# Auditory Brainstem Responses in Young Males With Fragile X Syndrome

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Fragile X syndrome (FXS) is the most common inherited cause of mental retardation resulting in developmental delays in males. Atypical outer ear morphology is characteristic of FXS and may serve as a marker for abnormal auditory function. Despite this abnormality, studies of the hearing of young males with FXS are generally lacking. A few studies have suggested that a significant proportion of individuals with FXS demonstrate prolonged auditory brainstem response (ABR) latencies. The purpose of this study was to determine whether young males with FXS display atypical auditory brainstem function compared to typically developing males when conductive and sensorineural hearing loss are ruled out as possible contributors to atypical findings. Participants were 23 males with FXS, 21 typically developing males who were matched for developmental age, and 17 typically developing males who were matched for chronological age. A battery of tests to assess peripheral hearing, cochlear function, and auditory pathway integrity through the level of the brainstem was completed. Males with FXS were similar to typically developing males who were matched for developmental age level or chronological age level on all measures. They had normal hearing sensitivity and middle ear function and scored similar to the typically developing children on the measures of auditory brainstem pathway integrity. In summary, ABRs in young males with FXS were within normal limits.

KEY WORDS: fragile X syndrome, auditory function, hearing, males, X-linked

Fragile X syndrome (FXS), an X-linked genetic condition, is the most common inherited cause of mental retardation, affecting 1 in every 4,000 individuals (Crawford, Acuna, & Sherman, 2001; Turner, Webb, & Robinson, 1996). In FXS, there is an absence of the fragile X mental retardation protein (FMRP) that is produced by the fragile X mental retardation-1 gene (FMR1). FMRP is believed to be essential for normal brain function. The resulting deficiency of FMRP appears to be responsible for the syndrome. Individuals with FXS vary in symptomatology, with males being more severely affected than females (Hagerman 2002; Mazzocco, 2000; U.S. Department of Health and Human Services, 2003). The majority of males with FXS have mental retardation, typically mild to moderate in degree, as well as difficulties in adaptive, social, and communication skills (Abbedutto & Hagerman, 1997; Bennetto & Pennington, 2002; Mazzocco, 2000; U.S. Department of Health and Human Services, 2003).

**Table 1.** Chronological and developmental age levels for boys with fragile X syndrome (FXS), typically developing developmental age matches (TD DA), and typically developing chronological age matches (TD CA).

| Age | FXS | TD DA matched | TD CA matched |
|---|---|---|---|
| *N* | 23 | 21 | 17 |
| Chronological age (months) | | | |
|   *M* | 131.6 | 56.7 | 130.6 |
|   *SD* | 19.3 | 11.0 | 20.4 |
|   Range | 95.1–163.1 | 38.3–78.7 | 97.1–162.6 |
| Leiter developmental age (months) | | | |
|   *M* | 64.8 | 64.5 | 160.2 |
|   *SD* | 7.1 | 10.8 | 55.9 |
|   Range | 51–80 | 52–85 | 90–251 |

It is commonly reported that males with FXS have prominent ears, which can include the loss of antihelical folds and cupped pinnae (Hagerman, 2002). Given this atypical morphology, it is unclear if auditory function is also affected. Several studies using the auditory brainstem response (ABR) have suggested that, compared to typically developing children, a significant proportion of individuals with FXS demonstrate prolonged waveform latencies (particularly wave V latencies) and interwave (I–V and/or III–V) latency intervals (Arinami, Sato, Nakajima, & Kondo, 1988; Gillberg, Persson, & Wahlstrom, 1986; Wisniewski, Segan, Miezejeski, Sersen, & Rudelli, 1991). Other evidence suggests longer I–III but shorter III–V latency intervals (Ferri et al., 1986), whereas at least one study (Miezejeski et al., 1997) reported that males with FXS have normal ABRs. While useful in examining neural integrity to the level of the brainstem, the ABR can be confounded by peripheral hearing loss. In past ABR studies, the majority of individuals (primarily adults) with FXS have not been evaluated by conventional audiometry. Therefore, it was not verified whether they had normal middle and inner ear function at the time the measures were collected. Otitis media is a middle ear condition that may result in conductive hearing loss and reportedly is prevalent among young children with FXS (Hagerman, Altshul-Stark, & McBogg, 1987). Consequently, a comprehensive study of hearing in children with FXS is needed to characterize more fully the auditory profiles of young males with FXS.

