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Behavioral and molecular genetics of reading-related AM and FM detection thresholds

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Abstract

Auditory detection thresholds for certain frequencies of both amplitude modulated (AM) and frequency modulated (FM) dynamic auditory stimuli are associated with reading in typically developing and dyslexic readers. We present the first behavioral and molecular genetic characterization of these two auditory traits. Two extant extended family datasets were given reading tasks and psychoacoustic tasks to determine FM 2 Hz and AM 20 Hz sensitivity thresholds. Univariate heritabilities were significant for both AM ($h^2=0.20$) and FM ($h^2=0.29$). Bayesian posterior probability of linkage (PPL) analysis found loci for AM (12q, PPL=81%) and FM (10p, PPL=32%; 20q, PPL=65%). Bivariate heritability analyses revealed that FM is genetically correlated with reading, while AM was not. Bivariate PPL analysis indicates that FM loci (10p, 20q) are not also associated with reading.

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Compliance with Ethical Standards

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Keywords

dynamic auditory sensitivity; AM processing; FM processing; heritability; language; reading

Introduction

Phonological awareness, an individual's ability to recognize differences in speech sounds, is an important component of language and reading development (Barker et al. 2013). Phonemes are unique components of a spoken language. Distinct phonemes can be similar sounding but differ in some acoustic feature and are dependent upon their acoustic environment. For example, words such as 'pad' and 'pat' differ because of the final consonants "d" and "t"; one is a voiced consonant where the vocal chords vibrate, and the other is voiceless where they vocal chords do not vibrate. A failure to develop adequate phonological processing skills can impede typical language development or typical reading development, or both.

Impaired sensitivity to acoustic changes in the speech signal may lead to poorly specified phoneme representations for spoken language with downstream effects on the phonological representations and syllabic transitions that are necessary for reading (Boets et al. 2011; Poelmans et al. 2011). The theory is that if readers perceive basic acoustic cues poorly, the result will be inaccurate perception of speech sounds that necessarily map poorly onto the visual symbols (letters) for reading (Law et al. 2014; McAnally and Stein 1996). Studies on the development of reading and reading disability or *dyslexia*, also support a theory known as the *auditory deficit hypotheses of reading* (Boets et al. 2011). This putative deficit includes processing of slower amplitude modulated (AM) and frequency (FM) modulated sounds that are important for human speech perception. There is controversy surrounding the precise nature of reported auditory impairments in dyslexia. For example, it is not known whether measured deficits are related to low-level sensory processing, or reflect a more generalized difference in brain function; and there is a lack of evidence to support claims of causality. Despite this, findings of statistically significant relationships between AM and FM sensitivity and reading ability are relatively consistent (Hamalainen et al. 2013). For a recent review of the differences in stimuli, methodological techniques and the potential interference of cognition and attention dependence on the tasks see de Wit et al. (2016).

Increased AM and FM thresholds negatively correlate with reading scores in individuals with dyslexia and in the general population. Specifically, FM 2 Hz and AM 20 Hz thresholds predict nonword reading performance (Talcott et al. 2003; Talcott et al. 2000; Witton et al. 2002). The link between auditory perception and reading has been demonstrated in previous studies showing a correlation between phonological processing and reading, thus indicating a potential role for sound perception for written language (Hodgson 1993). Several studies, including those that included children at risk for dyslexia due to family history, report significant associations between either AM or FM modulations and specific skills associated with reading development (Boets et al. 2007). Specifically, AM perception tasks, though varying in exact parameters and sometimes referred to as "rise time" in the literature, have been associated with phonological awareness, syllable detection and non-word reading

(Goswami et al. 2002; Hamalainen et al. 2013; Law et al. 2014). Likewise, increased FM thresholds have predicted reduced non-word and single word reading performance (Talcott et al. 2003; Talcott et al. 2000; Witton et al. 2002).

Given that numerous studies of reading traits have shown a substantial familial risk and a large genetic variance component (Boets et al. 2011; Carroll et al. 2014; Peterson and Pennington 2015), it is possible that AM and FM thresholds traits are likewise genetic. If AM and/or FM were genetic, it would still be possible for them to be genetically independent of reading, and this can be tested with genetic correlations, i.e., correlations using only the genetic variance. Here, we present the first study on the genetics of AM and FM processing thresholds at specific frequencies previously shown to be associated with reading (Witton et al. 2002). We were specifically interested in characterizing the genetic basis of how perceptual thresholds for the FM and AM frequencies relate to phonological decoding tasks (i.e., nonword reading; “words” that obey the rules of English but are not real words such as ‘shreated’) and single word reading. As these traits are related to phonological decoding in both persons with and without dyslexia, we propose that individual differences in AM and FM detection thresholds are not unique to a subgroup of persons with dyslexia. Rather, reading-associated AM/FM thresholds are heritable traits associated with phonologically-based ability, to include individuals either with or without phonological decoding problems.

