Musical rhythm abilities and risk for developmental speech-language problems and disorders: epidemiological and polygenic associations.

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Abstract

Impaired musical rhythm abilities and developmental speech-language related disorders are biologically and clinically intertwined. Prior work examining their relationship has primarily used small samples; here, we studied associations at population-scale by conducting the largest systematic epidemiological investigation to date (total N = 39,092). Based on existing theoretical frameworks, we predicted that rhythm impairment would be a significant risk factor for speech-language disorders in the general adult population. Findings were consistent across multiple independent datasets and rhythm subskills (including beat synchronization and rhythm discrimination), and aggregate meta-analyzed data showed that rhythm impairment is a modest but consistent risk factor for developmental speech, language, and reading disorders (OR = 1.32 [1.14 – 1.49]; p < .0001). Further, cross-trait polygenic score analyses indicate shared genetic architecture between musical rhythm and reading abilities, providing evidence for genetic pleiotropy between rhythm and language-related phenotypes.

Introduction

Developmental communication-related difficulties and disorders are highly prevalent. In the U.S. for example, speech and language disorders collectively affect between 3% to 16% of all children[1]; and global estimates for expressive and receptive language problems are in a similar range (0.4% to 25%)[2]. Established prevalences of specific speech-language and reading disorders are estimated as follows: language problems characteristic of developmental language disorder (DLD) at 3% - 7%[3,4], dyslexia at 3% - 10%[5], stuttering at 0.3% - 5.6%[6], and speech disorders of articulation or phonology at 10%[7] with higher prevalence in younger children (e.g. 15% - 16% at age 3)[8]. There are tremendous health and societal impacts of these disorders: individuals with developmental communication disorders are at increased risk for mental health disorders, poorer physical health, long-term issues with health-related quality of life[9], and poorer educational and socioeconomic outcomes[4,10–15]. Identifying risk factors for these disorders is therefore paramount for understanding, identifying, and treating them in order to facilitate communication skills across the population[16].

In the era of big data, population health approaches have begun to reveal the extensive public health burden and socio-economic impact of speech and language difficulties and disorders. For example, DLD - a neurodevelopmental disorder primarily affecting language development without a known biomedical etiology[17] - shows comorbidity with sleep disorders, neurodevelopmental disorders, auditory disorders, motor coordination disorders, and poorer mental and physical health outcomes.[4,15] Further, genetic risk for developmental stuttering is linked with increased likelihoods of suicidal ideation, obesity, hearing difficulties, and respiratory complications[18]; and stuttering is genetically correlated with asthma, allergic rhinitis, suicidal ideation, anxiety, ADHD, higher BMI, and lower sleep durations[19]. Dyslexia is genetically correlated with hearing difficulties, ADHD, pain in several areas of the body (e.g., chest, face, throat, neck, back), insomnia, loneliness/isolation, and overall health dissatisfaction[20].

Regardless of whether a given comorbidity is a biological cause or effect of the language-related disorder in question, understanding associated risk factors and medical comorbidities is crucial for a more complete profile of the biology and medical implications of these conditions.

Despite the pervasiveness and impact of communication-related problems and disorders, many speech-language and reading disorders remain systematically under-identified by educational and health professionals,[21–23] and many diagnostic and screening procedures are prone to inequities based on factors such as gender, socioeconomic status, minority status, and language background (e.g. bilingualism)[21,24]. These gaps are particularly crucial to address because developmental communication delays or disorders are sensitive to early intervention.[25–28] Therefore, novel efforts are much needed to facilitate and improve early identification, with the goal of increasing early intervention access for individuals, and maximizing therapeutic success.

Although communication-related disorders such as dyslexia, DLD, and stuttering exhibit distinct characteristic symptoms, there are commonalities across these disorders, and they are often comorbid with *each other* [29,30]. Further, the high heterogeneity of symptoms in speech-language disorders makes identifying and agreeing upon distinct "core deficits" in each disorder challenging and less practical. Instead, modeled on the emerging practice of utilizing transdiagnostic criteria in other disciplines,[31,32] identifying a set of possible behavioral and biological "dimensions" as risk factors that co-occur across disorders could bolster scientific and clinical understanding of communication disorders. Dimensional approaches are also more useful for developing personalized treatments (e.g., through the development of disorder subtypes or other comprehensive characterization of constellations of symptoms that practitioners can harness when developing a personalized treatment plan)[32]. Transdiagnostic, dimensional approaches are currently gaining traction in psychiatric epidemiology[33], but less so thus far in communication skills and disorders research. Therefore, there is an opportunity to identify non-linguistic risk factors and transdiagnostic comorbidities of language-related

disorders, as we characterize the full range of population variation in a given dimension - from typical to pathological - to improve understanding of disorders and associated dimensions[32].

Musical rhythm skills are an underutilized but potentially powerful factor that can explain a portion of the inter-individual variability in several speech-, language-, and reading-related outcomes[34], and could provide a relevant clinical marker to leverage for early identification efforts. Rhythm skills include a host of ways in which human perceptual, motor, and neurocognitive systems process timing and interval information in musical stimuli, e.g., accurately perceiving small differences between rhythms, extracting underlying beats from rhythmic information, and synchronizing motor movements to beats or rhythms (e.g. tapping). Isochronous tapping skills, one way to measure musical rhythm abilities, are impaired in multiple speech-language disorders, including stuttering,[35,36] dyslexia,[37] and DLD,[38,39] compared to control. Beat synchronization skills (e.g. tapping in time with a beat) are impaired in children with DLD[38,39] and adults with dyslexia[40], compared to controls. Despite rhythm and language skills being assessed with very different types of stimuli and tasks, there is an emerging range of studies suggesting that the biological underpinnings of rhythm and language are consistently linked. The *Atypical Rhythm Risk Hypothesis* posits that individuals with impairments in many different aspects of musical rhythm skills are at higher risk for developmental speech-language disorders[41]. This hypothesis provides an epidemiological context for the present work.

The present work is also grounded in the *Musical Abilities, Pleiotropy, Language, and Environment* (MAPLE) framework, which posits that shared polygenic architecture (i.e. genetic pleiotropy) underlies a portion of the overlap between musicality traits (including rhythm abilities) and communication traits (including, speech, language, and reading abilities)[34]. In support of the MAPLE framework, positive genetic correlations between musical rhythm abilities and language/reading-related abilities; and negative genetic correlations between rhythm abilities

and dyslexia, have been recently shown using group-level genomic results based on GWASs of rhythm abilities, language/reading abilities, and dyslexia[42].

Both the *Atypical Rhythm Risk Hypothesis* and the MAPLE framework outline a holistic view of how the brain, genes, and environment are thought to interact to result in population-scale associations between musical rhythm impairment and communication traits and disorders. For example, the MAPLE framework highlights the role of potentially mediating neural endophenotypes involving brain development, structure, and function; in the context of environmental pressures playing out across the lifespan[34]. Indeed, emerging genetic findings show that a subset of genomic loci associated with both musical rhythm impairment and dyslexia are involved in brain-cell-type specific gene regulation[42]. The same study also pinpointed a particular genomic locus jointly associated with individual differences in rhythm, dyslexia, and white matter connectivity[42]. As our understanding of particular neural systems influenced by shared genetic architecture between musical rhythm impairments and communication-related problems and disorders is still in its infancy, shared neurobiological underpinnings are a potential source of shared variance at the behavioral level. Current theories posit partially overlapping neural resources between musical rhythm and speech-language processing, particularly related to auditory-motor cortical networks and subcortical structures, which play a role in aspects of musical and language processing.[43,44] Large-scale epidemiological approaches capturing continuous population distributions of rhythm and language skills, as well as the disorder ends of the spectrum, can be a strong proof of concept test of these theories.

