of 20 (28) would be required for power of 0.8 and a significance level of 0.05. The effect sizes were about 0.21 for both CEOAEs and SSOAEs for the comparison between ADHD/Combined and Control boys. For an effect size of 0.21, a sample size of 714 would be required for power of 0.8 and a significance level of 0.05. No comparisons between ADHD/Combined and Control boys approached significance for either delay. Across subject groups and ears for the boys, the correlations between CEOAEs and SSOAEs ranged between 0.67 and 0.94.

Our standard analysis bandwidth for adults is 1–5 kHz, and all the results reported so far were based upon that bandwidth. For completeness, we also examined the results after filtering from 1–4 kHz, 1–6 kHz, and 1–8 kHz.
The left and right ears, respectively, of the ADHD/Inattentive group, and $N_{0.01}$ than for Caucasian-Americans [40]. To determine whether
numerous for African-Americans and Asian-Americans.

To determine whether ethnicity might be contributing to the CEOAE results obtained here, the male data were reanalyzed with the non-Whites removed. One boy was deleted from the Inattentive group and two boys were deleted from each of the other two groups (cf. Table 1). The result was that the various means changed by less than one standard error, and the basic pattern of the results was the same as before the deletions.

### 9. Results: finger-length data

The pattern of results for FLRs was much the same as for OAEs. The FLRs for boys diagnosed as ADHD/Inattentive were smaller than those of both Control boys and boys diagnosed as ADHD/Combined, and the FLRs for girls diagnosed as ADHD/Inattentive were smaller than those of Control girls (again, the sample size for the girls diagnosed as ADHD/Combined was too small to warrant their inclusion in the analyses).

The values of the FLRs for all of the six possible pairs of fingers on each hand are shown for the boys in Fig. 2. As can be seen, the mean value of the FLR was, for nearly every pair of fingers, larger for the Control boys than for the boys diagnosed as ADHD/Inattentive, and that was true for both hands. Because males typically exhibit smaller FLRs than females, the even-smaller ratios in the ADHD/Inattentive boys can be thought of as a hypermasculinization. Perhaps the most obvious difference between the two hands was that, for the right hand, the data for the boys diagnosed as ADHD/Combined were typically intermediate to those for the other two groups, but not so for the left hand.

Effect sizes and significance levels are shown in the top part of Table 3 for each of the pairwise comparisons between the three groups of male subjects. It is notable in both Fig. 2 and Table 3 that the most commonly studied length ratio (2D:4D) showed only small differences across groups. The large differences were for the ratios 2D:5D, 3D:5D, and 4D:5D, in ascending order. A similar pattern was seen in the comparisons between the Combined and Inattentive groups. The effect sizes for the two-hand averages for the comparison between the Control boys and the boys diagnosed as ADHD/Inattentive were 0.115, 0.676, 0.834, and 0.975, for the 2D:4D, 2D:5D, 3D:5D, and 4D:5D ratios, respectively; for the comparisons between the Control boys and the boys diagnosed as ADHD/Combined, the corresponding two-hand effect sizes were $-0.154$, $-0.129$, $-0.063$, and 0.042.

### Table 2

| Group and condition | CEOAEs | | SSOAEs | |
|--------------------|-------|-----------------|-------|
|                    | Left  | Right           | Left  | Right |
| Boys               |       |                 |       |       |
| Controls vs. ADHD/Inattentive | 0.968* | 0.947* | 1.051* | 0.695* |
| Controls vs. ADHD/Combined | 0.234 | $-0.151$ | 0.453 | $-0.226$ |
| ADHD/Combined vs. ADHD/Inattentive | 0.699 | 1.018* | 0.459 | 0.857* |
| Girls              |       |                 |       |       |
| Controls vs. ADHD/Inattentive | 0.834 | $-0.084$ | 0.259 | $-0.280$ |
| Girls and Boys     |       |                 |       |       |
| Control girls vs. Control boys | 0.233 | 0.067 | $-0.074$ | 0.085 |

* $P=0.104$.  
* $P=0.081$.  
* $0.01<P<0.05$; unpaired $t$-test, two-tailed. Positive entry designates greater masculinization. Ns for the boys are shown in Fig. 1; for the girls, $N=5$ and 4 for the left and right ears, respectively, of the ADHD/Inattentive group, and $N=13$ and 14 for left and right ears, respectively, of the Controls.
Finding evidence of hypermasculinization in a second physiological measure both supports the OAE findings and implies that the boys diagnosed as ADHD/Inattentive were exposed to hyper-androgenizing mechanisms at some point(s) early in development.