In this study, two different family cohorts were used to explore genetic heritabilities for amplitude and frequency modulations in individuals with and without language and reading impairments. A disorder known as specific language impairment (SLI) is diagnosed in children who fail to develop normal language without comorbid conditions such as intellectual disability or hearing loss (Li and Bartlett 2012). SLI and dyslexia are defined on distinct domains; however, the two disorders commonly co-occur, and both are associated with phonological processing deficits (Bishop and Snowling 2004; Catts et al. 2005; McArthur et al. 2000; Ramus et al. 2013). SLI is commonly studied in conjunction with dyslexia; studies suggest that the etiologies of autism spectrum disorder (ASD) and SLI partially overlap with regard to genetic risk for language difficulties (Bartlett et al. 2014; Marshall and van der Lely 2009; Newbury et al. 2014; Ramus et al. 2013).

Though our family sets were originally ascertained to study spoken language impairments, in previous work we have shown that our findings mirror results from two lines of research. First, our heritability estimates of reading measures are very close to those estimated in twins, suggesting that using families in lieu of twins is not problematic for estimating heritability (Logan et al. 2011). Second, our heritability estimates are very close to those estimated from both population-based samples and samples ascertained for reading disability. This indicates that using samples selected for a non-dyslexia diagnosis does not imply different underlying genetics for spoken and written language (Bartlett et al. 2012). Given the suitability of the sample, we sought to analyze the genetic relationships between FM 2 Hz and AM 20 Hz auditory traits and two reading traits by partitioning total variance into genetic and environmental variance components. With regard to AM and FM processing, the term “environment” can be thought to include experience-dependent development or plasticity. The establishment of genetic components led us to identify

molecular genetic loci via molecular genetic linkage analysis for these dynamic auditory perception traits.

Subjects and Methods

Subjects

The sample consisted of two sets of families that have been described elsewhere (Bartlett et al. 2012; Bartlett et al. 2014; Logan et al. 2011). The first sample consists a subset of a sample used for a series of studies on specific language impairment (SLI) genetics (Bartlett et al. 2004; Logan et al. 2011). We ascertained these families for one SLI proband and at least one additional family member with a language impairment. Here we present analysis on three large extended SLI pedigrees that were enrolled after the AM/FM tasks became available (i.e., it was not possible to test all families). A total of 111 subjects had reading and auditory data with each pedigree having sample sizes of 48, 26 and 36, respectively including a total of 14 language impaired individuals and 41 reading impaired persons.

The second sample is part of the New Jersey Language and Autism Genetics Study (NJLAGS) consisting of 51 families ascertained for both SLI and Autism, a complex neurodevelopmental disorder consisting of social interaction impairment with repetitive behavioral tendencies or narrow interests (Szatmari et al. 2007). Families were ascertained for the presence of both an autism proband and at least one other person in the family with a diagnosis of SLI and no less than five participants (affected and unaffected) per family (mean 6.9, SD 2.8, range 5–20). Family members received 22 standardized subtest measures of language and intelligence with additional reading measures. The final samples was comprised of a total of 234 subjects with at least some quantitative language phenotypic data, including 27 persons with ASD, 55 with SLI, and 152 unaffected. Subjects gave informed consent conforming to the guidelines for treatment of human subjects governed by the Institutional Review Board at Rutgers University. We have previously established (Bartlett et al. 2014); (2012) that for most cognitive traits, the quantitative genetics of these pedigrees is fully consistent with pedigrees from the general population and also similar to families selected for specific language impairment (Logan et al. 2011).

We note that unlike a twin study, where each family contributes one pair of family members for analysis, extended pedigrees include many more relative pairs per family, and these relative pairs are of different types and not exclusive. For example, a parent is part of a relative pair with each child, as well as with each of that parent's biological parents, their siblings, their aunts and uncles. Also note that many relationship pairs share genetics but not a common environment (e.g., cousin pairs). Given the ability to estimate non-shared environment, the extended family design can be used to estimate heritability, i.e. genetics alone, instead of just familiarity, i.e., genetics and share environment confounded, as would be the case using solely nuclear families.