The current work aims to investigate whether there is converging evidence for musical rhythm impairments as a risk factor for multiple developmental speech-language disorders in the general population. We examined behavioral and genetic associations between musical rhythm abilities and communication-related problems and disorders (including those related to

speech, language, and reading), using population health approaches. Guided by recent evidence-based frameworks[34,41], we conducted two main studies using data from five different study cohorts (total *N* = 36,950). Study 1 assessed whether lower performance on musical rhythm measures are associated with higher likelihood of developmental communication problems or disorders, using a retrospective design. Study 2 investigated whether musical rhythm and communication traits share polygenic architecture, by combining phenotypic and individual-level genetic data, and drawing on group-level genomic results of recent genome-wide association studies (GWASs) of musical rhythm[45] and language-related traits[46]. The current work achieves a large sample (total *N* = 39,092) by utilizing data from population-based cohort studies in which both musical rhythm and communication-related traits/constructs were measured.

Results

Study cohorts for epidemiological research questions are referred to throughout by the following names: (1) *Vanderbilt Online Musicality Study*; (2) *Rhythm Perception Study*; (3) *Rhythm Production and Synchronization Study*; (4) *Lifelines*; and (5) *Adolescent Brain and Cognitive Development (ABCD)*. Of these, the *Vanderbilt Online Musicality Study* and *ABCD* had individual-level genotyped data available, which enabled investigation of the genetic research questions. Figure 1 illustrates the various phenotyping tools utilized to measure musical rhythm traits across the cohorts, including objectively measured and self-reported abilities.

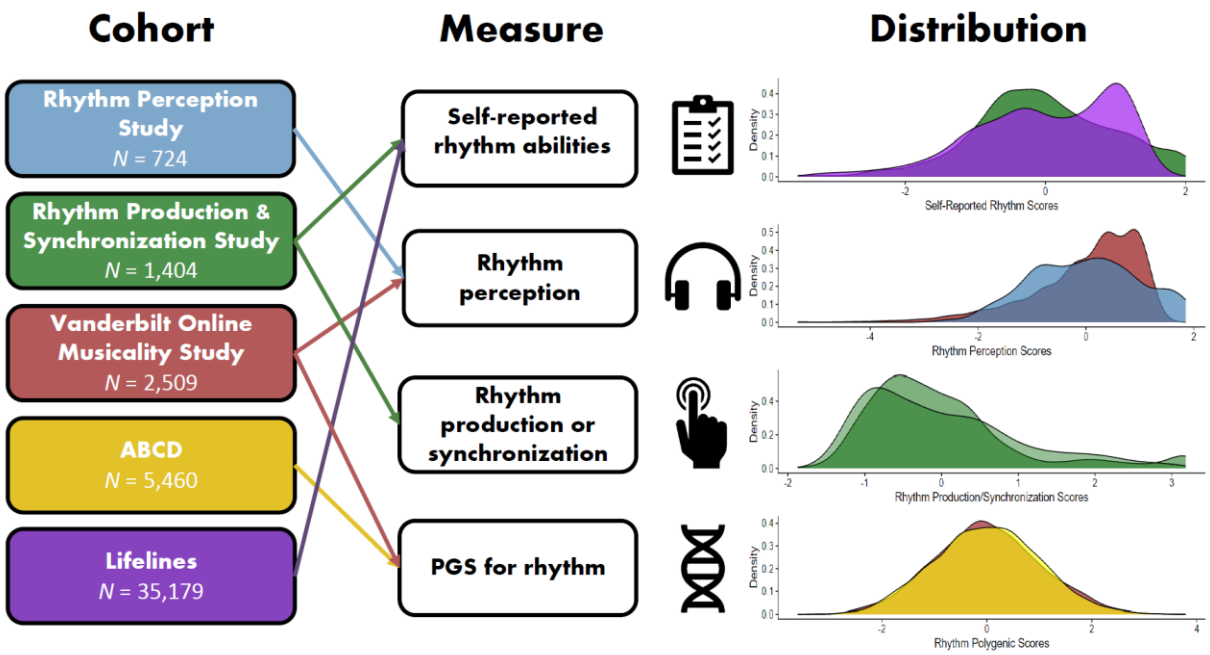

Figure 1. *All cohorts utilized in the present study are illustrated (left), with details about which rhythm traits were available within each cohort (center), spanning the following: genetics of rhythm (i.e., polygenic scores for rhythm), rhythm perception (e.g., rhythm discrimination), rhythm production (e.g., beat synchronization), and self-reported rhythm abilities. Distributions for rhythm scores in each cohort are visualized (right). Colors represent measures from the five different cohorts: reds = Vanderbilt Online Musicality Study; yellows = Adolescent Brain and Cognitive Development; blues = Rhythm Perception Study; greens = Rhythm Production & Synchronization Study; purples = Lifelines.*

Study 1: Epidemiological Results

In study 1, we investigated whether relatively weaker musical rhythm scores are associated with a higher likelihood of retrospectively reported history of speech-language problems or disorders. We tested this hypothesis across four study cohorts, which collectively represented four different musical rhythm traits. Figure 2 illustrates all association results, with all rhythm phenotypes reverse coded to test rhythm problems as a risk factor. Details of phenotypic measures related to musical rhythm abilities, and speech-language difficulties/disorders are given in *Methods.* All models controlled for age and sex effects.