The purpose of this study was to determine if young males with FXS display typical or atypical auditory brainstem function (neurologic integrity) compared to typically developing males when conductive and sensorineural hearing loss are ruled out as contributing factors. We hypothesized that males with FXS would demonstrate normal ABR findings when measures of peripheral hearing sensitivity were determined to be normal.

## Method
### Study Population

Participants were males with FXS and two groups of typically developing males, one matched on developmental age and the other on chronological age. See Table 1 for details about the study participants and their background.

#### Fragile X Syndrome

Study participants were 23 males with FXS who ranged in chronological age from 95.1 to 163.1 months (*M* = 131.6). All of the males with FXS were diagnosed with a full mutation, confirmed by DNA analyses. The boys had a mean age-equivalent score on the Leiter International Performance Scale—Revised (Roid & Miller, 1997) Brief IQ composite (a test of nonverbal cognitive abilities) of 64.8 months (range = 51–80 months). The young males with FXS were recruited from an ongoing longitudinal study of males with FXS or were referred from pediatric, genetic, or developmental clinics in North Carolina, South Carolina, Virginia, Maryland, and Georgia. We included young males with FXS who were talking in at least two to three word utterances and who had not been diagnosed with sensorineural hearing loss. Seventy-eight percent of the males in the study were Caucasian, and 22% were African American. Thirty-five percent of the boys' mothers had a terminal education level of a high school degree, and 65% had some college or a college degree.

#### Typically Developing Males

There were 21 typically developing males who were matched to the males with FXS on developmental

age (TD DA) and 17 typically developing males who were matched to the males with FXS on chronological age (TD CA). The TD DA boys ranged in age from 38.3 to 78.7 months ($M$ = 56.7) and had a mean score on the Leiter Brief IQ of 64.5 months (range = 52–85 months). The TD CA boys ranged in age from 97.1 to 162.6 months ($M$ = 130.6) and had a mean score on the Leiter of 160.2 months (range = 90–251 months). The mean chronological age of the 17 TD CA group was not significantly different from the CA of the 23 males with FXS, $F(1, 39) = 0.02$, $p = .89$. Furthermore, the Leiter Brief IQ age equivalents of the 21 TD DA matched boys were not significantly different from the 23 boys with FXS, $F(1, 42) = 0.01$, $p = .92$. The TD DA and TD CA males were recruited from pediatricians' offices, child care centers, and schools in North Carolina. Of the TD DA males, 71% were Caucasian, 19% were African American, and 10% were other. For the TD CA males, 82% were Caucasian, and 18% were other. For the mothers of the TD DA boys, 71% had some college or a college degree and 29% some graduate school or a graduate degree. For the TD CA boys, 47% had some college or a college degree and 53% some graduate school or a graduate degree.

## Auditory Test Battery

The audiologic test battery consisted of behavioral measures (pure-tone and speech audiometry) and physiologic measures (tympanometry and distortion product otoacoustic emissions [DPOAEs]) to evaluate peripheral hearing sensitivity and cochlear function, and the ABR to examine auditory brainstem pathway (neural) integrity. All testing was performed in a sound-treated room that met American National Standards Institute (ANSI) standards for allowable ambient noise levels (ANSI, 1999). An experienced audiologist in the assessment of difficult-to-test children adhered strictly to test protocols developed for the study. All clinical audiometric test equipment was calibrated, and daily listening (biologic) checks were performed.

All study protocols were approved annually by the School of Medicine Institutional Review Board at the University of North Carolina at Chapel Hill. Each child's parent or guardian provided informed consent at the time of the hearing assessment. Parents were informed when we found conductive or sensorineural hearing loss in a child during the study, and medical and follow-up audiologic referrals were made.

