Preschool musicality is associated with school-age communication abilities through genes related to rhythmicity

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Abstract

Early-life musical engagement is an understudied but developmentally important and heritable precursor of later (social) communication and language abilities. This study aims to uncover the aetiological mechanisms linking musical to communication abilities. We derived polygenic scores (PGS) for self-reported beat synchronisation abilities ($PGS_{rhythmicity}$) in children (N≤6,737) from the Avon Longitudinal Study of Parents and Children and tested their association with preschool musical (0.5-5 years) and school-age (social) communication and cognition-related abilities (9-12 years). We further assessed whether relationships between preschool musicality and school-age communication are shared through $PGS_{rhythmicity}$, using structural equation modelling techniques. $PGS_{rhythmicity}$ were associated with preschool musicality (*Nagelkerke*-R^2=0.70-0.79%), and school-age communication and cognition-related abilities (R^2=0.08-0.41%), but not social communication. We identified links between preschool musicality and school-age speech- and syntax-related communication abilities as captured by known genetic influences underlying rhythmicity (shared effect β=0.0065(SE=0.0021), *p*=0.0016), above and beyond general cognition, strengthening support for early music intervention programmes.

Keywords: musical engagement, communication, beat synchronisation, polygenic scoring analyses, structural equation modelling

Introduction

Human communication is a complex ability that enables us to develop and use language and cooperate with others, shaping communities and culture[1]. Communication with others requires speech-related (e.g. intelligibility and fluency of speech) and language-related (e.g. complexity of spoken grammar) skills, in addition to sufficient audible processing, while impairments thereof may result in communication disorders[2]. However, communication within a social setting, known as social communication or pragmatic language, also involves social interaction-related skills[3]. In particular, social communication requires (i) adequate language use, (ii) the adaptation of language to the listener or situation, and (iii) the adherence to conversational conventions (e.g. turn-taking or conversational rapport)[3]. Difficulties to communicate efficiently are, therefore, also characteristic of many mental health problems, including neurodevelopmental conditions[4].

The acquisition of communication skills in typically developing children is influenced by social, linguistic, and cognitive factors[5,6], but also other facets beyond traditionally defined general cognition and verbal skills. An understudied but developmentally important precursor of later (social) communication and language abilities is early-life musical engagement. Music is universal to human cultures[7]. Musicality (i.e. the suite of abilities involved in perceiving, producing and engaging with music including rhythmic abilities)[8] and communication share universal aspects including acoustic, motor and perceptual skills, suggesting a shared biological basis[9,10].

Rhythmic abilities emerge early in life and already new-borns can detect the beat in music[7]. In infancy, rhythmicity promotes social communication between the caregivers and the child[11,12]. In preschool children, rhythmic abilities are also related

to phonological segmentation and phonological awareness shaping language acquisition[13]. More generally, early-life music engagement has a beneficial impact on later-life communication aspects such as oral and written language[14,15], but also cognition and social skills[11]. Hence, deepening our understanding of links between early-life musicality, including rhythmic skills, and later (social) communication abilities may also help us to better understand the aetiological mechanisms underlying communication difficulties in children.

Genetic factors partially explain individual differences in both communication and musicality. Twin studies of communication-related traits have reported high heritability estimates[16]. Heritability estimates for pragmatic language (i.e. the use of language in conversation and social situations) and communication skills range from 58% to 79%[16]. Musicality-related traits are heritable too, with twin studies reporting a heritability of 50% for rhythm discrimination[17]. Recently, a genome-wide association study (GWAS) of self-reported beat synchronisation (i.e. a yes/no response to "Can you clap in time with a musical beat?") was conducted in a large, well-powered sample of 606,825 individuals[18]. Using genetic variants present in at least 1% of the general population (indexed by single-nucleotide polymorphisms, SNPs), this study reported a SNP-based heritability of 13-16%[18]. The availability of this large GWAS[18] enabled, for the first time, the study of genetic overlap between rhythmicity and other traits, demonstrating associations with language[19,20], mental health[21] and other musicality measures[22,23], mostly in adult populations.

Given phenotypic links between early musicality and speech-language skills[14,15], we hypothesised that these relationships may extend to communication phenotypes and manifest in shared genetic links, especially during an early developmental

window. Compared to phenotypic analyses, investigating genetic relationships may add specificity and robustness, as genetic approaches can adjust for confounding influences affecting many complex traits[24]. Adopting a genomic approach has, thus, important implications for theoretical frameworks predicting links between musicality and language[14,25], and for unravelling opportunities of support for children with communication difficulties.

