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Auditory Evoked Response Delays in Children with 47,XYY syndrome

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Abstract

47,XYY syndrome (XYY) is a male sex chromosome disorder where subjects have an X chromosome and two copies of the Y chromosome. XYY is associated with a physical phenotype and carries increased risk of neurodevelopmental disorders such as autism spectrum disorder (ASD). Latencies of auditory evoked responses measured by magnetoencephalography (MEG) have shown atypical prolongations in several neuropsychiatric and genetic disorders; specifically, delayed auditory responses have been observed in ASD. In this study, we investigated the associations of genotype and clinical phenotype with auditory processing. Whole cortex MEG recorded during a passive auditory paradigm (500Hz tones) was used to assess the auditory evoked response in 3 groups of male children: idiopathic autism (ASD-I), typically developing (TD) and XYY boys. Response waveforms were computed for left and right auditory cortex and latencies of the ~50ms (M50) and ~100ms (M100) components were determined. M50 latencies were significantly delayed compared to typically developing controls in children with ASD in the *right* hemisphere only, and in children with XYY in the *left* hemisphere only, irrespective of whether they met diagnostic criteria for ASD. Findings on the later M100 component trended in the same directions but did not attain significance, due to increased variance. Replicating previous findings, decreased M50 and M100 latencies with age were observed bilaterally. Overall, while XYY shares an electrophysiological phenotype (delayed evoked response latency) with idiopathic ASD, the hemispheric differences warrant further investigation.

Keywords

47; XYY syndrome; XYY; Autism Spectrum Disorder; M50; AEF; Magnetoencephalography

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Conflicts of Interests:

Dr. Roberts reports consulting agreements with CTF MEG, Ricoh, Spago Nanomedicine, Avexis and Prism Clinical Imaging.

Introduction:

The male sex chromosome aneuploidy disorder 47,XYY syndrome (hereafter, XYY) is associated with an increased risk for neurodevelopmental phenotypes, including developmental delays, difficulties with language, social-emotional difficulties, attention-deficit hyperactivity disorder and autism spectrum disorder (ASD) [1–5]. General intelligence is typically normal or only mildly diminished, although learning disabilities are common [3, 6]. Whereas XYY syndrome occurs in approximately 1 in 1000 males [7], XYY is actually diagnosed less frequently, likely because XYY-associated features, such as tall stature or developmental delays, are either not of clinical concern or are not clinically unique to XYY. ASD prevalence is significantly increased in XYY males, with rates as high as 19-50% in XYY [2, 8] compared with approximately 2.6% in the general male population [9]. This, coupled with the 4-1 male to female gender predominance in ASD, has led to the hypothesis that increased Y chromosome gene copy number in XYY leads to over-expression of Y-linked genes related to brain development and function, thereby increasing ASD risk [10, 11]. For instance, a recent XYY study by Ross, Tartaglia [11] found increased expression of *NLGN4Y*, a Y-chromosome gene coding for a trans-synaptic cell adhesion molecule, in boys with XYY versus XY controls, with higher expression of *NLGN4Y* associated with more severe autism symptoms.

The present study used magnetoencephalography (MEG) to examine main effects of diagnostic group (3 groups: idiopathic autism (ASD-I), typically developing (TD) and XYY boys) on the auditory evoked response component latencies in male children and adolescents (6-18 years). Past investigations of auditory evoked response have shown atypical neuromagnetic field components (M50, M100 etc.) in neuropsychiatric disorders such as ASD [12–15] and schizophrenia [16, 17], as well as in genetic disorders such as 16p11.2 deletion [18]. The goals of this study were to characterize the contribution of XYY to the timing of auditory evoked responses in comparison to ASD-I. Specifically we tested the hypothesis that boys with XYY would exhibit prolonged latencies (analogous to that observed in 16p11.2 deletion) comparable to delays observed in ASD-I. Further, we explored whether there would be an additional delay in children with XYY who met diagnostic criteria for ASD compared with boys with XYY who did not receive an ASD diagnosis. Implicit in this hypothesis is the reasoning that overexpression of Y-chromosome genes is detrimental to the generation of an age-appropriate evoked response.