For the girls, the outcomes for FLRs were much more consistent than they were for OAEs. The mean FLRs for the girls are shown in Fig. 3. The girls diagnosed as ADHD/Inattentive had smaller (masculinized) length ratios for every pair of fingers in both hands. Nevertheless, the differences again were smaller than for the boys; the effect sizes for the girls are shown in the middle of Table 3. Also, the pattern of results for girls was different from that for the boys. For example, for the girls, the 2D:4D ratio did exhibit some of the largest differences obtained, and the differences for ratios 3D:5D and 4D:5D were not large, as they were for the boys. Establishing whether these smaller differences and different patterns of results are attributable to different etiological mechanisms in boys and girls will require additional research.

The length ratios showing the largest effect sizes in Table 3 are those involving digit 5, which suggests that 5D was longer in the boys diagnosed as ADHD/Inattentive than in the boys diagnosed as ADHD/Combined or Control boys. Confirming that implication, the average 5D length in Inattentive boys was longer by 0.8 and 1.4 mm in the left and right hands, respectively, than the corresponding average 5D lengths in Control boys. In addition, the average lengths of 2D, 3D, and 4D in both hands all were slightly shorter than those for the Control boys; the range was 0.06–0.90 mm across the six fingers. Thus, the smaller length ratios for the boys diagnosed as ADHD/Inattentive were attributable to differences in both the numerators and the denominators of the ratios. The fact that the length of 5D played a major role in the differences reported here may eventually prove to be related to the timing of whatever prenatal (hormonal?) event is responsible for both the hypermasculinization of the finger-length ratios in the boys diagnosed as ADHD/Inattentive and the symptoms that led them to be so diagnosed.

**10. Correlations with IQ and reading ability**

To examine whether IQ and/or reading ability contributed to the pattern of findings, additional analyses were conducted. When the boys in all three groups were combined, none of the OAE measures correlated significantly with IQ scores. Of the 12 correlations calculated for hands, only the 4D:5D ratio of the left hand correlated significantly with the WISC-III prorated IQ score ($r = -0.33$, $P = 0.029$). However, regression analyses using the WISC-III prorated scores as a covariate revealed that the ADHD/Inattentive group still had a significantly smaller mean 4D:5D ratio than the ADHD/Combined group ($P = 0.007$). Correlations between the Reading subtest of the WRAT-III and CEOAE magnitude were 0.085 and $-0.096$ for the right and left ears, respectively. Correlations between WRAT-III Reading scores and the 12 possible FLRs (six for both left and right hands) ranged from $-0.043$ to $-0.279$. None of the correlations between the WRAT-III Reading scores and CEOAE or FLR measurements was significant for the boys. When the girls in all three groups were combined, none of the OAE or FLR measures correlated significantly with WISC-III prorated IQ or WRAT-III Reading scores.
Table 3
Effect sizes and significance levels for finger-length ratios in both hands for Caucasian boys (top) and girls (middle)

<table>
<thead>
<tr>
<th>Group and condition</th>
<th>Hand</th>
<th>2D:3D</th>
<th>2D:4D</th>
<th>2D:5D</th>
<th>3D:4D</th>
<th>3D:5D</th>
<th>4D:5D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls vs. ADHD/Inattentive</td>
<td>Left</td>
<td>−0.109</td>
<td>0.133</td>
<td>0.523</td>
<td>0.284</td>
<td>0.643</td>
<td>0.711*</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0.014</td>
<td>0.102</td>
<td>0.814*</td>
<td>0.176</td>
<td>0.922**</td>
<td>1.063**</td>
</tr>
<tr>
<td>Controls vs. ADHD/Combined</td>
<td>Left</td>
<td>−0.177</td>
<td>−0.466</td>
<td>−0.515</td>
<td>−0.362</td>
<td>−0.443</td>
<td>−0.307</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0.184</td>
<td>0.155</td>
<td>0.260</td>
<td>0.040</td>
<td>0.248</td>
<td>0.313</td>
</tr>
<tr>
<td>ADHD/Combined vs. ADHD/Inattentive</td>
<td>Left</td>
<td>0.051</td>
<td>0.545</td>
<td>0.974**</td>
<td>0.611</td>
<td>1.121**</td>
<td>1.061**</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>−0.184</td>
<td>−0.058</td>
<td>0.451</td>
<td>0.121</td>
<td>0.626</td>
<td>0.797*</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls vs. ADHD/Inattentive</td>
<td>Left</td>
<td>0.511</td>
<td>0.723</td>
<td>0.689</td>
<td>0.300</td>
<td>0.223</td>
<td>0.287</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0.501</td>
<td>0.621</td>
<td>0.720</td>
<td>0.379</td>
<td>0.475</td>
<td>0.285</td>
</tr>
<tr>
<td>Girls and Boys</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control girls vs. Control boys</td>
<td>Left</td>
<td>0.491</td>
<td>0.826*</td>
<td>0.784*</td>
<td>0.437</td>
<td>0.298</td>
<td>0.363</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>0.218</td>
<td>0.492</td>
<td>0.517</td>
<td>0.371</td>
<td>0.317</td>
<td>0.139</td>
</tr>
</tbody>
</table>