Here, studying a large longitudinal sample of 6,737 children from the Avon Longitudinal Study of Parents and Children (ALSPAC)[26,27], we, first, investigate whether polygenic load for rhythmicity is associated with a series of parent-reported preschool musicality and school-age communication abilities in a population-based sample. Next, we model structural relationships across associated phenotypes using a multivariate analysis framework. Finally, we study whether phenotypic relationships between preschool musicality and school-age communication are captured by the polygenic load for rhythmicity.

Methods

Participants

ALSPAC is a population-based longitudinal pregnancy-ascertained birth cohort from the United Kingdom[26,27] (estimated birth date 1991-1992, Supplementary Note 1). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Consent for biological samples has been collected following the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from

participants following recommendations of the ALSPAC Ethics and Law Committee at the time.

Phenotype information

Parent-reported measures of communication, social communication, musicality and nursery rhymes were assessed in ALSPAC children. Across all measures, at least 6,737 individuals had genetic and phenotypic data available. The study website contains details of all the available data through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data).

For this study, we define a developmental preschool window (0-5 years) before children enter key stages of school curricula in the UK (i.e. preschool and reception years), compared to a developmental school-age window (> 5 years), where children enter educational key stages (i.e. year 1 and above). Once children start schooling, many predictors of language-related phenotypes, such as phonological awareness, become reciprocally shaped by reading experience and may no longer reflect underlying aetiological mechanisms[28].

Phenotypic measures

Nursery rhymes (preschool). Parents answered whether they play pat-a-cake (i.e. a nursery rhyme where parent and children clap their hands together following the rhythm of the rhymes) or other clapping games with their child, representing an important developmental milestone[29]. Children's ability was assessed at 0.5 and 1.5 years of age using a 3-point Likert scale: "Yes does often", "Has only done once or twice", and "Has not done yet". Categorical scores were created aligning with developmental milestones[29]. At 0.5 years, the child was considered musically engaged

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if they had done the activity at least once or twice (1: "Yes does often" / "Has only done once or twice"), and non-musically engaged otherwise (0: "Has not done yet"). At 1.5 years, the child was considered musically engaged if they did it often (1: "Yes does often") and non-musically engaged otherwise (0: "Has only done once or twice"/"Has not done yet"), as typically developing children should be able to play nursery rhymes by one year[29].

Musicality-related measures (preschool and school-age). Parent reports of their child's ability to sing at least three songs, hum a tune, and clap in time with a musical beat were available at 5, 6 and 7 years using ALSPAC-specific questions assessing children's development, based on a 3-point Likert scale. Categorical scores were created for each measure representing whether the child was considered musically engaged (1: "Yes can do well"/ "Yes but not well") or not (0: "Has not yet done").

Social communication measures (school-age). Social communication measures were assessed by the parents using the Social and Communication Disorders Checklist (SCDC)[30] total score at ages 8, 11, 14 and 17 years. The SCDC is a 12-item questionnaire (3-point Likert scale; 1: "Not true", 2: "Quite/sometimes true", 3: "Very/often true") to be completed by parents about their children's social interaction and communication skills. The SCDC total score is a summation of the 12 items demonstrating high consistency (Cronbach's Alpha=0.86) and high reliability (0.84-0.93)[30].

Communication measures (school-age). Parents reported on children's communication skills at 10 years using seven subscales of the Children's Communication Checklist (CCC)[31]. The CCC is a 70-item questionnaire (3-point Likert scale, 1: "Certainly true", 2: "Somewhat true", 3: "Not true"). The subscales include (A)

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intelligibility and fluency, (B) syntax, (C) inappropriate initiation, (D) coherence, (E) stereotyped conversation, (F) use of conversational context, and (G) conversational rapport. In addition, the pragmatic communication score is created as a summary score using subscales C to G. CCC subscales have a moderate/high consistency (0.62-0.83) and high reliability (0.74-0.87)[31]. Within this study, we refer to subscales C and E as appropriate initiation and non-stereotyped conversation, respectively, to align with the direction of the effect (i.e. lower scores, more communication difficulties).