Methods:

Participants:

17 Subjects were eliminated based on neuropsychological assessment and inclusion/exclusion criteria or incomplete or artifact-contaminated data. Evaluable data were obtained from 33 typically developing (TD) male children, 62 male children diagnosed with ASD (ASD-I) and 25 male children with XYY (12 XYY+ASD/13 XYY-ASD), which will be reported on below. XYY subjects were recruited through the *eXtraordinarY Kids Clinics* (for children with sex chromosome variations), at Nemours/Alfred I. DuPont Hospital for Children and the Children's Hospital Colorado. Typically developing children as well as children with idiopathic ASD (i.e. no known genetic etiology) were recruited from the

Regional Autism Center of The Children's Hospital of Philadelphia (CHOP), from the local and regional community and from CHOP primary care practices. No genetic testing was performed to confirm XY status; assuming a 1/1000 XYY prevalence the expected number of XYY subjects in our XY cohort of 95 is no more than 1 and thus was considered unlikely and only a minor possible contributor to statistical noise.

All participants were selected according to the following criteria: (1) no history of traumatic brain injury or other significant medical or neurological abnormality, (2) no active psychosis, (3) no MRI contraindications, and (4) no known drug or alcohol use prior to any study procedure. Members of the typically developing group had no current or past history of DSM-5 Axis I disorders noted by parents during initial screening and had no symptoms of ASD, as measured by autism screening questionnaires (Social Responsiveness Scale-2: SRS-2 [19] and Social Communication Questionnaire: SCQ [20]) and direct observation on the Autism Diagnostic Observation Schedule-2nd edition (ADOS-2 [21]). In the ASD-I group and XYY+ASD group, diagnosis of ASD was established by expert clinical consensus of two clinical psychologists (JM and LB) using the ADOS-2, DSM-5 criteria, and parent questionnaires (SCQ and SRS-2). A measure of full-scale IQ (FSIQ) was obtained for all participants. The specific measure of FSIQ utilized varied depending on group and included the WISC-IV [22], WISC-V[23], and DAS-II [24]. The study was approved by the Children's Hospital of Philadelphia Institutional Review Board, and by the Human Studies Committee at Nemours DuPont Hospital for Children. Written informed consent and assent (when age-appropriate) was obtained from all participating families. Demographics are reported in Table 1 for the evaluable sample.

MEG and MRI data acquisition:

MEG data for each subject were recorded using a using whole-head 275 axial gradiometer CTF system (VSM MedTech, Coquitlam, BC) and synthetic third-order gradiometer noise correction. Data were acquired with a sampling rate of 1200Hz and no online filters. Electro-oculogram (EOG) (vertical EOG on the upper and lower left sides) and electrocardiogram (ECG) were also obtained. The participants' head position was monitored using three head position indicator (HPI) coils attached to the scalp. To aid in MRI/MEG coregistration 200+ points on the scalp and face were digitized for each participant using the probe position identification (PPI) system (Polhemus, Colchester, VT).

Following the most significant findings of Roberts, Khan [12] stimuli consisted of 500Hz sinusoidal tones presented using Eprime v1.1. Tones were presented binaurally via sound pressure transducers and sound conduction tubing to the participant's peripheral auditory canal via ear tip inserts (ER3A, Etymotic Research, IL, USA). Prior to data acquisition, each subject's auditory threshold was determined using 1 kHz tones (in keeping with standard audiometry practice and definitions, and noting little difference in auditory detection thresholds between 500Hz and 1kHz) of 300ms duration and 10ms rise time presented monaurally and varied incrementally until reaching auditory threshold for each ear. For the MEG experiment, tones were presented at 45-dB sensation level above this threshold. A total of 530 trials were presented. Each trial consisted of a 500Hz tone (300ms duration) with an inter-stimulus interval (ISI) that varied between 600ms and 2000ms. To minimize

fatigue during the experiment participants viewed (but did not listen to) a movie projected onto a screen.