Measures

Given previous research that found significant unique nonword reading variance predicted by AM 20 Hz and FM 2 Hz (Talcott et al. 2003), we evaluated thresholds at these

modulation rates, using the same method as in Witton et al. (2002). Stimuli were 1000-ms pure tones with a carrier frequency of 500 Hz, to which either a 20-Hz sinusoidal amplitude modulation (AM task) or a 2-Hz sinusoidal frequency modulation (FM task) was applied. The depth of modulation was varied as the dependent measure. Thresholds were determined through software that presents pairs of stimuli in a two-alternative forced-choice paradigm, with one unmodulated stimulus and one modulated stimulus in random order, separated by a 500-ms silent inter-stimulus interval. Subjects were asked to identify which stimulus was the modulated one. The depth of modulation was determined by an adaptive, weighted 1-up, 1-down staircase method (Kaernbach). Initial stimulus modulation depth was well above detection threshold, and was decreased by a factor of -1db on every correct response and increased by a factor of +3db for every incorrect answer. The procedure was terminated after 10 'reversals' (points where the response trajectory switched from correct to incorrect answers, or vice-versa). The geometric mean of the last 8 reversals was taken as threshold. A small percentage of random trials were presented with suprathreshold stimuli to assess attention to the task. The families also received single word reading (*Word Identification*) and single non-word reading (*Word Attack*) tasks from the Woodcock Reading Mastery Tests ((Woodcock 1997). We combined the two reading measures into a latent trait using the R (R Core Team 2013) structural equation modeling in pedigrees package *strum* version 0.6.2 (Morris and Song 2015) as described in (Song et al. 2015).

Statistical Analysis

Univariate heritabilities and bivariate genetic correlations were modeled with the Sequential Oligogenic Linkage Analysis Routines (SOLAR) package v4.3.1 (Almasy and Blangero 1998) as described previously (Bartlett et al. 2012; Logan et al. 2011). Briefly, the phenotypic variance is decomposed into components by regressing against the kinship matrix to estimate the genetic component of the variance and an identity matrix to estimate the individual environmental component. The kinship matrix specifies the degree of genetic relatedness of every pair of subjects in the study. Constraining the genetic variance component to zero corresponds to the null hypothesis of no genetic effect. Twice the difference in likelihoods between the constrained model and the full model yields the standard maximum likelihood ratio test statistic (Almasy and Blangero 1998). In our study, we applied the $P < .05$ threshold for statistical significance.

Covariates that were tested for significance in the model included age, age², PIQ, sex and ASD status. The distributions of the AM and FM traits were leptokurtotic with variance less than 1, both of which can be problematic for SOLAR as determined by the package authors (SOLAR 2003). We applied a log-power transformation with an offset constant to avoid negative numbers and multiplied by a constant to avoid variance below 1 as follows:

$$Trait_{transformed} = 10 \left(\sqrt{\log_{10}(Trait) + 3} \right)$$

After transformation, both traits had kurtosis < 2.

In order to identify molecular genetic loci for reading and dynamic auditory traits, we conducted linkage analysis using KELVIN (Vieland et al. 2011), a genetic modeling

platform we have applied previously in these families (Bartlett et al. 2004; Bartlett et al. 2002; Bartlett et al. 2014; Simmons et al. 2010). KELVIN provides several statistical metrics to quantify the evidence for linkage along the genome, and here we chose the posterior probability of linkage, or PPL (Vieland 1998). This method was chosen since it is easy to combine data across datasets, as we do here with our two family sets. The advantage to performing (essentially) a Bayesian meta-analysis across the two datasets comes from the way the PPL handles heterogeneity. The PPL has been shown to retain greater power for finding linkage with heterogeneous datasets than seen when using a single pooled analysis in which all of the data is analyzed as a single large dataset (Vieland et al. 2001). Therefore, the two sample sets were analyzed separately and then pooled together using Bayesian sequential updating as previously described (Bartlett et al. 2005). As described previously (Bartlett et al.; Bartlett et al. 2002), the prior probability of linkage is 2% (Elston and Lange 1975; Morton 1955) based on theoretical calculations. Posterior probabilities greater than this number indicate positive evidence for linkage. In order for positive linkage evidence to meet genome-wide standards for declaring a linkage, we apply the value of 30% based on our previous work (Bartlett et al. 2002).

The bivariate PPL is a straightforward extension of the quantitative PPL in Bartlett & Vieland (2007) to bivariate traits. The key extension occurs in the likelihood function for generating LOD scores (see the subsection “*The likelihood function for the QT-PPL*” in Bartlett & Vieland 2007). The core of the pedigree likelihood is $L(\mathbf{X}|\mathbf{G})$, letting $\mathbf{G}$ represent the genotypic data for a given pedigree and $\mathbf{X}$ the trait data. For univariate linkage, $L(x_i, g_i)$ is defined as $\gamma(X=x_i|\mu_j, \sigma_j^2)$, where γ is the probability density function (pdf) of the desired distribution, i indexes the individual, j indexes the three possible trait genotypes at a two-allele locus, AA, Aa, aa; and μ_j and σ_j^2 are the genotypic mean and variance for the j^{th} genotype, respectively. As implemented in Kelvin, γ is the standard normal distribution, though the assumption of normality is not strong (Bartlett & Vieland 2007; Vieland et al 2008). The bivariate PPL replaces with the standard bivariate normal distribution. This extension requires integration of the additional means and variances and the correlation between the two traits attributable to the test locus. Integration then proceeds the same as Equation 2 of (Bartlett & Vieland 2007).