Verbal cognition-related measures (school-age). Due to recent findings of genetic overlap between language-related traits and musicality[19], we included measures of children's verbal abilities (verbal IQ) and phonological working memory (nonword repetition). Both scores were assessed at 9 years and measured with an abbreviated form of the Wechsler Intelligence Scale for Children (WISC-III)[32] and the Nonword Repetition Test (NWRT)[33], respectively (Supplementary Note 2).

Genetic information

Genotyping was performed using the Illumina HumanHap550 quad chip. Standard genetic quality control checks at the SNP and individual level were carried out in PLINK[34] (Supplementary Note 3). After quality control, our study comprised 8,226 unrelated children (51% males) of European genetic ancestry and 465,740 SNPs with high-quality direct genotyping data, which were imputed to the Haplotype Reference Consortium reference panel (version r1.1) using the Sanger Imputation Server (https://imputation.sanger.ac.uk).

Polygenic scores

Approach. Polygenic scores (PGS) are a weighted sum of alleles associated with a trait of interest that are carried by an individual[35]. A "discovery" GWAS of the trait of interest (here rhythmicity) is used to extract the respective weights for each genetic variant. The "target" sample (here ALSPAC) is used to calculate, for each individual, their genetic propensity score for the trait of interest based on the genetic variants they carry, and to run, across all individuals, an association analysis between such score and a set of phenotypes.

Discovery sample. In this study, we used GWAS summary statistics on self-reported beat synchronisation adjusted for sex, age and genetic quality control measures (hereafter referred to as rhythmicity)[18] from 23andMe Inc., including 606,825 individuals of European descent (91,5% controls, 64% females). Note that the original authors validated this self-reported rhythmicity measure using PGS and an independent experiment[18], and, additionally, this measure showed overlap with well-validated music tests in follow-up studies[23].

Target sample. To generate $PGS_{rhythmicity}$ in ALSPAC children, we extracted a set of common (minor allele frequency>1%) and well-imputed (imputation INFO score>0.8) HapMap 3 SNPs (N=985,350).

PGS calculation. $PGS_{rhythmicity}$ were computed using PRS-CS[36], a method that applies a continuous-shrinkage parameter to adjust the effect sizes of the genetic markers. Using these re-estimated effect sizes, PGSs were generated with PLINK[34] and, subsequently, Z-standardised. Note that PRS-CS does not require the selection of a p-value, as required for clumping and thresholding methods[36].

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Association analysis. Logistic (binary phenotypes) or linear (continuous phenotypes) regression models were used to test for the association of ALSPAC phenotypes with $PGS_{rhythmicity}$. Regression analyses were corrected for age, sex and the first ten ancestry-informative principal components. The variation explained by the $PGS_{rhythmicity}$ was expressed in terms of regression R^2 for continuous traits and, in analogy, *Nagelkerke*-R^2 for binary traits (Supplementary Note 4).

Multiple-testing threshold. We computed the effective number of phenotypes across the initial set of 25 phenotypes. We carried out matrix Spectral Decomposition[37], which identifies the number of independent phenotypes based on phenotypic correlations. This yielded a multiple-testing threshold of 2.5×10^{-3} (0.05/20 estimated independent phenotypes).

Identification of phenotypic factor structures

We model phenotypic relationships for traits associated with $PGS_{rhythmicity}$ (i.e. measures with $PGS_{rhythmicity}$ $p<0.05$) using a data-driven approach (Supplementary Note 5). To do so, first, we estimated the number of factors using principal component analysis based on the phenotypic correlation matrix. Second, we split the sample into two random halves, matched for sex and missingness patterns. Third, we fitted an exploratory factor analysis (EFA) to the first half of the sample (N=3,048). To approximate the EFA factor structure, we retained standardised EFA factor loadings (λ), capturing at least 1% of the phenotypic variation ($|\lambda|>0.1$). Fourth, the identified EFA structure was used to inform subsequent confirmatory factor analysis (CFA), fitted in the other half of the sample (N=3,053). CFA model fit was assessed using the comparative fit index (CFI), the Tucker–Lewis index (TLI), the Root Mean Square Error of Approximation (RMSEA) and the Standardised Root Mean Square Residual

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(SRMR) parameters (Supplementary Note 5). EFA and CFA models were fitted using both orthogonal (varimax) and oblique (oblimin) rotation in *lavaan* (R::lavaan,v0.6-14)[38].

To control for covariate effects, EFA and CFA were conducted with transformed phenotypes, adjusting for age, sex and the first ten ancestry-informative principal components (Supplementary Note 5). Note that joint analyses of multiple phenotypes within a factor analysis framework do not require adjusting for multiple-testing.