Using BESA 6.0 (BESA®, Gräefelfing – Germany), MEG data was downsampled to 500Hz and artifact correction was applied to remove eye blink activity as outlined in Edgar et al. [25]. Non-eye blink artifacts were rejected by amplitude and gradient criteria (amplitude >300 fT, gradients >25 fT/cm). Artifact-free epochs were then averaged. After the MEG session, structural magnetic resonance imaging (sMRI) provided T1-weighted, 3D MPRAGE anatomical images for source localization (3T Siemens Verio scanner; voxel size 1 mm³).

Source localization:

Source localization was accomplished using anatomical constraints. A rigid body registration between MEG and sMRI was achieved using 3 anatomical landmarks (nasion and right and left pre-auricular points) as well as the additional 200+ head shape points.

For all participants, measures were obtained for the 50ms (M50) and 100ms (M100) components of the left and right auditory response. The primary generator of the M50 and M100 can be well-modeled by a single dipole [26] located in the left and right Heschl's gyrus. Therefore, after coregistering the MEG and sMRI data, each participant's left and right Heschl's gyrus was visually identified and a dipole source was placed approximately a third of the length along Heschl's gyrus (with the most medial aspect of Heschl's gyrus the starting point). If two Heschl's gyri were present, the dipole was placed between the two Heschl's gyri. After placing the left and right auditory dipoles for each participant, each dipole source was oriented separately at the maximum of the M50 and M100 response for each participant. Thus, although estimates of left and right auditory activity were obtained using an anatomical constraint, the orientation of the M50 and M100 dipoles were optimized individually for each participant and for each hemisphere. As detailed elsewhere, several studies note the advantages of using prior knowledge in brain electromagnetic source analysis [27, 28].

Dipole orientations were obtained after applying a 1 (12 dB/octave, zero phase) to 55-Hz (48 dB/octave, zero phase) band-pass filter and a 60-Hz notch filter with a 5-Hz bandwidth. The presence of an M50 was determined as the peak of the first negative-going deflection satisfying amplitude (greater than 1.5 standard deviations above baseline), latency (between 35-125ms), and hemisphere-dependent (ingoing and outgoing magnetic flux) topography criteria. The broad latency range used accommodates the known developmental trajectory of the M50 response which shortens considerably over the period 6-18 years of age. Similarly, the presence of the M100 was determined based on latency (between 80-195ms) and hemisphere flux topography. In particular, an M100 was scored if the flux topography was characteristic of the M100 response, was preceded by M50 (flux topography opposite M100), and followed by M200 (flux topography same as M100). For all subjects, final M50 and M100 latencies were first determined by independent scoring by two members of the study team (JE, MK). In the few cases where there was disagreement of component assignment (<5% and generally arising from atypical waveform morphology), the case was jointly examined to obtain a consensus score (JE, MK).

Statistical Analysis:

Given the often reported lateralization of auditory evoked magnetic field responses to a range of experimental stimuli [29] as well as the reported asymmetric auditory latency delays in ASD, group differences in M50 and M100 latency were investigated separately in each hemisphere. JMP 13 (SAS Institute Inc.) was used to create separate general linear models (GLMs) of the M50 and M100 latency in each hemisphere. Main effects of Group (XYY, TD and ASD-I) were investigated with age as a covariate, allowing an ageXgroup interaction. Subsequent post-hoc analysis investigated XYY status (XYY vs. TD) and ASD diagnosis (ASD-I vs TD) as well as assessing potential additional impact of ASD diagnosis within the XYY cohort (XYY+ASD vs XYY-ASD).

Results:

Demographics:

As detailed in Table 1, no significant age differences were observed between groups (TD: 11.8 ± 3.0 Yrs; ASD-I: 11.8 ± 2.6 Yrs; XYY: 12.4 ± 3.6 ; $p=0.72$). In agreement with expected behavioral phenotypes, Group had a significant effect on FSIQ scores (TD: 115.1 ± 14.1 ; ASD-I: 99.5 ± 19.6 ; XYY: 91.8 ± 13.3 ; $p<0.01$). Post-hoc analysis of FSIQ found significantly lower scores in both ASD-I and XYY groups (p 's < 0.01) compared with TD subjects and marginally significantly ($p=0.06$) lower FSIQ in XYY subjects compared with ASD-I subjects.