### Pure-Tone Audiometry

Hearing sensitivity was classified as normal or impaired based on pure-tone audiometry. We used 20 dB HL at each test frequency (1000, 2000, and 4000 Hz) as the minimal response level (or cut-off) for classifying a response as normal. Responses to test stimuli were obtained using a behavioral procedure (either conditioned play audiometry or conventional) appropriate for the child's developmental abilities. Pure-tone stimuli were presented via an audiometer (Grason-Stadler, Model 16) with insert earphones and, in a few cases, standard earphones (Telephonics TDH-50) if a child would not tolerate the inserts. Appropriate correction values were used when switching between earphone types. For inclusion in the study, the child had to demonstrate reliable responses at levels less than or equal to 20 dB HL at each test frequency (1000, 2000, and 4000 Hz) in each ear.

### Speech Reception Audiometry

A speech reception threshold (SRT) for the right and left ear was obtained for each child using earphones (as above). The SRT was obtained with spondee words (e.g., *hotdog*) and was recorded as the lowest level (in dB HL) at which the child could correctly repeat the words with 50% accuracy. The child was asked to repeat the word beginning at a suprathreshold level. Subsequently, the speech presentation level was decreased in 10-dB steps until the first miss (incorrect response), which was followed by a standard bracketing procedure with a step size of 5 dB. If the child was unable to repeat words verbally, then six spondee picture cards were used and the child was asked to point to a picture. The SRT was the level (in dB HL) at which the child pointed to the correct word with approximately 50% accuracy. For the analysis, the SRT for each ear was considered normal (in a manner similar to the pure-tone testing described above) if the SRT was less than or equal to 20 dB HL.

### Tympanometry

Middle ear function was evaluated with a commercially available tympanometer (Grason-Stadler, Model 33), using a 226-Hz probe tone and a positive-to-negative pump speed of 50 daPa/s. Acoustic admittance magnitude, a measure of middle ear mobility, was measured in acoustic millimhos (mmho) over an ear-canal pressure range of +200 to −400 daPa. The static admittance value was obtained by subtracting the admittance at +200 daPa from the peak value. Tympanometric width, a method of defining the shape of the tympanogram, was calculated automatically according to the pressure interval corresponding to a 50% reduction in static admittance. Middle ear function was considered normal if acoustic admittance was ≥0.2 mmho in each ear and tympanometric width was ≤250 daPa in each ear.

## DPOAEs

Otoacoustic emissions (OAEs) were measured to assess cochlear outer hair cell function. DPOAEs were recorded in a sound-treated room using a commercially available instrument (Grason-Stadler, Model 60). It presented a series of simultaneous tone pairs (f1 and f2) at intensities of 65 dB SPL (L1) and 55 dB SPL (L2), respectively, to each ear using an f2/f1 ratio of 1.21. The f2 frequencies varied from approximately 2000 to 4000 Hz. Measurements included amplitude of the distortion product (DP amplitude), noise floor, and signal-to-noise ratio (DP amplitude minus noise floor). DPOAEs were considered normal when recorded at a signal-to-noise ratio greater than or equal to 3 dB for at least three of the four f2 frequencies (2000, 2500, 3187, and 4000) in each ear.

## ABRs

The ABR, which was used to examine neurological integrity, was measured with commercially available evoked potential recording system (Nicolet Spirit). Click stimuli (100 μs rarefaction) were presented at 70 dB nHL via insert earphones at a rate of 27.7/s. The EEG was amplified and bandpass-filtered from 30 to 3000 Hz. Recordings were obtained for each ear from a high forehead placement (Fz), for the noninverting electrode, to ipsilateral mastoids (A1/A2), for the inverting electrodes. The ground electrode was placed on the contralateral mastoid. Electrode impedances were maintained at less than 5000 ohms during the ABR measurements, which were made with the boys resting quietly, without sedation, in a reclining chair. Responses to 2,000 stimuli were obtained in two separate runs for each ear. Absolute latencies were recorded in milliseconds for waves I, III, and V; interwave latency intervals (in milliseconds) were calculated for waves I–V for each ear and then averaged. An audiologist conducted the measurements and interpreted the ABR. Response properties were verified independently by a second audiologist who had experience interpreting the ABR. She was blind to whether each boy had FXS or was TD DA or TD CA.