Positive entry designates greater masculinization. Ns for the boys and girls are shown in Figs. 2 and 3, respectively. Unpaired \( t \)-test, two-tailed: *0.01 < \( P < 0.05 \); **0.001 < \( P < 0.01 \).

11. Resampling

The issue of the experiment-wise error rate with such a large number of pairwise comparisons was addressed using a resampling technique. The goal was to estimate the probability of obtaining effects as large as those shown in Tables 2 and 3 from random data. The general strategy was as follows: the subjects from the three groups of boys were pooled and a sample the size of the boys diagnosed as ADHD/Inattentive was drawn at random without replacement from the pool. Then a second sample the size of the Control boys was drawn from the remainder of the pool. The means and SDs for the three samples so created were used to calculate all the relevant two-group effect sizes for the various measures. This resampling procedure was repeated 10,000 times, and the number of times the mean effect size equaled or exceeded the mean effect size obtained from the original data (subsequently called the benchmark effect sizes) was recorded. From this sum, an estimated probability of chance occurrence was calculated. The resamplings were done separately for OAEs and FLRs, primarily because of the difference in sample sizes for the two types of measure.

The calculations were done multiple ways, but the result was basically the same. For both OAEs and FLRs, the effect sizes actually obtained between the boys in the Inattentive and Control groups were matched only rarely in the resampling process. We offer this demonstration as evidence that our findings were not solely attributable to the large number of pairwise comparisons made.

12. Basic sex difference

Although the primary interest here was comparisons within sex, there also is value in comparing the data obtained from the two groups of control subjects. Past research has shown that the CEOAEs of females are generally stronger than those of males (e.g. [14,31]). That pattern existed here, but the sex differences were much smaller than those we measured recently in young adults [31]. The effect sizes for the basic sex differences in OAEs are shown at the bottom of Table 2. Examination of the data revealed that the CEOAEs of the Control boys were quite similar to those for young adult males, but the CEOAEs of the Control girls were not similar to those for young adult females. The two-ear average for the Control boys here was only 0.25 dB smaller than the CEOAE value for young adult males, and the standard deviations also were highly similar [31]. This makes us even more confident about the direction and magnitude of the various differences between groups reported here for the boys. However, the two-ear average for our Control girls was more than 4 dB smaller than that for the young adult females, and the standard deviation was one-third larger. It appears that this sample of Control girls had atypically weak CEOAEs for some reason. Had they been more typical, not only would the basic sex difference have been larger (bottom of Table 2), but the differences between the ADHD/Inattentive and Control girls also would have been larger (middle of Table 2). We know of no evidence that CEOAEs strengthen in females following puberty. The atypically weak CEOAEs in our Control girls emphasizes that our CEOAE results for girls must be interpreted with caution.

Past research has shown that the FLRs of females are generally larger than those of males, and these sex differences are generally larger for the right hand than for the left (e.g. [20,24]). The former outcome was obtained here, but not the latter. As can be seen at the bottom of Table 3, every one of the effect sizes for the sex differences in FLRs was positive, and thus in accord with the literature on the directionality of the sex differences in FLRs. However, those effect sizes were mostly larger for the left hand than for the right, and this is opposite to the typical finding with young adults. Examination of the data...
revealed that the hierarchy of lengths of the fingers for both hands of both the Control boys and the Control girls was 3D > 4D > 2D > 5D, which is the same hierarchy as observed for young adults [24]. Further examination revealed that the absolute lengths of the FLRs for both Control girls and Control boys were slightly larger than those for their Caucasian counterparts among the young adults we measured recently [24], and the standard deviations also were generally slightly larger. That examination revealed nothing anomalous to explain the smaller sex differences in the FLRs for the right hand. For example, the FLRs for the Control girls were not markedly different from those of young adult females the way their CEOAEs were. The differences between the means were simply smaller for the right hand than for the left. We suspect that the explanation lies in sampling fluctuations associated with the small Ns.

13. Discussion

Here, we have reported evidence from two quite different physiological measures that boys diagnosed as ADHD/Inattentive type are hypermasculinized both relative to Control boys and to boys diagnosed as ADHD/Combined type. This provides evidence in the 4th domain suggested by Cantwell [4].