Results

We first calculated baseline Pearson correlation coefficients between the two auditory traits (AM and FM $\rho=0.45$, $P<.05$) and each of the two auditory traits with reading (AM-reading $\rho=0.19$, $P<.05$; FM-reading $\rho=0.30$, $P<.05$). We note family datasets do have the subtle complexity that genetic relationships imply partial non-independence across participants. This non-independence, while a violation of the Pearson correlation assumptions, may or may not have detrimental effects on the estimation. To assess if our whole family correlations were appropriate, we repeated the analysis by only using data from founders (persons in the dataset with no parental data such as grandparents at the top of the pedigree and persons that married into the family). In all cases, the correlations were significant, though slightly lower (AM and FM $\rho=0.35$, $P<.05$; AM-reading $\rho=0.13$, $P<.05$; FM-reading $\rho=0.26$, $P<.05$).

Heritability was measured jointly with both datasets. As shown in Table 1, heritability for the dynamic auditory traits, both AM and FM, were significant. While studies show dynamic auditory traits and reading traits are phenotypically correlated, here we assessed if additive genetics at least partially mediates that relationship as measured by genetic correlation. We therefore conducted bivariate variance component analyses to assess the degree of genetic correlation versus environmental correlation (or both) for both AM and FM. Both AM and FM thresholds show a significant environmental correlation but are not genetically correlated.

Univariate heritability for reading was significant (Table 1) as expected. We next assessed the genetic and environmental correlation of the AM and FM tasks with reading. FM and reading presented with a genetic correlation ($P < .05$) but without a corresponding environment correlation ($P > .05$). In contrast, the AM task is environmentally correlated with reading and instead has no genetic correlation with reading.

Linkage Analysis

We evaluated the genome for linkage with the two auditory phenotypes. For auditory traits that are genetically correlated with reading, this would also potentially identify novel reading loci. Genome-wide posterior probability of linkage analyses of both AM 20 Hz and FM 2 Hz are summarized in Figure 1. There were three peaks that met our genome-wide criteria for declaring linkage, with no overlap in results between the two traits. FM 2 Hz provides evidence of linkage on chromosome 20 with a maximum PPL of 65% and also on chromosome 10 with a PPL of 33%. AM 20 Hz provides evidence of linkage on chromosome 12 with a PPL of 51%. Additional details on these peaks are provided in Table 2.

Bivariate PPL of the auditory traits analyzed jointly with reading traits for linkage was conducted to determine if the two FM 2 Hz loci were also related to reading. No bivariate PPL peaks met our significance criteria.

Discussion

We presented the first genetic analysis to investigate the relationship between reading-associated dynamic auditory thresholds and reading ability in extended families. The results demonstrate significant univariate genetic variance for both measured AM and FM traits. Despite both traits being correlated and both traits having a genetic component, their correlation is mediated only through the environment. The AM trait showed an environmental correlation for reading, but not a genetic correlation, while FM showed the opposite trend whereby its correlation with reading was only through genetics. Genome-wide analysis further implicated two chromosomal regions for the FM trait, neither of which also corresponded to reading according to bivariate PPL analysis. Our data suggest that FM processing may offer important insights into the wider reading phenotype as well as the global speed of sound processing but may not be a suitable trait for finding additional novel reading loci.

After determining what proportion of variance in dynamic auditory thresholds is attributed to genetic factors versus environmental factors, we were interested in gene mapping the dynamic auditory thresholds, in their own right and also as an avenue towards finding additional genes for reading impairment. Based on the success of our first task, where heritability analysis does indicate a genetic correlation between FM and reading, we proposed that gene mapping FM 2 Hz threshold was a possible way to map novel reading loci. However, bivariate analysis on chromosomes 10 and 20 do not support this hypothesis. Bivariate heritability analysis indicated that FM 2 Hz is genetically correlated with reading impairment, accounting for much of the significant phenotypic correlation between the FM and reading (Talcott et al. 1999). Given that FM threshold and reading ability appear to have common genetics, we believed that FM processing may be a suitable trait for mapping genes related to reading ability, and so PPL analysis was conducted. The FM 2 HZ PPL loci on chromosomes 10 and 20 have not been associated with dyslexia and reading previously and were thought to be possible novel areas of interest for reading genetics. Bivariate PPL indicated that this was not the case and that these loci are not significantly associated with reading. It is more likely that the genetic correlation between FM and reading is being driven by polygenic factors not captured by a linkage signal.