# Results
## Data Analyses

Results for pure-tone and speech audiometry, tympanometry, and cochlear function (DPOAEs) are summarized in Table 2 for each of the three groups. For the analyses of the ABR, we averaged the right and left ear responses for each boy. Those values were essentially identical and symmetric for the three groups

**Table 2.** Percentage (out of total) of males with FXS and TD DA and TD CA controls who were considered by our criteria (see text) to have normal findings on each auditory measure.

| Auditory measures | FXS (N = 23) | TD DA (N = 21) | TD CA (N = 17) |
|---|---|---|---|
| Pure-tone and speech audiometry | | | |
|   Pure-tone thresholds | 95.7 | 100 | 100 |
|   Speech reception thresholds | 100 | 100 | 100 |
| Tympanometry | | | |
|   Static admittance | 100 | 100 | 100 |
|   Tympanic width | 95.7 | 100 | 94 |
| DPOAEs | 90.5[a] | 95 | 100 |

*Note.* DPOAEs = distortion product otoacoustic emissions.

[a] 19/21 assessments; 2 boys did not have interpretable otoacoustic emissions.

when rounding to 0.01 ms. The ABR results are summarized in Table 3.

## Pure-Tone and Speech Audiometry

Twenty-two (95.7%) of the 23 boys with FXS and all (100%) of the TD DA and TD CA matched boys demonstrated normal pure-tone findings. The 1 boy with FXS who did not reach the normal pure-tone criteria yielded a response at 25 dB HL at one frequency, for one ear only. All of the boys in each group demonstrated normal SRTs ≤ 20 dB HL in both ears.

## Tympanometry

Static admittance for all of the boys in each of the three groups was within normal limits (≥0.2 mmho in each ear). All boys, except 1 with FXS and 1 TD CA, demonstrated normal tympanometric width (≤250 daPa in each ear). The male with FXS who did not meet the criterion for tympanometric width had a width of 380 daPa, and the TD CA male had a tympanometric width of 295 daPa.

## DPOAEs

DPOAEs were successfully recorded for 21 of the 23 boys with FXS. Two boys failed to meet the passing criteria (signal-to-noise ratio ≥3 dB for at least three of the four f2 frequencies in each ear). One of these 2 boys also did not pass the pure-tone threshold and the tympanometric criteria, suggesting the result was related to middle ear dysfunction (otitis media). For the 2 boys for whom OAE testing was unsuccessful and the 1 male with FXS who did not show signs of otitis media, all other auditory measures tested were within normal limits. However, movement and/or vocalizations were noted during their assessment, and

**Table 3.** Means (and standard deviations) in milliseconds of auditory brainstem response (ABR) measures for males with FXS and for TD DA and TD CA control groups, excluding males who had an abnormal auditory test result and including all males.

| ABR | FXS | TD DA matched | TD CA matched |
|---|---|---|---|
| Excluding males who had an abnormal auditory test result | N = 19 | N = 20 | N = 16 |
| Wave I latency M (SD) | 1.69 (0.10) | 1.67 (0.11) | 1.67 (0.10) |
| Wave III latency M (SD) | 3.87 (0.14) | 3.91 (0.13) | 3.85 (0.13) |
| Wave V latency M (SD) | 5.84 (0.18) | 5.87 (0.17) | 5.84 (0.15) |
| I–V latency interval M (SD) | 4.16 (0.16) | 4.20 (0.16) | 4.17 (0.17) |
| All study males | N = 23 | N = 21 | N = 17 |
| Wave I latency M (SD) | 1.69 (0.10) | 1.67 (0.12) | 1.67 (0.10) |
| Wave III latency M (SD) | 3.89 (0.15) | 3.91 (0.13) | 3.86 (0.13) |
| Wave V latency M (SD) | 5.87 (0.20) | 5.87 (0.17) | 5.85 (0.15) |
| I–V latency interval M (SD) | 4.18 (0.19) | 4.19 (0.16) | 4.17 (0.17) |

these confounding activities may have compromised their test results. One child in the TD DA group failed to meet the passing criteria for DPOAE, although all of the other auditory measures were within normal limits by our criteria. Noise also may have compromised the test results for this young participant.