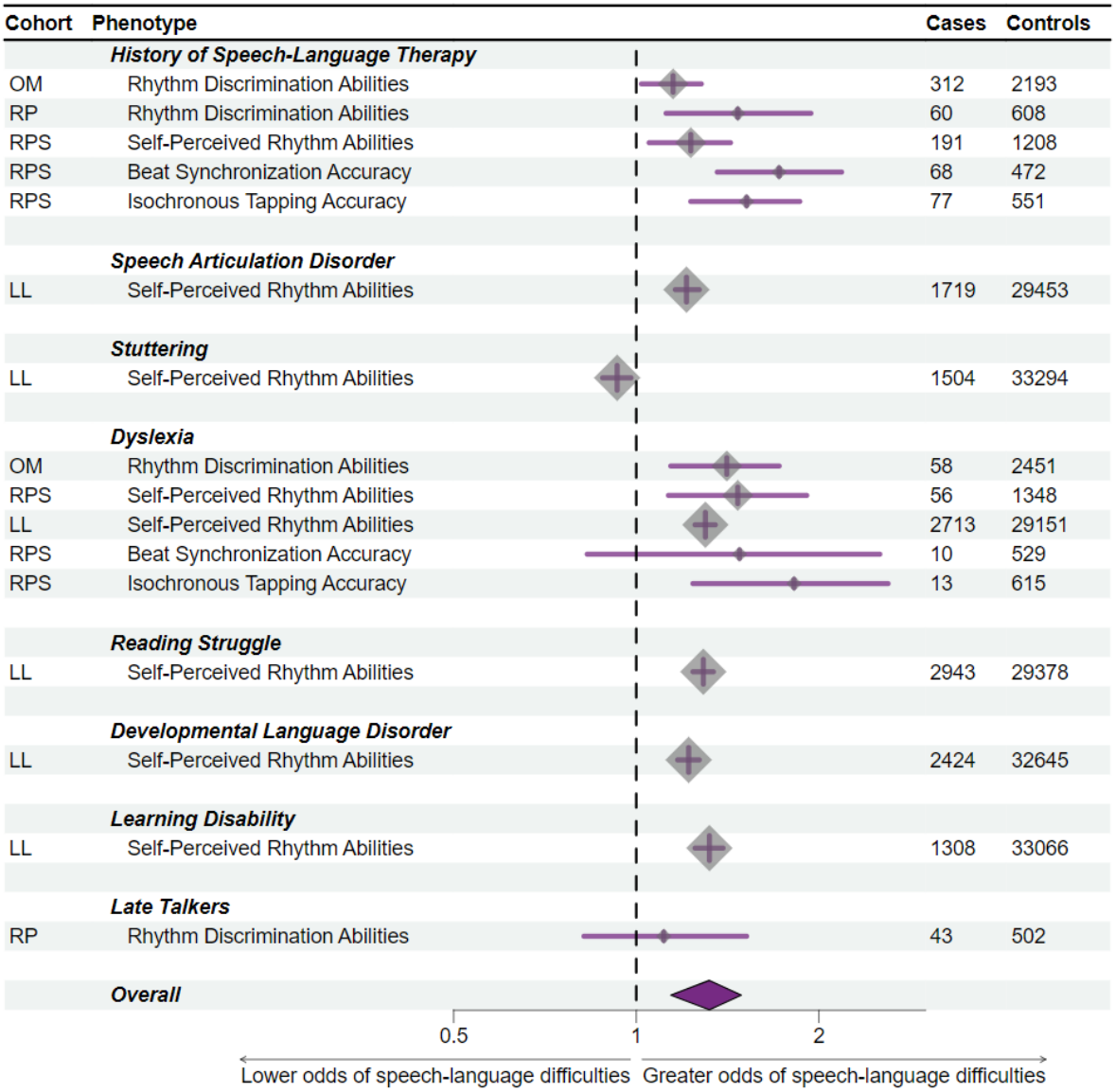

Figure 2. *Forest plot of associations between lower scores on rhythm phenotypes, and history of speech-language problems and disorders, across four cohorts. Rows represent specific rhythm phenotypes assessed (e.g., beat synchronization accuracy), and Ns for cases and controls, within each speech-language problem or disorder assessed (e.g., dyslexia). X-axis is represented on a logarithmic scale, relative to the vertical dashed line (OR = 1). Values to the right of the X-axis represent up to twice as high odds of having a history of speech-language difficulties or disorder for every 1 SD lower scores for every rhythm phenotype, and values to the left represent up to half the odds. Grey diamond marker sizes represent either small (N*

<1,000), medium (between 1,000 - 30,000), or large (N>30,000) samples. Overall meta-regression odds ratio is represented by the purple diamond (OR = 1.32 [1.14 – 1.49]; p < .0001). Cohorts are identified using the following abbreviations: ***OM*** *= Vanderbilt Online Musicality Study;* ***RP*** *= Rhythm Perception Study;* ***RPS*** *= Rhythm Perception and Synchronization Study;* ***LL*** *= Lifelines.*

Specific Communication-related Problems/Disorders and Musical Rhythm Abilities

History of Speech-Language Therapy. First, we investigated **musical rhythm discrimination abilities**, which capture perceptual sensitivity to auditory rhythms. A 1 SD decrease in rhythm scores was associated with a 15% higher likelihood of having received speech-language therapy as a child, in the *Vanderbilt Online Musicality Study* (*N* = 2,505; *OR* = 1.15 [1.02 - 1.28]; p = .008739) and a 47% higher likelihood in the *Rhythm Perception Study* (*N* = 668; *OR* = 1.47 [1.12 - 1.94]; *p* = .009). Second, we investigated **self-reported rhythm abilities**. A 1 SD decrease in self-reported rhythm scores was associated with a 23% higher likelihood of having received speech-language therapy as a child, in the *Rhythm Production and Synchronization Study* (*N* = 1,399; *OR* = 1.23 [1.05-1.43]; *p* = .008629). Next, in a subset of participants from the *Rhythm Production and Synchronization Study*, we investigated **musical beat synchronization abilities**. A 1 SD decrease in rhythm scores was associated with a 72% higher likelihood of having received speech-language therapy as a child (*N* = 540; *OR* = 1.72 [1.36 - 2.18]; $p = 5.61 \times 10^{-6}$). Finally, in a subset of participants from the *Rhythm Production and Synchronization Study,* we investigated **isochronous tapping abilities.** A 1 SD decrease in rhythm scores was associated with a 52% higher likelihood of having received speech-language therapy as a child (*N* = 628; *OR* = 1.52 [1.23 - 1.86]; *p* = 1.3e-3).

Speech or Articulation Problem/Disorder and Stuttering. First, we investigated associations between **self-reported rhythm abilities** and likelihood of having a history of speech articulation problems or disorders. In *Lifelines,* 5.84% of the adult sample reported a history of speech/articulation problems or disorder. A 1 SD decrease in rhythm scores was associated with a 21% higher likelihood of having a speech or articulation disorder in *Lifelines* (*N* = 31,172; *OR* = 1.21 [1.16 - 1.27]; *p* = 4.60e-16). Next, we investigated associations with stuttering, also in *Lifelines*. 4.52% of the adult sample reported a history of stuttering. Results showed that a 1 SD decrease in rhythm scores were significantly associated with 7% *lower* likelihood of having a stutter (N = 34,798; *OR* = 0.93 [0.88 - 0.98]; p = .0067). That is, rhythm impairment was significantly associated with *lower* likelihood of stuttering (Fig. 2), which was not the expected direction based on previous findings.[19,36,47,48] It is possible that our results reflect higher exposure to rhythm-based therapies in individuals who stutter [49].

Dyslexia and Reading Struggles. First, we investigated associations between **musical rhythm discrimination abilities** and a history of reading disorder. A 1 SD decrease in rhythm scores was associated with a 41% higher likelihood of having received a dyslexia diagnosis in the *Vanderbilt Online Musicality Study* (*N* = 2,509; *OR* = 1.41 [1.14 - 1.72]; *p* = 2.4e-3). Second, we examined **self-reported rhythm abilities** and a history of reading disorder. A 1 SD decrease in rhythm scores was associated with a 47% higher likelihood of having received a dyslexia diagnosis in the *Rhythm Production and Synchronization Study* (*N* = 1,404; *OR* = 1.47 [1.13 – 1.91]; p = 4.2e-3); and a 30% higher likelihood in *Lifelines (N* = 31,864; *OR* = 1.30 [1.25 – 1.35]; *p* < 2.2e-5). A 1 SD decrease in rhythm scores was also associated with a 29% higher likelihood of having a history of reading struggles in *Lifelines (N* = 32,321; *OR* = 1.29 [1.24 – 1.34], *p* < 2.2e-5). In *Lifelines*, 9.31% of the adult sample reported a history of dyslexia, and 10.02% of the sample reported a history of reading struggles. In subsets of participants from the *Rhythm Production and Synchronization Study*, a 1 SD decrease in **isochronous tapping**

accuracy was associated with an 82% times higher likelihood of having a dyslexia diagnosis (*N* = 628; *OR* = 1.82 [1.24 – 2.6]; *p* = 1.3e-3). However, **beat synchronization accuracy** was not significantly associated with dyslexia (*N* = 539; *OR* = 1.48 [0.83 – 2.52]; *p* = .16).