Genetic characterisation of phenotypic structures

We tested whether the correlation between phenotypic factors was attributable to shared genetic variation with $PGS_{rhythmicity}$ while keeping the identified CFA factor structure otherwise fixed. Specifically, we incorporated $PGS_{rhythmicity}$ into the CFA model structure by applying a framework analogous to mediation analysis (Supplementary Figure 1)[39]. Note that the indirect effect within a mediation framework will estimate the shared genetic effect between two phenotypic factors as captured by $PGS_{rhythmicity}$ (hereafter referred to as shared effect).

Adjustment for genetic confounding

We generated rhythmicity GWAS[18] summary statistics excluding genetic effects shared with the EA GWAS summary statistics[40] (rhythmicity-EA) by using a GWAS-by-subtraction framework[41]. GWAS-by-subtraction is an approach that fits a Cholesky model in genomic structural equation modelling[42] (R::genomicSEM, v0.0.5) based on GWAS summary statistics from two traits, in our case, rhythmicity and EA (Supplementary Figure 2). Within the EA GWAS, EA was measured in years of education adjusted for sex, year of birth, their interaction and genetic quality control

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234 measures[40]. To avoid sample overlap , ALSPAC and 23andMe individuals were

235 excluded from EA summary statistics (personal communication with A. Okbay)[40].

236 Using the derived $GWAS_{rhythmicity-EA}$, we created $PGS_{rhythmicity-EA}$. Following guidelines

237 by the original authors[41], the effective sample size of the $GWAS_{rhythmicity-EA}$ was

238 estimated as N=143,800.

Results

Study design

241   To understand the relationships between preschool musicality and school-age

242 (social) communication abilities, we studied up to 6,737 unrelated children of

243 European descent from the ALSPAC cohort adopting a two-stage research design

244 (Figure 1). Within the first stage, we identify measures that genetically overlap with

245 $PGS_{rhythmicity}$, including validation of ALSPAC-specific musicality measures. Within the

246 second stage, we model the phenotypic structure across $PGS_{rhythmicity}$-associated

247 measures ($PGS_{rhythmicity}$ $p<0.05$), focussing on relationships between preschool

248 musicality and school-age communication as captured by the shared polygenetic load

249 with $PGS_{rhythmicity}$.

250   Our analyses comprised a total of 25 measures (Table 1) assessed during

251 preschool (6 months to 5 years, 5 measures) and school-age (6 to 17 years, 20

252 measures) years. Preschool measures include two infant ALSPAC-specific nursery

253 rhyme measures and three early childhood ALSPAC-specific musicality measures. Six

254 ALSPAC-specific school-age musicality measures were screened but showed ceiling

255 effects (low cell counts) as the majority of children are already musically engaged at

256 this developmental stage (Table 1). School-age communication measures comprised

257   four SCDC social communication measures across childhood and adolescence, and

258   eight mid-childhood CCC communication measures. Additionally, we studied school-

259   age verbal cognition-related measures linked to rhythmicity, i.e. WISC-III verbal IQ and