## ABR

We examined absolute and interwave latencies for each boy's right and left ear ABRs. We deleted from our analysis the ABRs for the 4 males with FXS, 1 TD DA male, and 1 TD CA male who had any atypical findings on the pure-tone, tympanometry, or DPOAE measures. Interaural differences in ABR latencies for waves I, III, and V were within 0.01 ms for the males with FXS, 0.03 ms for the TD DA, and 0.01 ms for the TD CA. We therefore averaged the right and left ear ABRs for each child to determine whether the boys with FXS yield similar responses to those of the TD DA and TD CA boys after peripheral hearing loss was eliminated as a confounding variable. The ABR latencies (in milliseconds) for waves I (1.67–1.69), III (3.85–3.91), and V (5.84–5.87), and the interwave latency interval for waves I–V (4.16–4.20; see Table 3), were similar for the boys with FXS and the TD DA and TD CA groups based on multivariate analysis of variance (Wilks's lambda), $F(6, 100) = 0.32$, $p = .92$. These ABR values were consistent with published findings (Chiappa, 1997; Stockard, Stockard, Westmoreland, & Corfits, 1979) for typically developing children.

When all boys were considered in the analysis regardless of middle ear or OAE results, ABR indices (in milliseconds) for absolute latency of waves I (1.67–1.69), III (3.86–3.91), and V (5.85–5.87) and for the interwave latency interval for waves I–V (4.17–4.19)

(see Table 3) were similar for the boys with FXS and the TD DA and TD CA groups based on multivariate analysis of variance (Wilks's lambda), $F(6, 112) = 0.24$, $p = .96$.

## Discussion

After controlling for peripheral hearing loss, males with FXS were similar in their ABR findings to those measured from typically developing males matched for either developmental or chronological age. Thus, the boys with FXS had a pattern of response consistent with normal auditory pathway integrity up to the level of the lower auditory brainstem.

These results are consistent with the normal ABR findings reported by Miezejeski et al. (1997) but are inconsistent with four other studies that reported atypical ABR measurements for individuals with FXS (Arinami et al., 1988; Ferri et al., 1986; Gillberg et al., 1986; Wisniewski et al., 1991). Miezejeski et al. reported typical ABR interpeak latencies for 13 males with FXS from 2 to 28 years of age compared to controls with other mental retardation and a control group without mental retardation. Arinami and colleagues (1988) compared 12 adolescent and adult males with FXS (ages from 15 to 44 years) to a control group matched for gender and age. They reported that the boys with FXS had longer wave V latencies and prolonged I–V and III–V interpeak latencies, but did not differ in wave I or III absolute latencies or in the I–III interwave intervals when compared to the control group. Wisniewski et al. (1991) studied 12 individuals (gender not presented) drawn from a larger sample of 2–70-year-olds and found that ABRs were normal in 7 of 12 participants. The 5 participants who displayed

atypical ABRs also had late waves, especially III–V, with particularly long latencies. Similarly, Gillberg et al. (1986) reported prolonged latencies (specific waves were not reported) for 6 of 7 males with FXS, ages 2 to 17 years. In contrast, Ferri et al. (1986) reported longer I–III latencies but shorter III–V intervals for 8 young males with FXS (mean age of 13.2 years).