Developmental Language Disorder (DLD). Here, we investigated associations between **self-reported rhythm abilities** and likelihood of reporting a history of DLD-related symptoms as measured by our DLD proxy variable, in *Lifelines* (see *Methods*). A 1 SD decrease in rhythm scores was associated with 22% higher likelihood of being identified as a "DLD likely" case compared to "DLD not likely" controls (*N* = 35,069; *OR* = 1.22 [1.17 – 1.27]; *p* < 2e-16). These results are consistent with previous work on relatively impaired rhythm abilities in children with DLD compared to typically developing children[38,39]. 7.43% of the adult sample was classified as a DLD-likely case.

Learning Disabilities. Here, we investigated associations between **self-reported rhythm abilities** and a history of receiving support for learning disabilities, in *Lifelines.* 3.96% of the adult sample reported having a history of learning disabilities. A 1 SD decrease in rhythm scores was associated with 32% higher likelihood of learning disabilities (*N* = 34,374; *OR* = 1.32 [1.25 – 1.39]; *p* < 2.2e-16).

Late Talkers. Here, we investigated associations between **musical rhythm discrimination abilities** and late language emergence in the *Rhythm Perception Study.* Rhythm scores were not significantly associated with being a late talker (*N* = 545; *OR* = 1.11 [0.82 – 1.52]; *p* = .54), though the association trended in the expected direction.

Meta-analysis Results

A mixed effects meta-analysis model using restricted maximum likelihood (REML) estimations showed that a 1 SD decrease in musical rhythm scores was associated with a 1.32 times higher likelihood of reporting a history of speech and language problems or disorders (*N* =

39,092; *OR* = 1.32 [1.14 – 1.49]; $p < .0001$; Fig. 2). Models included nested random effects to account for significant heterogeneity found across data cohorts ($Q = 208.54$; $df = 15$; $p < .0001$), and for partially overlapping samples across datasets. These results converge with previous large-scale evidence showing that individuals with time-based congenital amusia, which is characterized by impaired rhythm and timing perception in musical stimuli occurring in the absence of brain injury or hearing loss, have significantly higher rates of neurodevelopmental disorders and learning disabilities compared to controls, including dyslexia, speech disorder, dyscalculia, attentional disorder, memory problems, and spatial orientation difficulties[50].

Taken together, Study 1 findings were consistent with predictions of the *Atypical Rhythm Risk Hypothesis.* Across several large cohorts, we found that weaker rhythm skills - measured through self-report and task performance - were associated with higher likelihood of clinical speech-language outcomes, including the presence of problems and disorders. These results extend similar previous findings in smaller samples of individuals with specific developmental speech-language disorders (see [41] for review).

Study 2: Genetic Results

In study 2, we systematically tested genetic predictions of the MAPLE framework[34], which proposes shared genetic architecture between rhythm and language traits, in two independent cohorts (*Vanderbilt Online Musicality Study* and *ABCD*). These cohorts were selected because either musical rhythm and/or speech-language phenotypes had been measured in individuals, and individual genotypes were available. Polygenic score (PGS) analyses were conducted, for which for two sets of PGSs were computed: (1) PGSs for musical beat synchronization abilities (based on a GWAS in 606,825 individuals[45]); (2) PGSs for word reading abilities (based on a GWAS in 27,190 individuals[46]). Details of GWAS discovery samples, polygenic scoring, and target samples for PGS application, are given in *Methods*. All statistical models controlled for population substructure variation.

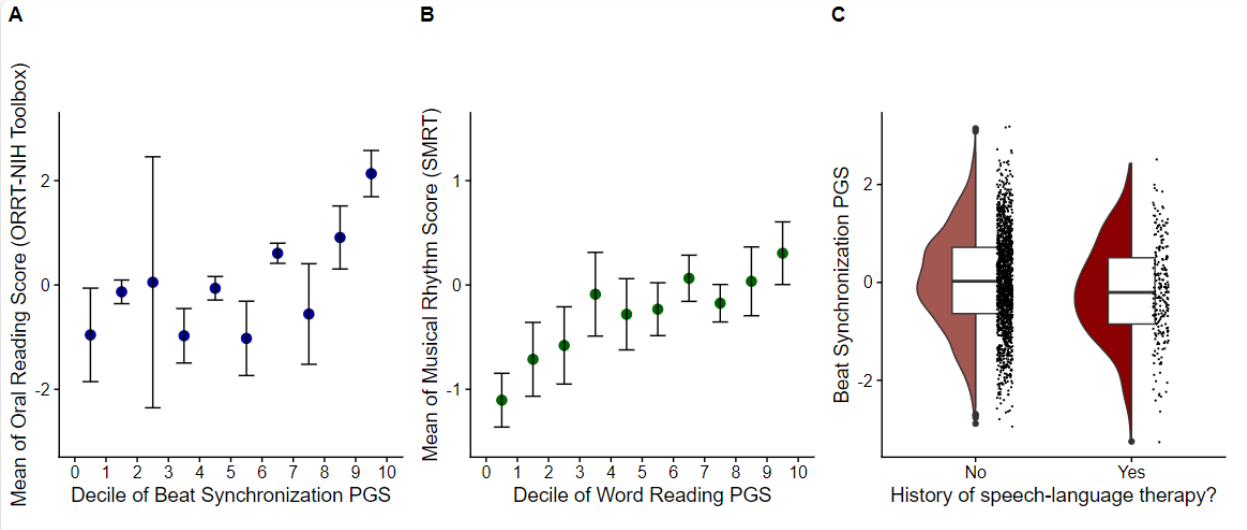

Figure 3. *PGS analyses show significant and positive cross-trait associations between (A) genetic predisposition for stronger rhythm skills, and a reading phenotype (i.e., oral reading); (B) genetic predisposition for stronger reading skills, and a rhythm phenotype (i.e., musical rhythm discrimination); (C) genetic predisposition for stronger rhythm skills, and a clinical speech-language phenotype (i.e., speech-language therapy in childhood). For continuous phenotypes (A and B), means and SEs are shown for each decile of PGSs. For the binary phenotype (C), median, interquartile range, and distribution of PGSs for phenotypic cases ("Yes") and controls ("No") are shown.*

Shared Genetic Architecture Between Reading Abilities and Musical Rhythm Abilities

First, we investigated whether **genetic predispositions for musical beat synchronization abilities** are associated with language-related abilities (here, word reading). Beat synchronization PGSs were associated with higher oral word reading (i.e., decoding) scores, as measured by the Toolbox Oral Reading Recognition Test (T-OORT)[51] (*N* = 5,390; *β* = 0.05; SE = 0.01; p = 1.1e-4), in the *ABCD* study. This significant positive association may be driven primarily by beat synchronization PGSs in the highest deciles (Fig. 3A). To contextualize

the effect size of beat synchronization PGSs on word reading scores (1 SD increase in beat synchronization PGS corresponds to a 0.05 SD increase in reading scores), we draw readers' attention to our findings that a 1 SD increase in word reading PGSs[46] correspond to a 0.14 SD increase in T-OORT word reading scores in the same *ABCD* cohort, after controlling for covariates (N = 5,390; β = 0.14; SE = 0.01, p < 2e-16).