Within the XYY group, no significant effect of ASD (XYY+ASD vs XYY-ASD) was observed in either age (XYY-ASD: 12.8 ± 3.6 yrs; XYY+ASD: 11.9 ± 3.7 yrs; $p=0.28$) or FSIQ (XYY-ASD: 92.9 ± 11.7 ; XYY+ASD: 90.9 ± 15.4 ; $p=0.75$).

Rates of Evaluable Data:

As seen in Table 2, within the evaluable sample ($N=120$, defined by the presence of at least one scoreable latency) both M50 and M100 responses were observed in most participants in both hemispheres. Logistic regression tests were used to investigate effects of age, group and hemisphere on the presence or absence of the M50 and M100. No significant effects of group were observed for either latency (M50: $p=0.7$; M100: $p=0.45$). A marginally significant effect of hemisphere was observed for the M100 latency ($p=0.09$) with M100s observed more reliably in the right hemisphere (96%) than in the left (92%) with no observed effect of age ($p=0.7$). For the M50 a marginally significant effect of age was observed ($p=0.09$) with no effect of hemisphere ($p=0.3$).

A GLM was used to investigate the effects of age, group and FSIQ on the number of artifact-free trials. A significant effect of FSIQ (slope: 0.35 trials / FSIQ unit; $p=0.03$) was observed, as were marginally significant relationships with age (slope: 1.5 trials / yr; $p=0.1$) and group (TD: $479 \pm 5.6SE$; ASD-I: $471 \pm 3.98SE$; XYY: $460 \pm 6.23SE$; $p=0.09$). While this suggest that subject compliance may be related to the number of artifact-free trials (younger XYY and ASD subjects with a lower FSIQ had fewer evaluable trials) it is important to stress that more than 300 trials were obtained in all individuals; nearly 3 times the number of trials widely used in the field to evaluate evoked auditory responses [12, 13, 25, 30].

M50 and M100 Latencies:

Representative waveforms showing the left auditory evoked response from a typically developing and XYY subject are shown in Figure 1a. Analogous waveforms have been previously reported in children with ASD (Roberts et al., 2010).

Statistical analysis of the M50 and M100 latency were performed separately in the left and right hemisphere using general linear models to investigate main effects of group, and covarying for age and considering an age x group interaction. Significant associations (all p 's < 0.001) with age were found bilaterally for both the M50 (Right: -2.6 ms/year, Left: -3.1 ms/year) and M100 (Right: -5.9 ms/year, Left: -6.4 ms/year) latencies.

For the M100 latency no significant group (Left: $p=0.4$; Right $p=0.5$) or group x age interactions (Left: $p=0.9$; Right: $p=0.8$) were observed. Examining the M50 latency, in the left hemisphere both group (TD: 74.0 ± 12.2 ; ASD: 77.6 ± 12.2 ; XYY: 81.5 ± 12.2 ; $p=0.04$) and group x age ($p<0.01$) were significant. In the right hemisphere M50, group was marginally significant (TD: 71.0 ± 16.0 ; ASD-I: 76.1 ± 10.6 ; XYY: 72.5 ± 9.4 ; $p=0.09$) and group x age was significant ($p=0.04$). Post-hoc analysis contrasting M50 latencies of patient groups (ASD-I, XYY) vs TD found significant M50 prolongations in the *right* hemisphere in ASD-I subjects only (TD vs ASD: +5.60ms, $p=0.04$; TD vs XYY: +1.91ms, $p=0.56$), while in the left hemisphere significant prolongations were observed in XYY subjects (TD vs XYY: +7.98ms, $p=0.01$) with only a tendency for latency prolongation in ASD-I (TD vs ASD-I: +3.95ms, $p=0.12$). Within the XYY cohort no significant additional effects of ASD diagnosis were observed in any measure (Left M50: $p=0.4$; Right M50: $p=0.5$; Left M100: $p=0.4$; Right M100: $p=0.6$). To better illustrate the group effect, group marginal means (age corrected to cohort mean age of 12.0 years for more ready comparison) $\pm$ standard deviations are reported in Table 2 and are shown in Figure 1-B (Left M50) and Figure 1-C (Right M50).