We believe the reason for the previous reports of atypical brainstem function among males with FXS is most likely due to the lack of control of peripheral hearing loss as a confounding factor on the ABR. We know that peripheral impairments (conductive or sensory) may affect the ABR, and this factor did not appear to be accounted for in the early studies. Hagerman et al. (1987), using a retrospective review of medical records, reported that otitis media in the first 5 years of life was more prevalent among young males with FXS than among typically developing siblings and unrelated typical males. Multiple studies have shown that children with a history of otitis media with effusion (OME) have prolonged ABR latencies (Folsom, Weber, & Thompson, 1983; Gravel et al., 2004; Hall & Grose, 1993). Furthermore, although we were able to compare our ABR data to previous studies of young males with FXS, we did not find comparison studies that used pure-tone findings, speech audiometry, and middle ear function as inclusion criteria, or that examined cochlear function directly using OAE measures.

These results, while supporting the hypothesis that boys with FXS have normal brainstem function, should be considered carefully because only 23 boys with FXS participated in the study. However, our findings, particularly for ABR, were so similar between the boys with FXS and typically developing boys that it is not clear that a larger sample would have contributed additional information. It also is possible that there are differences between males with FXS and typically developing boys in higher level (midbrain and cortical) auditory function that might have been revealed if middle latency or cortical responses were assessed. ABRs are early auditory evoked potentials, occurring in the first 10 ms following stimulation. They reflect electrophysiologic responses of the eighth cranial nerve and auditory brainstem pathway. Auditory middle latency responses arise at later response times from sites in the midbrain, whereas late evoked responses and auditory event-related potentials arise much later and from cortical structures. Recently, several researchers have reported atypical N100 and P300 amplitudes in individuals with FXS (Castren, Paakkonen, Tarkka, Ryynanen, & Partanen, 2003; Rojas et al., 2001; St. Clair, Blackwood, Oliver, & Dickens, 1987). We must also consider that our exclusionary developmental criteria (i.e., boys had to be between 7 and 13 years of age using at least two to three word utterances) may

have eliminated males with FXS most at risk for hearing difficulties. We included a minimum age and linguistic level so the boys with FXS would be able to maintain the attention and persistence to complete the auditory tests without sedation. Finally, since we were interested in brainstem-level auditory processing in children with normal peripheral hearing sensitivity, we excluded males with FXS who had known sensorineural hearing loss.

This study had several strengths compared to previous studies examining the auditory brainstem integrity of young males with FXS. First, the study compared the males with FXS to typically developing males, including matched samples of both chronological and developmental age boys. Having both control groups allowed us to compare these boys to others who were physiologically similar (chronological age match) and who were developmentally similar (similar nonverbal cognitive skills). Second, the boys were tested with a battery of measures that ensured that hearing was within the normal range for pure tones and speech, middle ear function (as measured by tympanometry), and cochlear function. This was critical in interpreting ABRs, as no dysfunction at the peripheral level influenced the electrophysiological findings. Thus, we were able to verify that the boys had normal brainstem auditory function. Third, hearing was tested using objective physiological measures (OAE and ABR) as well as behavioral tests (pure-tone audiometry and speech reception thresholds) that require a volitional response. Fourth, compared to previous studies using the ABR with children, adolescents, and adult males, all of our study participants with FXS were between 7 and 13 years of age. Finally, the boys with FXS all had an FXS diagnosis that was confirmed by DNA analyses.

## Summary and Conclusions

The results of this study indicated that the ABRs of young males with FXS do not differ from typically developing males when confounding peripheral hearing loss is eliminated. It is possible, however, that males with FXS may have processing problems at higher levels of the auditory system. Most males with FXS have moderate degrees of mental retardation and speech and language delays (Abbeduto & Hagerman, 1997; Bennetto & Pennington, 2002; U.S. Department of Health and Human Services, 2003). Our results suggest that these delays are not likely due to brainstem-level auditory deficits. Moreover, we saw little evidence of middle-ear findings suggestive of OME in these 7-to-13-year-olds with FXS. Thus, we conclude from these findings that elementary school–age males with FXS are similar to typically developing males on ABR indices.

## Acknowledgments

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