Next, we investigated whether genetic predispositions for word reading abilities are associated with **musical rhythm discrimination abilities.** Higher word reading PGSs were associated with higher scores on the rhythm subtest of the Swedish Musical Discrimination Test[52] (*N* = 1,788; β = 0.08; SE = 0.025; *p* = 1e-3) in the *Vanderbilt Online Musicality Study*. Figure 3B illustrates mean scores on the musical rhythm discrimination task for each decile of word reading PGSs. This effect size is similar in magnitude to associations found in previous studies between beat sychronization PGSs and measured musical rhythm discrimination skills: *Vanderbilt Online Musicality Study*[53]: *N* = 1,792; β = 0.11, *p* = 3.2e-6; and the *Study of Twin Adults: Genes and Environment* (STAGE)[54]: *N* = 5648; β = 0.11, p < .001.

To understand whether **genetic predispositions for musical beat synchronization abilities** explain variability in phenotypic word reading scores over and above genetic predispositions for word reading, we also tested the model with both rhythm and reading PGSs included as predictors. Controlling for the effects of word reading PGSs, beat synchronization PGSs uniquely explained 5% of the variability in phenotypic word reading scores (*N* = 5,390; β = 0.05; *SE* = 0.01; *p* = 1e-3; adj. R^2 = 0.019, model *p* < .0001), which is the same effect size as when not controlling for word reading PGSs. Genetic correlations between word reading and beat synchronization abilities, based on the same GWASs used here, were recently reported to be rG = 0.18, SE = 0.04, p = 1.84E-05[42].

Shared Genetic Architecture between Speech-Language Problems/Disorders and Musical Rhythm Abilities

Here, we investigated whether **genetic predispositions for musical beat synchronization abilities** are associated with higher likelihood of having a history of speech-language disorders. Higher beat synchronization PGSs were associated with higher likelihood of reporting a history of speech-language therapy, in the *Vanderbilt Online Musicality Study* (*N* = 1,685; *OR* = 1.22 [1.05 - 1.41]; *p* = 7.6e-3). Figure 3C illustrates the difference in medians and distributions of beat synchronization PGS across the Yes cases and No controls for speech-language therapy history.

Taken together, Study 2 results show that polygenic architecture for musical rhythm skills (here, beat synchronization) explain a proportion of variability in measured language-related skills (here, word reading), and that the size of this effect is meaningful given the extent to which polygenic architecture for word reading explains variability for the same trait (measured word reading abilities) in the same cohort. Further, polygenic architecture of rhythm predicts reading scores over and above the predictive value of known polygenic architecture of reading, suggesting that real-life reading skills draw upon biology shared with musical rhythm skills.

Discussion

Consistent with the predictions of the *Atypical Rhythm Risk Hypothesis*, Study 1 found converging epidemiological evidence that rhythm impairments are a transdiagnostic risk factor for developmental communication-related disorders, at unprecedented sample sizes, and across four independent cohorts. Rhythm impairments, measured in several different ways, were associated with increased likelihood of several clinical speech-language outcomes including: speech-language therapy, articulation disorders, stuttering, dyslexia, reading struggles, DLD, speech or articulation disorders, reading struggles, and learning disabilities. Our retrospective design (compared to cross-sectional designs) enabled us to capture a history of speech, language, or reading struggles that adults may have experienced at earlier developmental stages, even if problems had since resolved.

Results here can help expand our understanding of dyslexia, and learning disabilities, and speech and language delays/problems. For example, our large-scale findings about musical rhythm and dyslexia are an impetus for current theories to go beyond the importance of *speech* rhythm processing[55–57] and perception[58], further investigating the role of *musical* rhythm. Dyslexia-related findings here were consistent with previous studies in modest samples showing lower musical rhythm perception scores in children and adults with dyslexia compared to controls[59–61], as well as significant associations between rhythm discrimination and reading skills[62]. Further, our large-scale findings about rhythm and learning disabilities may further capture patterns with speech-language disorders (which are often comorbid with learning disabilities, and classified in overlapping way[63]); or may capture the role of rhythm and timing in neurodevelopmental disorders more broadly, as has been previously highlighted[64]. Last, based on current referral practices in the US and other countries, our large-scale findings about rhythm and history of speech-language therapy may serve as a proxy for developmental speech-language delays, which are known to hinder educational and socioeconomic trajectories.

Study 2 results suggest genetic pleiotropy between musical rhythm and language traits (reading-related traits), consistent with the broad genetic predictions of the *Atypical Rhythm Risk Hypothesis*[41]; and with specific predictions of the MAPLE framework[34] pertaining to cross-trait polygenic score analyses between musicality and language traits. Specifically, genetic predispositions for reading abilities predicted rhythm scores in one cohort; and genetic predispositions for beat synchronization abilities predicted reading scores in a second cohort. Further, genetic predispositions for beat synchronization abilities predicted reading scores, after controlling for the genetic effects of reading captured by word reading PGSs, suggesting that underlying biology related to rhythm is an additional source of inter-individual variability in speech and language traits. Study 2 results also converge with recent findings of genetic

pleiotropy between rhythm impairments, language and reading traits, and dyslexia (reading disorder), using complementary genomic methods[42].

Our use of *Lifelines,* a very large cohort representative of the local population, allowed us to evaluate population prevalences for certain disorders. Here, DLD, stuttering, and dyslexia prevalence was found to be within the range of previous estimates (with dyslexia at the higher end of previous estimates, and approximately 10% of the sample experiencing struggles with reading). Speech/articulation disorder prevalence on the other hand were lower than previous estimates. Although, given the overall underidentification of developmental disorders of communication, self-reports of a given disorder are still likely to miss the full extent of disorder cases. Due to the current difficulty of objectively assessing speech and language at large scale, self-reports remain common, but methodological advances are being made towards large-scale phenotyping of the relevant traits[58,65,66], including industry initiatives such as Reading Screen and Language Screen (OxEd and Assessment: https://oxedandassessment.com/getting-started/); and machine-learning approaches to extracting clinical cases from health records, e.g. for stuttering and DLD[15,18,67].

Future studies should aim to build or tap into existing longitudinal epidemiological cohorts to explore the role of rhythm abilities across different stages of language development and learning, particularly at inflection points known to be important for the development of temporal and motor processing, language skills, and domain-general cognitive mechanisms (e.g. executive function). Longitudinal studies could also investigate relationships between the genetics of rhythm traits, and different *trajectories* of language development and outcomes, e.g. delineating the extent to which particular rhythm traits (or genetic predispositions for them) are risk factors for language disorders in subsets of individuals with late vs early manifestations or resolutions of symptoms.