We found the correlation between our AM and FM tasks was only environmental in nature, with no genetic component. This environmental correlation indicates that co-experience for sounds with AM and FM drives the phenotypic correlation in families. The lack of a genetic correlation shows that genes are not responsible for the observed trait similarity. Additionally, the environmental correlation of AM 20 Hz and reading ability indicates that the similarity between these two measures is driven mostly by a common set of environmental experiences, not shared genetics. Finding environmental drivers of AM and reading correlations is without obvious precedent in the literature. Yet, finding malleable environmental variables could provide insight into treatments for reading impairments.

In order to ensure the auditory trait data used in the variance component analysis were normally distributed, a condition needed for valid p-values, we performed a log-power transformation of the trait data to reduce excess kurtosis. Without the transformation the parameter estimates for univariate heritability were essentially the same, though the genetic correlations were greatly reduced, rendering them non-significant. It is well appreciated that the choice of scale can affect genetic interpretations. In the present study, the scale does matter, as the test of heritability and genetic correlations would be potentially invalid without the transformation. Additional work outside the scope of the present study would be needed to evaluate this particular non-normal distribution and its effect on type-I error. It will be important for future researchers to note our transformation when developing genetic models of these traits, in order to ensure comparable results.

One caveat to our data is the way the families were ascertained. One set of families was ascertained to have two persons with language impairment (Bartlett et al. 2002) while the other required one person with ASD and a separate person with language impairment (Bartlett et al. 2012). Though a large sample of families from the general population would be considered the ideal data for understanding individual differences in auditory traits, the use of families ascertained for a different purpose can also be informative if an ascertainment

correction is applied, as was performed in this study. Ascertainment corrections have long been applied to variance component analyses of complex traits (Beatty and Liang 1987; Boehnke and Lange 1984; Spence et al. 1977), though the practice has also been subject to debate (Burton 2002; Burton et al. 2000; Epstein 2002; Glidden 2002; Glidden and Liang 2002). Taken together, it is safe to assert that ascertainment correction methods are available, but they should not be applied without caution. We have used ascertainment correction on these samples previously when studying language, reading and related traits, and obtained a high degree of consistency with previously published studies using population based and ascertained data. There are no other genetic datasets on AM and FM processing for us to validate against, so while it is reasonable to conclude that our estimates are appropriately derived, further data from other studies are needed.

Our datasets lack a measure of sustained attention, which would be a helpful covariate to remove measurement error and perhaps allow us to stratify the sample or to remove subjects with attention deficits. We note two important factors when considering the role of attention in our samples. One, these families do have extensive family history data with information on comorbid psychiatric diagnoses including attention deficits disorder and we do not find any declared cases. Two, these samples were ascertained for language impairments, which is not highly comorbid for attention deficits in stark contrast to dyslexia datasets. These factors suggest that attention is not confounding our results though other datasets will be needed to verify this point.

The behavioral and molecular genetics of auditory processing traits is still developing and any potential genetically mediated associations with reading have yet to be fully demonstrated. We presented the first attempt to link the two domains using genetics, and while it is clear that genetics does play a role in AM and FM tasks related to reading, the use of these traits as endophenotypes for mapping reading genetics remains to be demonstrated.

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References

- Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet.* 1998; 62(5):1198–1211. [PubMed: 9545414]
- Bartlett CW, Flax JF, Fermano Z, Hare A, Hou L, Petrill SA, Buyske S, Brzustowicz LM. Gene x gene interaction in shared etiology of autism and specific language impairment. *Biol Psychiatry.* 2012; 72(8):692–699. [PubMed: 22704665]
- Bartlett CW, Flax JF, Logue MW, Smith BJ, Vieland VJ, Tallal P, Brzustowicz LM. Examination of potential overlap in autism and language loci on chromosomes 2, 7, and 13 in two independent samples ascertained for specific language impairment. *Hum Hered.* 2004; 57(1):10–20. [PubMed: 15133308]