The strong implication is that these boys diagnosed as ADHD/Inattentive were subjected to a hyper-androgenization process at some point during development. Because the sex differences in OAEs and FLRs both exist early in life (e.g. [15,20, p. 15]), it seems reasonable to presume that the hyper-androgenization occurred prenatally or perinatally. If this reasoning is correct, it suggests that boys diagnosed as ADHD/Inattentive were affected by an additional (presumably hormonal) factor not affecting boys diagnosed as ADHD/Combined. This indication of a distinct pathophysiological mechanism for the ADHD/Inattentive type is consistent with recent data on event-related potentials [41], which also suggested that ADHD/Inattentive and ADHD/Combined are qualitatively distinct groups. The absence of a hypermasculinization in the OAEs or FLRs of boys diagnosed as ADHD/Combined appears to be additional evidence that the Inattentive and Combined types defined by the DSM-IV are not versions of a common disorder, but different disorders deserving of separate nosology, treatment, and research perspectives [5,1].

The present data are less clear about the potential etiological differences between the Inattentive and Combined categories for girls diagnosed with ADHD. We had data from very few girls diagnosed as ADHD/Combined. Also, the CEOAEs for the Control girls appeared atypically weak compared to adult norms, which makes it difficult to know how to interpret the modest suggestion of a masculinization seen in the CEOAEs of girls diagnosed as ADHD/Inattentive relative to the Control girls. However, the FLRs of the girls diagnosed as ADHD/Inattentive were universally smaller than (masculinized) those of the Control girls, and several of those effect sizes were moderately large [37]. Perhaps the best characterization of the situation is that there is now sufficient evidence of a possible masculinization in the girls diagnosed as ADHD/Inattentive to warrant additional research using physiological and neurocognitive measures that are known to discriminate between the sexes.

In this study, the only OAE measured was the CEOAE. Because CEOAE measures are so highly correlated with measures of spontaneous OAEs [14], it is highly likely that
the hypermasculinization reported here also will be evident in spontaneous OAEs, where the magnitude of effect might be even larger than for CEOAEs. Because the sex and ear differences in OAEs exist in newborns as well as in adults (e.g. [15]) and because OAEs are quite stable characteristics through life, OAEs (perhaps in conjunction with FLRs) might come to have value for identifying a population of young males at risk for developing the Inattentive type of ADHD.

The active elements in the cochlea that are involved in the production of OAEs are commonly characterized as the cochlear amplifiers. Strong cochlear amplifiers are thought to give rise both to strong OAEs and good hearing sensitivity (e.g. [42,19]). Thus, the finding of weaker OAEs in boys diagnosed as ADHD/Inattentive carries the implication that their hearing also is less sensitive than that of the Control boys. The effect should be small, meaning that they still should fall in the normal range, but the implication exists and is worth testing. There are reports of reduced auditory processing in ADHD such as difficulty with auditory figure-ground discrimination [43]. These findings have traditionally been attributed to more central processes; however, the present data reveal the existence of a peripheral disorder in addition to whatever central disorders of auditory processing may exist. Children with ADHD also have been found to be different from Control children on certain other behavioral auditory tasks [44,45], but only children diagnosed as ADHD/Combined were tested in those studies.

Another physiological auditory measure exhibiting substantial sex differences is auditory evoked potentials or AEPs [46]. A finding of AEP hypermasculinization only in boys diagnosed as ADHD/Inattentive obviously would provide confirmation of the hyper-androgenization implied by the OAE and FLR data reported here. Also of interest is whether boys diagnosed as ADHD/Inattentive are hypermasculinized on other tasks that exhibit large sex differences, such as directing projectiles [47] and mental rotation [48].

In most studies on FLRs, only the 2D:4D ratio is calculated. Had we calculated only the 2D:4D ratio here, we would not have seen any evidence of the strong hypermasculinization that existed in those length ratios involving finger 5D for boys diagnosed as ADHD/Inattentive. We believe that this example stands as strong evidence for the validity of the diagnostic distinction between the ADHD/Inattentive and Combined types.

Cantwell [4] provided a compelling case for the empirical approach to child psychiatry, which calls for a reliable and valid classification system informed by the investigation of multiple clinical domains. Accordingly, he argued that two disorders which are truly different should be distinguishable in facets other than merely clinical phenomenology. Perhaps the most compelling of these levels—and, at the time of Cantwell’s 1990 paper, the most elusive—is that of etiological distinction. In this spirit, we suggest that, in addition to identifying a new potential etiological pathway for ADHD/Inattentive, our results provide strong evidence for the validity of the diagnostic distinction between the ADHD/Inattentive and Combined types.

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