260   NWRT non-word repetition scores, capturing known links[19].

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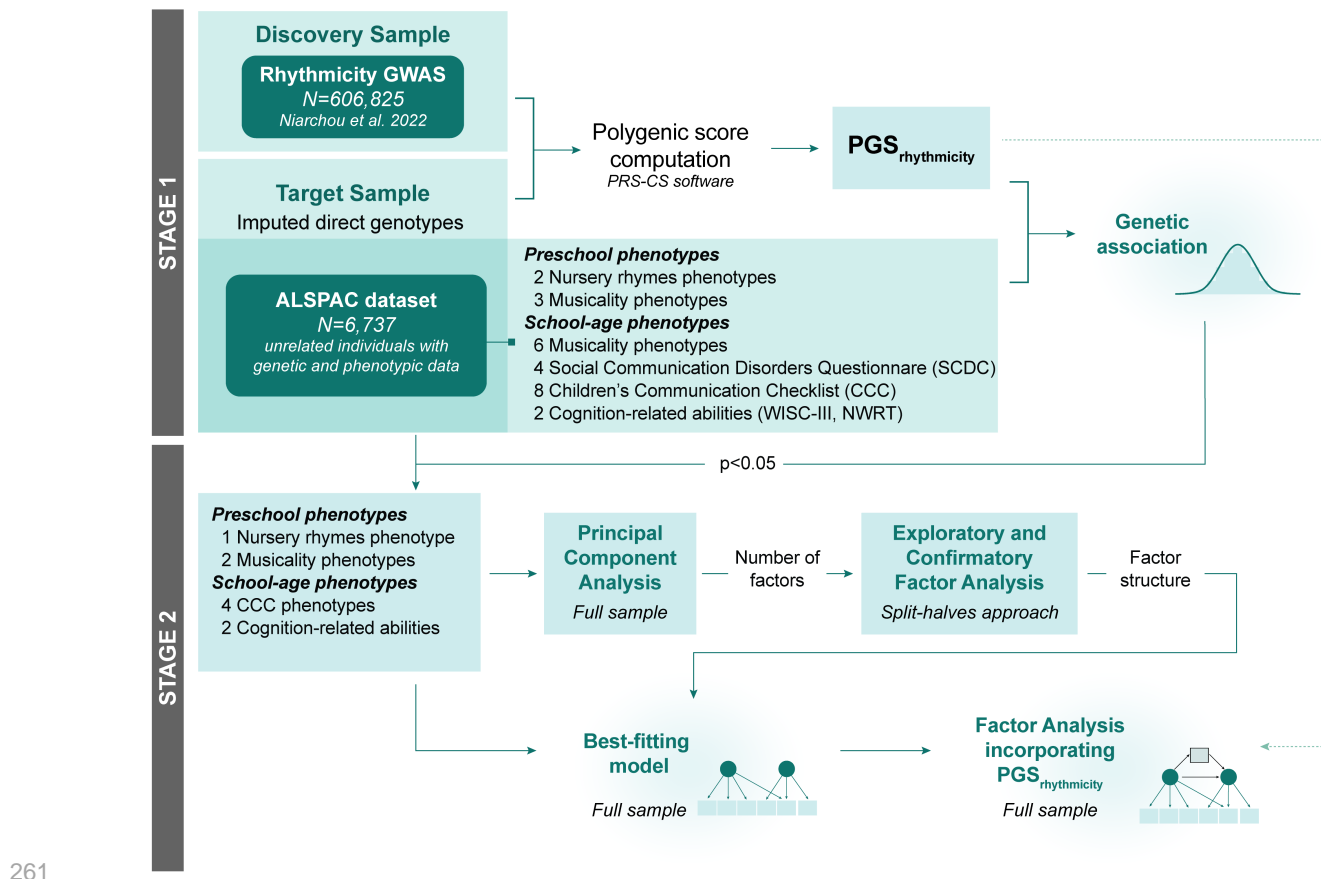
Figure 1. Study design. Analyses were carried out in 6,737 unrelated children of European descent from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort adopting a two-stage research design. In Stage 1, we constructed polygenic scores (PGS) for self-reported beat synchronisation[18] (PGS$_{rhythmicity}$) on ALSPAC individuals. Within Stage 2, we explored the phenotypic structure across phenotypes with PGS$_{rhythmicity}$ $p<0.05$. To do so, we computed principal component analysis (PCA) and exploratory and confirmatory factor analysis, as described in the Methods. Finally, we mapped the PGS$_{rhythmicity}$ to the factor structure, using methods analogous to mediation analysis.

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271   Table 1. Descriptive information on the ALSPAC measures included in this study.