- Bartlett CW, Flax JF, Logue MW, Vieland LJ, Tallal P, Brzustowicz LM. Further evidence for linkage of specific language impairment to 13q21 from an American sample. *Am J Hum Genet.* 2002; 71(4):437–437.
- Bartlett CW, Flax JF, Logue MW, Vieland VJ, Bassett AS, Tallal P, Brzustowicz LM. A major susceptibility locus for specific language impairment is located on 13q21. *Am J Hum Genet.* 2002; 71(1):45–55. [PubMed: 12048648]
- Bartlett CW, Hou L, Flax JF, Hare A, Cheong SY, Fermano Z, Zimmerman-Bier B, Cartwright C, Azaro MA, Buyske S, Brzustowicz LM. A genome scan for loci shared by autism spectrum disorder and language impairment. *Am J Psychiatry.* 2014; 171(1):72–81. [PubMed: 24170272]
- Beatty TH, Liang KY. Robust inference for variance components models in families ascertained through probands: I. Conditioning on proband's phenotype. *Genet Epidemiol.* 1987; 4(3):203–210. [PubMed: 3609720]
- Bishop DV, Snowling MJ. Developmental dyslexia and specific language impairment: same or different? *Psychological bulletin.* 2004; 130(6):858–886. [PubMed: 15535741]
- Boehnke M, Lange K. Ascertainment and goodness of fit of variance component models for pedigree data. *Prog Clin Biol Res.* 1984; 147:173–192.
- Boets B, Vandermosten M, Poelmans H, Luts H, Wouters J, Ghesquiere P. Preschool impairments in auditory processing and speech perception uniquely predict future reading problems. *Res Dev Disabil.* 2011; 32(2):560–570. [PubMed: 21236633]
- Boets B, Wouters J, van Wieringen A, Ghesquiere P. Auditory processing, speech perception and phonological ability in pre-school children at high-risk for dyslexia: a longitudinal study of the auditory temporal processing theory. *Neuropsychologia.* 2007; 45(8):1608–1620. [PubMed: 17303197]
- Burton PR. Comment on “Ascertainment adjustment in complex diseases”. *Genet Epidemiol.* 2002; 23(3):214–218. [PubMed: 12384973]
- Burton PR, Palmer LJ, Jacobs K, Keen KJ, Olson JM, Elston RC. Ascertainment adjustment: where does it take us? *Am J Hum Genet.* 2000; 67(6):1505–1514. [PubMed: 11078478]
- Carroll JM, Mundy IR, Cunningham AJ. The roles of family history of dyslexia, language, speech production and phonological processing in predicting literacy progress. *Dev Sci.* 2014; 17(5):727–742. [PubMed: 24581037]
- Catts HW, Adlof SM, Hogan TP, Weismer SE. Are specific language impairment and dyslexia distinct disorders? *J Speech Lang Hear Res.* 2005; 48(6):1378–1396. [PubMed: 16478378]
- de Wit E, Visser-Bochane MI, Steenbergen B, van Dijk P, van der Schans CP, Luigje MR. Characteristics of Auditory Processing Disorders: A Systematic Review. *J Speech Lang Hear Res.* 2016; 59(2):384–413. [PubMed: 27082630]
- Elston RC, Lange K. The prior probability of autosomal linkage. *Ann Hum Genet.* 1975; 38(3):341–350. [PubMed: 1137348]
- Epstein MP. Comment on “Ascertainment adjustment in complex diseases”. *Genet Epidemiol.* 2002; 23(3):209–213. [PubMed: 12384972]
- Glidden DV. Rejoinder on “ascertainment adjustment in complex diseases”. *Genet Epidemiol.* 2002; 23(3):219–220. [PubMed: 12384974]
- Glidden DV, Liang KY. Ascertainment adjustment in complex diseases. *Genet Epidemiol.* 2002; 23(3):201–208. [PubMed: 12384971]
- Goswami U, Thomson J, Richardson U, Stainthorpe R, Hughes D, Rosen S, Scott SK. Amplitude envelope onsets and developmental dyslexia: A new hypothesis. *Proc Natl Acad Sci U S A.* 2002; 99(16):10911–10916. [PubMed: 12142463]
- Hamalainen JA, Salminen HK, Leppanen PH. Basic auditory processing deficits in dyslexia: systematic review of the behavioral and event-related potential/field evidence. *J Learn Disabil.* 2013; 46(5):413–427. [PubMed: 22323280]
- Hodgson JM. Phonological Processes in Literacy - a Tribute to Liberman, Isabelle, Y. - Brady, Sa, Shankweiler, Dp. *Appl Psycholinguist.* 1993; 14(1):127–133.
- Kaernbach C. Simple Adaptive Testing with the Weighted up-down Method. *Percept Psychophys.* 1991; 49(3):227–229. [PubMed: 2011460]