Discussion and Conclusion:

The focus of this study was to evaluate the relative contributions of genetic group and ASD diagnosis to the timing of the auditory evoked response, specifically the latency of the M50 and M100 component. A primary result was a pronounced latency prolongation in *left* hemisphere auditory evoked response in boys with XYY (left M50: 7.9ms; $p<0.05$, Left M100: 12.3ms; $p>0.1$) and in the *right* hemisphere in boys with ASD-I (right M50: 5.6ms; $p<0.05$, right M100: 8.8ms; $p>0.1$), consistent with prior reports of latency prolongation in ASD-I.

Past studies [13, 31] have hypothesized that delays in the early auditory evoked responses may result from atypical maturation of the thalamocortical white-matter pathways or atypical synaptic transmission and may functionally underlie subsequent higher-order neuronal dysfunction. Although the genetic contributions to these mechanisms remains to be directly investigated, delayed auditory latencies in XYY suggests the potential role for Y-chromosome genes in these developmental processes. Interestingly, whereas most reports of latency differences in ASD have emphasized delays in the right hemisphere, the XYY effects were lateralized to the left hemisphere, potentially suggesting an asymmetric role for

Y-chromosome genes. Although hemisphere differences have not been extensively studied in XYY, several reports have highlighted neural asymmetries in other populations with sex chromosome aneuploidy such as Turner's syndrome (45,X), Klinefelter's (47,XXY) or Triple-X (47,XXX) syndrome [32–34].

Significant age relationships were observed in left and right M50 and M100 latencies. These maturational rates, showing decreased latency with age (M50: ~2ms per year, M100: ~6ms per year), are in line with previous reports [13] and appear similar in XYY, reflecting ongoing maturation.

Some limitations are of note. First, there was an observed difference in the number of artifact free trials in XYY subjects. While a potential limitation of the study, this difference is likely negligible due to the large number of trials presented. For instance, the fewest number of artifact-free trials in this study was 315, with auditory latencies robustly estimated using as few as 100 trials in other studies [12, 13, 25, 30]. Second, although extremely unlikely given the 1/1000 prevalence of XYY in the general male population, without karyotypes in the full cohort it is impossible to rule out the presence of XYY subjects within the typically developing or, particularly, ASD-I groups. Nonetheless we estimate the number of XYY individuals falsely included in either of these groups to be no more than 1. Finally, future studies are needed to investigate the potential contributions of testosterone, pubertal stage and unmeasured genetic variation on auditory latency measures (and thus potential impact on group difference findings).

In summary, the presence of an additional Y-chromosome in 47,XYY subjects had a significant effect on the left M50 latency (delay of 7.9ms). This prolongation is not only more pronounced than has been reported in idiopathic ASD (~4ms for the M50 [13]), and indeed the delay observed in the ASD-I cohort in this study, but also exhibits a left hemisphere bias in contrast to the predominantly right hemispheric effect seen in ASD-I. Thus, while the electrophysiological phenotype of delayed evoked response component latency is similar between ASD-I and XYY, the hemispheric differences in the observation thereof provide a tantalizing avenue for future investigations. Similar to auditory latency prolongations observed in other genetically defined groups – e.g. 16p11.2 DEL [18], the additional influence of an ASD diagnosis within the genetically defined group (in this case, XYY) was small compared with the primary effects of the genetic condition.

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References:

1. Bardsley MZ, et al., 47,XYY Syndrome: Clinical Phenotype and Timing of Ascertainment. *J Pediatr*, 2013.

2. Bishop DV and Scerif G, Klinefelter syndrome as a window on the aetiology of language and communication impairments in children: the neuroligin-neurexin hypothesis. *Acta Paediatr*, 2011 100(6): p. 903–7. [PubMed: 21418292]
3. Robinson A, et al., Sex chromosome aneuploidy: the Denver Prospective Study. *Birth Defects Orig Artic Ser*, 1990 26(4): p. 59–115. [PubMed: 1708685]
4. Ross J and Hoeft F, Introduction: cognitive profiles in sex chromosome disorders. *Dev Disabil Res Rev*, 2009 15(4): p. 269. [PubMed: 20014365]
5. Ross JL, et al., Behavioral and Social Phenotypes in Boys With 47,XYY Syndrome or 47,XXY Klinefelter Syndrome. *Pediatrics*, 2012 129(4): p. 769–78. [PubMed: 22412026]
6. Netley CT, Summary overview of behavioural development in individuals with neonatally identified X and Y aneuploidy. *Birth Defects Orig Artic Ser*, 1986 22(3): p. 293–306. [PubMed: 3814782]
7. Stochholm K, Juul S, and Gravholt CH, Diagnosis and mortality in 47,XYY persons: a registry study. *Orphanet J Rare Dis*, 2010 5: p. 15. [PubMed: 20509956]
8. Tartaglia NR, et al., Autism Spectrum Disorder in Males with Sex Chromosome Aneuploidy: XXY/Klinefelter Syndrome, XYY, and XXYY. *J Dev Behav Pediatr*, 2017 38(3): p. 197–207. [PubMed: 28333849]
9. Baio J, et al., Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. *MMWR Surveill Summ*, 2018 67(6): p. 1–23.
10. Bishop DV, et al., Autism, language and communication in children with sex chromosome trisomies. *Arch Dis Child*, 2011 96(10): p. 954–9. [PubMed: 20656736]
11. Ross JL, et al., Behavioral phenotypes in males with XYY and possible role of increased NLGN4Y expression in autism features. *Genes Brain Behav*, 2015.
12. Roberts TP, et al., MEG detection of delayed auditory evoked responses in autism spectrum disorders: towards an imaging biomarker for autism. *Autism Res*, 2010 3(1): p. 8–18. [PubMed: 20063319]
13. Roberts TP, et al., Maturational differences in thalamocortical white matter microstructure and auditory evoked response latencies in autism spectrum disorders. *Brain Res*, 2013 1537: p. 79–85. [PubMed: 24055954]
14. Demopoulos C, et al., Magnetoencephalographic Imaging of Auditory and Somatosensory Cortical Responses in Children with Autism and Sensory Processing Dysfunction. *Front Hum Neurosci*, 2017 11: p. 259. [PubMed: 28603492]
15. Stephen JM, et al., Development of Auditory Evoked Responses in Normally Developing Preschool Children and Children with Autism Spectrum Disorder. *Dev Neurosci*, 2017 39(5): p. 430–441. [PubMed: 28772264]
16. Edgar JC, et al., Temporal and frontal cortical thickness associations with M100 auditory activity and attention in healthy controls and individuals with schizophrenia. *Schizophr Res*, 2012 140(1-3): p. 250–7. [PubMed: 22766129]
17. Wang Y, et al., Overlapping auditory M100 and M200 abnormalities in schizophrenia and bipolar disorder: a MEG study. *Schizophr Res*, 2014 160(1-3): p. 201–7. [PubMed: 25468188]
18. Jenkins J 3rd, et al., Auditory Evoked M100 Response Latency is Delayed in Children with 16p11.2 Deletion but not 16p11.2 *Duplication*. *Cereb Cortex*, 2016 26(5): p. 1957–64. [PubMed: 25678630]
19. Constantino JN, et al., Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. *Journal of autism and developmental disorders*, 2003 33(4): p. 427–433. [PubMed: 12959421]
20. Rutter M, Bailey A, and Lord C, The social communication questionnaire: Manual. 2003: Western Psychological Services.
21. Lord C, et al., Autism Diagnostic Observation Schedule- 2nd ed. 2012, Torance (CA): Western Psychological Services.
22. Wechsler D, Wechsler intelligence scale for children - Fourth Edition. 2003: Psychological Corporation.
23. Wechsler D, Wechsler intelligence scale for children - Fifth Edition. 2014: Psychological Corporation.