Together, results of Study 1 and 2 can inform research, screening and identification, and clinical intervention efforts for speech-language disorders. For example, our results provide compelling evidence supporting musical rhythm impairments as a transdiagnostic risk factor for developmental speech-language disorders, consistent with recent theoretical proposals.[41,64] Transdiagnostic approaches are particularly compelling given that comorbidities are often found between clinically distinct speech-language and reading disorders[29]. We argue that results of the present work lay the groundwork for future research to consider musical rhythm abilities (including perception, production, and synchronization skills) a transdiagnostic dimension or "domain" of impairment in development speech-language disorders going forward, e.g. within a Research Domain Criteria (RDoC) model (as has been used to frame research in psychiatric disorders).[31,32] Other relevant domains for speech-language disorders may include sensorimotor, cognitive, or social processes that overlap to some extent with each other, and with rhythm abilities.

Further, the development and validation of musical rhythm based screening tools could enhance early identification of individuals at-risk for developmental speech-language disorders, especially individuals who are missed by current efforts[21–24]. For example, rhythm-based screeners would not require different tools and norms to be developed for multilingual children, making them more readily usable across the world. Rhythm-based screeners may also be more cost-effective and have broader reach for identifying children who may benefit from monitoring and support from parents, teachers, and/or speech-language pathologists but do not meet clinical thresholds for speech-language disorders at present, or in the future[68]. Music/rhythm based therapies for children, if developed and validated in the future, could be naturally motivating, engaging, reinforcing, and predictable[69], offering a meaningful complement to current interventions for DLD, dyslexia, and other developmental difficulties and disorders related to communication. Future well-powered intervention studies are needed to evaluate the

effectiveness of rhythm-based therapies for speech-language disorders (see 68 for extended discussion). In contrast to other theories about temporal processing as a shared mechanism between musical rhythm perception, speech perception, and language/reading development[55], the present work takes a broader systems approach to demonstrating rhythm impairment as a persistent *risk factor,* without it needing to be a *core deficit,* in line with new frameworks in psychiatric epidemiology[70].

Our findings also support and complement prior multidisciplinary work on the shared development, neurobiology, and evolution of musicality and language-related traits[34,43,44]. Interdependent relationships between rhythm abilities and speech-language skills acquisition likely start as early in development as the fetal brain, to facilitate the processing of rhythms in the social environment across infancy, childhood, and beyond[71–73]. Relatedly, a recent evolutionary framework posits that rhythm and communication traits co-evolved to support credible signaling in communicative behaviors that are key to survival, namely parent-child coordination.[74] Further, the genetic architecture of beat synchronization skills, word reading skills, and developmental dyslexia are all enriched for genes involved in fetal brain development[45], which further highlights the developmental significance of rhythm abilities.[75] The *revised Vocal Learning Hypothesis* posits partially overlapping neural substrates underlying beat perception and synchronization (i.e. rhythm) and vocal learning in humans (i.e. speech-related abilities), with auditory-motor neural circuits now supporting beat perception and synchronization thought to have co-evolved with, or convergently evolved with, vocal learning mechanisms[43,76]. Our results are consistent with the predictions of the The revised Vocal Learning Hypothesis. As delineated in [34] and [41], the influences of shared genetic architecture can be mediated through both shared and non-shared neural mechanisms underlying rhythm and language, including developmental, function, and structural aspects of the brain. Viewing our results alongside this prior work, it is possible that disruptions to genetic, neural, or

environmental influences on human rhythm lead to cascading effects on (neuro)developmental disorders[64], including those related to communication.

As big-data approaches to investigating developmental speech-language disorders improve and increase, the costly and long-term health burden of living with communication-related disorders will become even more apparent. Our retrospective design and findings linking adult rhythm skills with clinical speech-language histories, emphasize that not only are developmental histories of speech-language disorders or problems *prevalent* in the general population; but also that the childhood rhythm impairments often seen in the context of speech-language disorders appear to *persist* into adulthood. This work lays the foundation for future investments by the communication sciences and disorders research community (among others) in studying musical rhythm skills. Future efforts in building and sharing large-scale epidemiological and genomic data focused on communication-related traits can enable transdiagnostic and dimensional approaches to advance personalized medicine (e.g. through identifying disorder subtypes), building on the current evidence base. In the long run, these efforts will pave the way for paradigm shifts in early identification, screening, and intervention tools, and improved quality of life for those living with communication-related disorders.

Methods

Results reported here draw on data from five study cohorts including the *Vanderbilt Online Musicality Study*, *Rhythm Perception Study*, *Rhythm Production and Synchronization Study*, *Adolescent Brain and Cognitive Development Study* and *Lifelines*. Samples and materials for each are described below.

Vanderbilt Online Musicality Study

The *Vanderbilt Online Musicality Study* investigated the genomics of musicality – including musical rhythm perception and music engagement – as well as relationships between

musicality and speech-language traits including speech rhythm perception. Procedures and sample recruitment for the study are detailed in previous work[53,58].

Participants and Procedures

The present study included N = 2,509 participants from the original study cohort for phenotypic analyses; and N = 1,792 for genetic analyses. Participants completed an online battery of surveys and behavioral tests administered online (internet-based) through Research Electronic Data Capture (REDCap) software, a secure web platform for building and managing research databases and surveys[81]. These included a brief musical engagement questionnaire, a brief headphone test, two auditory tasks (a musical rhythm task and a speech rhythm task), and a demographic questionnaire. A subset of participants consented to DNA-extraction from mailed-in saliva samples. All procedures, including the informed consent forms, were approved by the Vanderbilt Institutional Review Board. Speech rhythm task data is reported elsewhere [58].

Measures

Swedish Musical Discrimination Test (Rhythm Subtest). Participants were asked to listen to 18 pairs of rhythmic sequences, and decide whether the sequences were same or different. Rhythmic sequences comprised brief sine tones (500 Hz; inter-onset intervals: 150, 300, 450, or 600 ms) with a total duration of 60 seconds. Each sequence in a pair of rhythms was separated by a 1 second gap. Participants only heard each pair once before making their same/different decision. The test included 2 practice trials, and an attention check item interspersed with test trials. The task yielded rhythm discrimination scores from 0 to 18, which were standardized (z-scored) prior to logistic regressions, and inverse-rank transformed prior to linear regressions for the analyses reported here, to mitigate skews in the data (consistent with prior studies[52]) and meet the assumptions of normality of residuals.

Self-reported History of Speech-Language Therapy. Participants were asked a single-item question, “Did you receive speech language therapy as a child?”, with response options “Yes”, “No”, or “I don’t know”. “I don’t know” responders (*N* = 28) were excluded from models.

Self-reported History of Dyslexia. Participants were asked a single-item question, “Have you ever been diagnosed with dyslexia?”, with response options “Yes”, “No”, or “I don’t know”. “I don’t know” responders (*N* = 19) were excluded from models.