- Law JM, Vandermosten M, Ghesquiere P, Wouters J. The relationship of phonological ability, speech perception, and auditory perception in adults with dyslexia. *Front Hum Neurosci*. 2014;8482.
- Li N, Bartlett CW. Defining the genetic architecture of human developmental language impairment. *Life sciences*. 2012; 90(13–14):469–475. [PubMed: 22365959]
- Logan J, Petrill SA, Flax J, Justice LM, Hou L, Bassett AS, Tallal P, Brzustowicz LM, Bartlett CW. Genetic covariation underlying reading, language and related measures in a sample selected for specific language impairment. *Behav Genet*. 2011; 41(5):651–659. [PubMed: 21193955]
- Marshall CR, van der Lely HKJ. Effects of Word Position and Stress on Onset Cluster Production: Evidence from Typical Development, Specific Language Impairment, and Dyslexia. *Language*. 2009; 85(1):39–57.
- McAnally KI, Stein JF. Auditory temporal coding in dyslexia. *Proc Biol Sci*. 1996; 263(1373):961–965. [PubMed: 8805833]
- McArthur GM, Hogben JH, Edwards VT, Heath SM, Mengler ED. On the “specifics” of specific reading disability and specific language impairment. *J Child Psychol Psychiatry*. 2000; 41(7):869–874. [PubMed: 11079429]
- Morris N, Song Y. strum: STRUctural Modeling of Latent Variables for General Pedigree. 2015
- Morton NE. Sequential tests for the detection of linkage. *Am J Hum Genet*. 1955; 7(3):277–318. [PubMed: 13258560]
- Newbury DF, Monaco AP, Paracchini S. Reading and language disorders: the importance of both quantity and quality. *Genes*. 2014; 5(2):285–309. [PubMed: 24705331]
- Peterson RL, Pennington BF. Developmental dyslexia. *Annu Rev Clin Psychol*. 2015;11283–307.
- Poelmans H, Luts H, Vandermosten M, Boets B, Ghesquiere P, Wouters J. Reduced sensitivity to slow-rate dynamic auditory information in children with dyslexia. *Res Dev Disabil*. 2011; 32(6):2810–2819. [PubMed: 21645986]
- R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing; Vienna, Austria: 2013. <http://www.r-project.org/>
- Ramus F, Marshall CR, Rosen S, van der Lely HK. Phonological deficits in specific language impairment and developmental dyslexia: towards a multidimensional model. *Brain: a journal of neurology*. 2013; 136(Pt 2):630–645. [PubMed: 23413264]
- Simmons TR, Flax JF, Azaro MA, Hayter JE, Justice LM, Petrill SA, Bassett AS, Tallal P, Brzustowicz LM, Bartlett CW. Increasing Genotype-Phenotype Model Determinism: Application to Bivariate Reading/Language Traits and Epistatic Interactions in Language-Impaired Families. *Hum Hered*. 2010; 70(4):232–244. [PubMed: 20948219]
- Song YE, Stein CM, Morris NJ. strum: an R package for structural modeling of latent variables for general pedigrees. *BMC genetics*. 2015:1635.
- Spence MA, Westlake J, Lange K. Estimation of the variance components for dermal ridge count. *Ann Hum Genet*. 1977; 41(1):111–115. [PubMed: 921216]
- Szatmari P, Paterson AD, Zwaigenbaum L, Roberts W, Brian J, Liu XQ, Vincent JB, Skaug JL, Thompson AP, Senman L, Feuk L, Qian C, Bryson SE, Jones MB, Marshall CR, Scherer SW, Vieland VJ, Bartlett C, Mangin LV, Goedken R, Segre A, Pericak-Vance MA, Cuccaro ML, Gilbert JR, Wright HH, Abramson RK, Betancur C, Bourgeron T, Gillberg C, Leboyer M, Buxbaum JD, Davis KL, Hollander E, Silverman JM, Hallmayer J, Lotspeich L, Sutcliffe JS, Haines JL, Folstein SE, Piven J, Wassink TH, Sheffield V, Geschwind DH, Bucan M, Brown WT, Cantor RM, Constantino JN, Gilliam TC, Herbert M, LaJonchere C, Ledbetter DH, Lese-Martin C, Miller J, Nelson S, Samango-Sprouse CA, Spence S, State M, Tanzi RE, Coon H, Dawson G, Devlin B, Estes A, Flodman P, Klei L, McMahon WM, Minshew N, Munson J, Korvatska E, Rodier PM, Schellenberg GD, Smith M, Spence MA, Stodgell C, Tepper PG, Wijsman EM, Yu CE, Roge B, Mantoulan C, Wittemeyer K, Poustka A, Felder B, Klauck SM, Schuster C, Poustka F, Bolte S, Feineis-Matthews S, Herbrecht E, Schmotzer G, Tsiantis J, Papanikolaou K, Maestrini E, Bacchelli E, Blasi F, Carone S, Toma C, Van Engeland H, de Jonge M, Kemner C, Koop F, Langemeijer M, Hijmans C, Staal WG, Baird G, Bolton PF, Rutter ML, Weisblatt E, Green J, Aldred C, Wilkinson JA, Pickles A, Le Couteur A, Berney T, McConachie H, Bailey AJ, Francis K, Honeyman G, Hutchinson A, Parr JR, Wallace S, Monaco AP, Barnby G, Kobayashi K, Lamb JA, Sousa I, Sykes N, Cook EH, Guter SJ, Leventhal BL, Salt J, Lord C, Corsello C, Hus V, Weeks