24. Elliott CD, Differential Ability Scales - Second Edition. 2007, San Antonio, TX: Harcourt.
25. Edgar JC, et al., Auditory encoding abnormalities in children with autism spectrum disorder suggest delayed development of auditory cortex. *Mol Autism*, 2015 6: p. 69. [PubMed: 26719787]
26. Herdman AT, et al., Determination of activation areas in the human auditory cortex by means of synthetic aperture magnetometry. *Neuroimage*, 2003 20(2): p. 995–1005. [PubMed: 14568469]
27. Scherg M and Berg P, Use of prior knowledge in brain electromagnetic source analysis. *Brain Topogr*, 1991 4(2): p. 143–50. [PubMed: 1793688]
28. Edgar JC, et al., By our bootstraps: Comparing methods for measuring auditory 40 Hz steady-state neural activity. *Psychophysiology*, 2017 54(8): p. 1110–1127. [PubMed: 28421620]
29. Howard MF and Poeppel D, Hemispheric asymmetry in mid and long latency neuromagnetic responses to single clicks. *Hear Res*, 2009 257(1-2): p. 41–52. [PubMed: 19647788]
30. Oram Cardy JE, et al., Prominence of M50 auditory evoked response over M100 in childhood and autism. *Neuroreport*, 2004 15(12): p. 1867–70. [PubMed: 15305126]
31. Roberts TP, et al., Developmental correlation of diffusion anisotropy with auditory-evoked response. *Neuroreport*, 2009 20(18): p. 1586–91. [PubMed: 19898261]
32. Rezaie R, et al., The influence of sex chromosome aneuploidy on brain asymmetry. *Am J Med Genet B Neuropsychiatr Genet*, 2009 150B(1): p. 74–85. [PubMed: 18454450]
33. Rae C, et al., Enlarged temporal lobes in Turner syndrome: an X-chromosome effect? *Cereb Cortex*, 2004 14(2): p. 156–64. [PubMed: 14704212]
34. Itti E, et al., The structural brain correlates of cognitive deficits in adults with Klinefelter's syndrome. *J Clin Endocrinol Metab*, 2006 91(4): p. 1423–7. [PubMed: 16403821]

Figure 1:

Evoked response waveforms from the left auditory cortex (Fig1-A) are shown for two 11-year-old subjects (one XY and one TD). Age corrected (to 12.0 yrs) auditory M50 latencies for the left (Fig1-B) and right (Fig1-C), hemispheres are shown. Significant M50 (marked with *) prolongations in *left* hemisphere were observed in boys with XY (7.9ms; $p < 0.05$) and in the *right* hemisphere in boys with ASD-I (5.6ms; $p < 0.05$).

Table 1:

Demographic Information

	TD (N=33)	ASD-I (N=62)	XYX (N=25)	XYX-ASD (N=13)	XYX+ASD (N=12)
Age (years)	11.8 ± 3.0	11.9 ± 2.6	12.4 ± 3.6	12.8 ± 3.6	11.9 ± 3.7
Age Range (Years)	8.1 - 17.7	7.5 - 17.9	6.1 - 17.7	6.1 - 17.7	6.3 - 17.6
FSIQ	115.1 ± 14.2	99.5 ± 19.6	91.8 ± 13.3	92.6 ± 11.7	90.9 ± 15.4

Group means and standard deviations are shown for age, and full-scale IQ (FSIQ)

Table 2:

Rates of Evaluable data

	Right M50	Left M50	Right M100	Left M100
TD	31 (93%)	32 (96%)	31 (93%)	30 (91%)
ASD-I	59 (95%)	60 (97%)	60 (97%)	59 (95%)
XYX	25 (100%)	24 (96%)	25 (100%)	21 (84%)
Total	114 (95%)	117 (97%)	116 (96%)	110 (92%)

Table 3:

Age Corrected M50 Latencies: Evoked Auditory Latencies (M50, M100) for the right and left hemisphere were age corrected to the cohort mean of 12.0 years. Group means $\pm$ standard deviations are shown.

	Right M50	Left M50	Right M100	Left M100
TD	71.0 $\pm$ 16.0	74.0 $\pm$ 12.2	126.6 $\pm$ 36.4	127.9 $\pm$ 33.6
ASD-I	76.1 $\pm$ 10.6	77.6 $\pm$ 12.2	135.5 $\pm$ 44.1	137.2 $\pm$ 42.1
XYX	72.5 $\pm$ 9.4	81.5 $\pm$ 12.2	129.5 $\pm$ 24.2	140.2 $\pm$ 26.8