Polygenic Scores (PGSs) for Word Reading Abilities. PGSs are weighted sums of the estimated effects of a large number of genetic variants on a specific phenotype, with the weights derived from a large-scale genome-wide association study (GWAS). In the present study, we derived PGSs for word reading in our target sample (*Vanderbilt Online Musicality Study* participants), based on models derived from a GWAS of measured oral reading (i.e., reading words aloud) performance in a discovery sample of *N* = 27,180 individuals of European genetic ancestries, meta-analyzed across 18 cohorts[46]. PGSs for individual participants were computed using PRS-CS software[82]. Once PGSs were derived for each participant, they were standardized (z-scored) within each genetic ancestry group as previously done in *Vanderbilt Online Musicality Study* data[53]. This approach improves the application of PGS models to mismatched-ancestry target samples (useful here due to the presence of more diverse genetic ancestries represented in our target sample compared to the discovery sample).

Polygenic Scores (PGSs) for Beat Synchronization Abilities. PGSs for beat synchronization abilities in *Vanderbilt Online Musicality Study* participants utilized in the present analyses were derived from a GWAS of beat synchronization skills[45], using PRS-CS models[82], as reported previously[53].

Rhythm Perception Study

The original aim of the Rhythm Perception Study was to determine whether self-reported rhythm measures (specifically, responses to the question “can you clap in time with a musical beat?”) were correlated with task-based rhythm perception measures. Sample characteristics and study procedures have been previously detailed in[45]: *Phenotype Experiment 1*.

Participants and Procedures

The study sample consisted of $N = 724$ participants (333 females), aged 18-73 years old ($Mean_{Age}$ = 36.1 years; SD = 10.9 years), who were recruited anonymously in Amazon’s Mechanical Turk.

Measures

Self-reported History of Speech-Language Therapy. Participants were asked the single-item question, “Did you receive speech language therapy as a child?”, with response options “Yes”, “No”, or “I don’t know”. “I don’t know” responders (N = 16) were excluded from models.

Self-reported Late Talker Status. Participants were asked the single-item question, “Were you a late talker?”, with response options “Yes, “No”, or I don’t remember. “I don’t remember” responders (N = 147) were excluded from models.

Beat-based advantage (BBA). The BBA is a 32-item musical rhythm perception task. Participants hear two rhythms and decide if they are the same or different. On a randomized half of the trials, the task yields a raw accuracy score, from which d’ scores (ratio between hits and misses) were computed, as derived from signal detection theory[83] and used previously to

analyze BBA data[84,85]. d' scores were used as the dependent variable in all analyses. Rhythmic stimuli, procedures, and analysis have been previously detailed in[45] (*Phenotype Experiment 1*).

Rhythm Production and Synchronization Study

The original aim of the Rhythm Production and Synchronization Study was to determine whether a self-reported beat synchronization measure (i.e., "can you clap in time with a musical beat?") is a valid proxy for objectively measured beat synchronization ability. Further, the study aimed to explore behavioral associations between rhythm/beat synchronization and assorted traits found to be genetically correlated with beat synchronization. The study was pre-registered through the Open Science Framework (https://osf.io/exr2t) in July 2020, prior to data collection. Sample characteristics and study procedures have been previously detailed[45] (*Phenotype Experiment 2*).

Participants and Procedures

This internet-based study consisted of a beat synchronization task to assess the accuracy of participants' tapping in time with musical excerpts, and a series of questionnaires assessing self-reported rhythm, musicality/music engagement, selected health traits, confidence as a personality trait, and demographics. A total of *N* = 1,404 participants were included in this study, a subset of whom also had data for the isochronous tapping task (*N* = 628) and a further subset of whom had data for the beat synchronization task (*N* = 540). Tapping responses were measured using the Rhythm Experiment Platform (REPP)[86], a robust cross-platform solution for measuring sensorimotor synchronization in online experiments that has high temporal fidelity, and can work efficiently using hardware and software available to most participants online.

Measures

Isochronous tapping task. This task served as practice trials for the musical beat synchronization task. It consisted of four 15 second trials of isochronous tapping to a metronome beat (two trials with an inter-onset interval of 500 ms and two trials with an inter-onset interval of 600 ms). Participants were included in analyses if they had at least one valid trial per inter-onset interval (i.e. 500 ms or 600 ms). The task yields a measure of tapping asynchrony, therefore lower scores indicate better beat synchronization accuracy. Tapping asynchrony was therefore reverse coded for regression analyses and forest plots, to remain consistent with the direction of all other rhythm phenotypes, i.e., higher scores indicate better rhythm performance (see [86] for more details on the implementation of the practice phase).

Musical beat synchronization abilities. Following the practice phase (isochronous tapping), the participants were presented with the main beat synchronization task consisting of eight trials (four musical excerpts, each played twice), with each trial 30 s long. The order of presentation of the practice trials and test trials was randomized for each participant. Beat synchronization abilities were measured through a beat synchronization task. Participants heard a song and were asked to tap to the musical beat until the music ended. To help participants find the beat, a metronome marking the beats in the first 11 seconds of the clip was added to the stimulus. After the metronome stopped, participants were instructed to continue tapping to the same beat at a steady pace (see [86] for more details and validation of the beat synchronization task). Tapping responses were measured through REPP[86].

Self-reported rhythm abilities. Participants responded to 7 questions about self-reported rhythm abilities, which were then composited into an overall score. The composite score captures several self-reported interactions with rhythm including beat synchronization abilities, importance of rhythmic ability to identity, struggles with rhythm perception, and urge to “groove” or move to a beat.

Adolescent Brain Cognitive Development (ABCD) study

The *ABCD* study is the largest long-term study of brain development and child health ever conducted in the United States (US). Coordinated data collection is ongoing across 21 sites in the US, aiming to follow a cohort of 11,500 nine- and- ten-year old children, and their parents/guardians, from pre-adolescence to young adulthood (for a total of ten years). *ABCD* study data comprises genetic data and other biospecimens; a comprehensive set of phenotypes spanning the following domains: physical health, mental health, brain imaging, biospecimens, neurocognition, substance use, and culture and environment. ABCD genetic and phenotypic data used in the present study were obtained from the open-access National Institute of Mental Health (NIHM) Data Archive (https://data-archive.nimh.nih.gov/abcd). The ABCD cohort also consists of data from 1,720 twins. Participating children and families were largely recruited through US school systems, optimizing for diversity and representativeness of the national population on dimensions such as gender, race and ethnicity, socioeconomic status, and urbanicity. Recruitment and overall design of the ABCD study for single-birth children[87] and twins[88] have been detailed previously.

Participants

N = 5,460 participants of European genetic ancestry (2,571 females; $Mean_{Age}$ = 9.46 years; *SD* = 0.54 years) were included in the study, after applying genetic quality control (QC) protocols to open-access imputed genetic data at the individual level (see *Supplement* for QC details).

Measures

Polygenic Scores (PGSs) for Beat Synchronization. Similar to the PGS models for beat synchronization derived for *Vanderbilt Online Musicality Study* participants[53], we derived PGSs for musical beat synchronization in *ABCD* participants (our target sample here) from the beat synchronization GWAS[45]**,** using PRS-CS models[82].