- DE, Volkmar F, Tauber M, Fombonne E, Shih A. Mapping autism risk loci using genetic linkage and chromosomal rearrangements. *Nat Genet.* 2007; 39(3):319–328. [PubMed: 17322880]
- Talcott JB, Gram A, Van Ingelghem M, Witton C, Stein JF, Toennesen FE. Impaired sensitivity to dynamic stimuli in poor readers of a regular orthography. *Brain Lang.* 2003; 87(2):259–266. [PubMed: 14585295]
- Talcott JB, Witton C, McLean MF, Hansen PC, Rees A, Green GG, Stein JF. Dynamic sensory sensitivity and children's word decoding skills. *Proc Natl Acad Sci U S A.* 2000; 97(6):2952–2957. [PubMed: 10688885]
- Vieland VJ. Bayesian linkage analysis, or: How I learned to stop worrying and love the posterior probability of linkage. *Am J Hum Genet.* 1998; 63(4):947–954. [PubMed: 9758634]
- Vieland VJ, Huang Y, Seok SC, Burian J, Catalyurek U, O'Connell J, Segre A, Valentine-Cooper W. KELVIN: a software package for rigorous measurement of statistical evidence in human genetics. *Hum Hered.* 2011; 72(4):276–288. [PubMed: 22189470]
- Vieland VJ, Wang K, Huang J. Power to detect linkage based on multiple sets of data in the presence of locus heterogeneity: Comparative evaluation of model-based linkage methods for affected sib pair data. *Hum Hered.* 2001; 51(4):199–208. [PubMed: 11287741]
- Witton C, Stein JF, Stoodley CJ, Rosner BS, Talcott JB. Separate influences of acoustic AM and FM sensitivity on the phonological decoding skills of impaired and normal readers. *Journal of cognitive neuroscience.* 2002; 14(6):866–874. [PubMed: 12191454]
- Woodcock, RN. Woodcock Reading Mastery Tests-Revised examiners manual. AGS; Circle Pines, MN: 1997.

Figure 1.

Posterior Probability of Linkage Analysis for Dynamic Auditory Traits in families with Autism Spectrum Disorder and Specific Language Impairment.

PPL linkage of AM 20 Hz and FM 2 Hz for NJLAGS and SLI subsets sequentially updated together. One peak on chromosome 12 for AM 20 Hz, one peak on chromosome 10 for FM 2 Hz, and one peak on chromosome 20 for FM 2 Hz reached significance in which PPL exceeded 30%.

Table 1

Heritability of latent reading trait and two dynamic auditory traits in families with Autism Spectrum Disorder (ASD) and Specific Language Impairment (SLI)

	Univariate ^a			Environmental Correlation ^b			Genetic Correlation ^c		
	<i>h</i> ²	SE	p-value	<i>P</i> _E	SE	p-value	<i>P</i> _G	SE	p-value
AM (20 Hz)	0.197	0.093	0.0129						
FM (2 Hz)	0.294	0.120	0.0005						
AM,FM				-0.285	0.101	1×10 ⁻⁸	0.298	0.344	0.996
Reading	0.742	0.089	5×10 ⁻¹⁰						
AM, Reading				-0.298	0.095	0.003	-0.402	0.386	0.190
FM, Reading				0.062	0.175	0.248	0.354	0.194	1×10 ⁻⁴

^aUnivariate heritability analysis indicated that each of traits in the study have significant degree of heritability

^bDefines as residual correlation that is not due to shared genetics

^cA p-value <.05 implies that the two traits in question have shared genetic etiology to some degree

Table 2

Peak linkage regions separated by subset

Chromosome	cM	<i>NJLAGS</i>	<i>SLI</i>	<i>Sequentially Updated</i>
		PPL	PPL	PPL
10	15	0.3309	0.014	0.240
10	19	0.4131	0.015	0.325
10	20	0.1199	0.015	0.084
20	20	0.4780	0.016	0.404
20	26	0.7087	0.016	0.645
20	29	0.4232	0.016	0.361
12	63	0.3497	0.070	0.678
12	64	0.5149	0.070	0.808
12	66	0.3471	0.060	0.636

PPL peak regions for NJLAGS begin when PPL reaches significance ($PPL > .30$) and end when PPL falls below .30. Comparisons of PPL peaks were based off of NJLAGS peak locations given SLI did not display significant peaks. Note that sequentially updated PPL showed decreased peaks for FM on both chromosomes, suggesting NJLAGS is driving the linkage signal seen for FM.