NIH Toolbox Oral Reading Recognition Test (T-ORRT). The T-ORRT is a standardized assessment of reading decoding skills that is part of the NIH Toolbox Cognition Battery [51]. In

this test, participants are asked to read aloud letters and words, pronouncing them as accurately as possible. This standardized test of oral reading ability yields an uncorrected as well as an age-adjusted score. Uncorrected T-OORT scores (i.e. not adjusted for age norms) were used in all present analyses, since age was included as a covariate in all models. The task yielded reading scores from 67 to 119, which were inverse rank transformed prior to linear regressions for the analyses reported here, to mitigate skews in the data and meet the assumptions of normality of residuals.

Genetic Quality Control (QC)

PLINK v1.90b6.9[89] was used to perform SNP and sample quality control (QC). 11,099 individuals had available genotype data for 516,598 SNPs. SNPs were excluded if they were indels, were duplicated, had genotyping rate <0.95, or minor allele frequency (MAF) < 0.05. Samples were excluded if they had a missing genotyping rate greater than 10%. A set of 232,613 common, autosomal, independent SNPs were selected by pruning LD using a window of 50 variants and a shift of 5 variants between windows, with an r2 cut-off of 0.5, and excluding high-LD and non-autosomal regions. These SNPs were used to identify sex mismatches, and flag outliers for heterozygosity. We used PRIMUS[90] to assess relatedness. To identify a set of unrelated individuals, we randomly excluded one subject from each pair with a pi-hat > 0.1875. Genetic principal components were calculated using PLINK for the total sample. In order to define a subset of homogeneous ancestry, we selected individuals of the most represented ancestry; European. A final sample consisting of 5,460 participants (2,889 males, 2,571 females) unrelated European participants were kept.

The imputed genotypes data (NDA Study 10367) had been imputed using the TOPMed imputation server with Eagle v.2.4 phasing and TOPMed mixed ancestry reference. Using PLINK, we filtered to keep SNPs with imputation quality scores above 0.7, minor allele frequency (MAF) > 0.05, and lifted to the hg19 reference panel. SNPs were filtered if they had a missing genotype rate less than 0.1.

Lifelines

Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons living in the North of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. Design and sample characteristics of the Lifelines study have been previously detailed [91,92].

Participants

For the present analyses, a total of 35,179 Lifelines participants (21,328 females and 13,851 males; aged 18-96 years) completed the “Speech, Language and Musicality” questionnaire.

Measures

All questions were asked in Dutch; English translations of questions and answer options are given below.

Self-reported rhythm abilities. Participants were asked two items about self-reported rhythm abilities, which were composited into an overall score for self-reported rhythm. Included items were: “I can tap in time to a musical beat” and “I struggle to feel the rhythm when listening to, playing, or dancing with music”, which could be answered using a seven-option likert scale ranging from completely disagree to completely agree. The final composite score ranged from 2 to 14, with a higher score indicating better self-reported rhythm ability.

Self-reported Dyslexia. Presence of dyslexia was examined using the question “People with dyslexia read very slowly and/or have a lot of difficulty with spelling. Do you have dyslexia?”. Participants who answered “Yes, I have been diagnosed with dyslexia” and “I presume I have dyslexia, but I have never been tested” were considered dyslexic (*N* = 2,719),

those who answered “No” were considered to not have dyslexia (*N* = 29,234), and those who answered “No, I suppose not” were excluded (*N* = 3,175).

Self-reported Stuttering. Presence of stuttering at present or in the past was examined using the question “People who stutter have difficulty with pronouncing words fluently. For example, they repeat syllables or words, linger on sounds and/or block while talking. Have you ever stuttered, or do you currently stutter?”. Participants were included as a person who stutters or stuttered if they answered one of the following: “Yes, I stuttered as a child, but I do not stutter anymore”; “Yes, I started stuttering as a child and I still have a stutter”; “Yes, as a young person/adult I stuttered for a while, but I do not stutter anymore” or “Yes, I started stuttering as a young person/adult and I still stutter”, and if they also reported stuttering onset before 20 years of age (*N* = 1,510). Those who answered “No, I have never stuttered” were considered non-stuttering controls (*N* = 33,385). People who reported an age of onset of stuttering at or later than 20 years of age (*N* = 61), a duration of maximally one year (*N* = 160), or did not report an age of onset (*N* = 32), were excluded from analyses.

Self-reported Speech or Articulation Problem. Presence of a speech or articulation problem was examined using the question “People with a speech or articulation problem may for example lisp, have an unclear pronunciation and/or use the wrong sounds. Do you have or did you have a speech or articulation problem?”. Participants who answered “Yes, I have had a speech or articulation disorder in the past” and “Yes, I still have a speech or articulation disorder” were considered to have a speech or articulation problem (*N* = 1,727), those who answered “No” were considered to not have a speech or articulation problem (*N* = 29,536), and those who answered “No, I suppose not” were excluded (*N* = 3,877).

Self-reported Learning Disability. Presence of a learning disability was examined using the question “Did you receive extra support in school for a learning disability?”. Participants who answered “Yes” were considered to have a learning disability (*N* = 1,314), those who answered

"No" were considered to not have a learning disability (*N* = 33,159), and those who answered "I'm not sure" were excluded (*N* = 653).

Self-reported Reading Problems. Presence of reading problems during primary education was examined using the question "Did you struggle in primary school with learning to read, compared to your peers?". Participants who answered "I struggled more" or "I struggled much more" were considered to have a reading problem (*N* = 2,954), participants who answered "I struggled much less", "I struggled less" or "Similar to my peers" were considered not to have a reading problem (*N* = 29,469), and those who answered "I do not know (anymore)" were excluded (*N* =2,756).

DLD proxy. Since DLD usually requires a formal diagnosis by a speech-language pathologist, direct ascertainment of DLD is less feasible in large-scale data cohorts and epidemiological efforts. Researchers have therefore employed creatively designed approaches for developing DLD proxies, including assigning cut-off scores for standardized language measures[93]; machine-learning techniques for classifying DLD cases[15,67], or thresholds based on self-reported speech and language measures[4], which is similar to the approach we used here. Our DLD proxy incorporated many key symptoms of DLD, namely consistent and prominent difficulties with spoken expression, written expression, and word finding, based on self-report items. DLD was inferred through three self-report questions: (1) "Do people correct your writing because of grammar or spelling mistakes?"; (2) "Do you have a hard time finding the right words or making your sentences express what you want to say?"; and (3) "How often do you have words 'on the tip of your tongue' or word finding problems?". Responses to these questions were on a four-option scale ("very often/all the time", "somewhat often/more often than most people I know", "occasionally/about as often as most people", and "rarely"). A binary DLD proxy score was derived, to enable comparison with odds ratios across other research questions and phenotypes. This process yielded two response statuses: (a) DLD likely (cases); (b) DLD not likely (controls). Participants were assigned to DLD likely (case) status (*N* = 2,426) if they

responded with the lowest score (experiences difficulties with language “very often”) on at least one of three domains of difficulty (i.e., written expression; spoken expression; word finding); in addition to responding with the second lowest score (experiences difficulties with language “somewhat often”) on at least two of the three domains. All other participants (*N* = 32,753) were assigned to DLD not likely status (controls).

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