Variable	N	Males / Females	Yes/No	Mean age (SD)
Preschool nursery rhymes				
Nursery rhymes 0.5Y	6737	3426/3311	4437/2300	0.52 (0.05)
Nursery rhymes 1.5Y	6696	3434/3262	862/5834	1.51 (0.04)
Preschool musicality phenotypes				
Can sing at least 3 songs 5Y	6043	3098/2945	89/5954	4.78 (0.07)
Can hum a tune 5Y	6022	3091/2931	241/5781	4.78 (0.07)
Can clap to a beat 5Y	5968	3057/2911	403/5565	4.78 (0.07)
School-age musicality phenotypes (excluded from structural modelling)				
Can sing at least 3 songs 6Y	5676	2893/2783	43/5633	5.79 (0.08)
Can hum a tune 6Y	5674	2893/2781	108/5566	5.79 (0.08)
Can clap to a beat 6Y	5640	2872/2768	141/5499	5.79 (0.08)
Can sing at least 3 songs 7Y	5531	2815/2716	42/5489	6.78 (0.09)
Can hum a tune 7Y	5527	2817/2710	53/5474	6.78 (0.09)
Can clap to a beat 7Y	5498	2804/2694	68/5430	6.78 (0.09)
Variable	N	Males / Females	Mean score (SD)	Mean age (SD)
School-age communication phenotypes (CCC)				
Intelligibility and fluency 10Y	5,645	2850/2795	35.31 (1.88)	9.64 (0.10)
Syntax 10Y	5,628	2841/2787	31.84 (0.57)	9.64 (0.10)
Appropriate initiation 10Y	5,623	2837/2786	26.75 (2.40)	9.64 (0.10)
Coherence 10Y	5,628	2841/2787	34.85 (1.99)	9.64 (0.10)
Non-stereotyped conversation 10Y	5,606	2829/2777	26.87 (2.47)	9.64 (0.10)
Use of conversational context 10Y	5,549	2803/2746	29.84 (2.09)	9.64 (0.10)
Conversational rapport 10Y	5,549	2802/2747	32.51 (1.95)	9.64 (0.10)
Pragmatic score 10Y	5,524	2789/2735	150.86 (7.76)	9.64 (0.10)
School-age social-communication phenotypes (SCDC)				
SCDC score 8Y	5,486	2814/2672	2.82 (3.70)	7.64 (0.11)
SCDC score 11Y	5,383	2710/2673	2.34 (3.52)	10.71 (0.08)
SCDC score 14Y	5,009	2501/2508	2.53 (3.57)	13.89 (0.11)
SCDC score 17Y	4,169	2020/2149	2.84 (3.78)	16.84 (0.36)
School-age cognition-related abilities				
Nonword repetition 9Y (NWRT)	5,398	2693/2705	7.26 (2.51)	8.62 (0.26)
Verbal IQ 9Y (WISC-III)	5,378	2671/2707	107.98 (16.68)	8.62 (0.26)

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Polygenic association analysis

During the first stage of our study, we screened the 25 phenotypes (Table 1) for polygenic overlap with rhythmicity (Figure 1). We found evidence for an association between $PGS_{rhythmicity}$ and 11 measures at the nominal level ($p<0.05$, Figure 2, Supplementary Table 1), five of which passed the multiple-testing threshold ($p<0.0025$, Figure 2). Specifically, we observed positive links between $PGS_{rhythmicity}$ and playing nursery rhymes at 6 months ($\beta=0.097(SE=0.026), p=1.9 \times 10^{-4}$) and between $PGS_{rhythmicity}$ and preschool musicality-related abilities at 5 years, including humming a tune ($\beta=0.23(SE=0.067), p=5.7 \times 10^{-4}$) and clapping to a beat ($\beta=0.22(SE=0.053), p=2.2 \times 10^{-5}$). The identified genetic overlap with musicality-related measures confirms previous findings[18] and extends known associations between $PGS_{rhythmicity}$ and music engagement to an earlier developmental window. Genetic associations with $PGS_{rhythmicity}$ were also observed for school-age communication abilities as measured by four CCC subscales at 10 years: intelligibility and fluency ($\beta=0.12(SE=0.025), p=1.3 \times 10^{-6}$), syntax ($\beta=0.022(SE=0.0075), p=3.2 \times 10^{-3}$), appropriate initiation ($\beta=-0.068(SE=0.032), p=3.2 \times 10^{-2}$) and conversational rapport ($\beta=0.067(SE=0.026), p=9.3 \times 10^{-3}$), although only the first one passed the multiple-testing threshold. The two school-age cognition-related measures, verbal IQ ($\beta=-0.55(SE=0.22), p=1.5 \times 10^{-2}$) and nonword repetition ($\beta=0.24(SE=0.034), p=5.1 \times 10^{-13}$) also showed overlap with $PGS_{rhythmicity}$, although only the latter passed the multiple-testing threshold. The overlap between rhythmicity and nonword repetition confirms, using individual-level genetic data, previously reported findings based on summary statistics[19] (Figure 2, Supplementary Table 1). Overall, the proportion of variance explained by $PGS_{rhythmicity}$ was modest (~0.4-0.96%), yet in line with other studies of complex traits[43]. In contrast to speech- and language-related aspects of

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communication, there was little evidence for overlap between PGS$_{rhythmicity}$ and social communication abilities (as measured with the SCDC) or the CCC subscales that are related to the use of language in a social context (Figure 2).
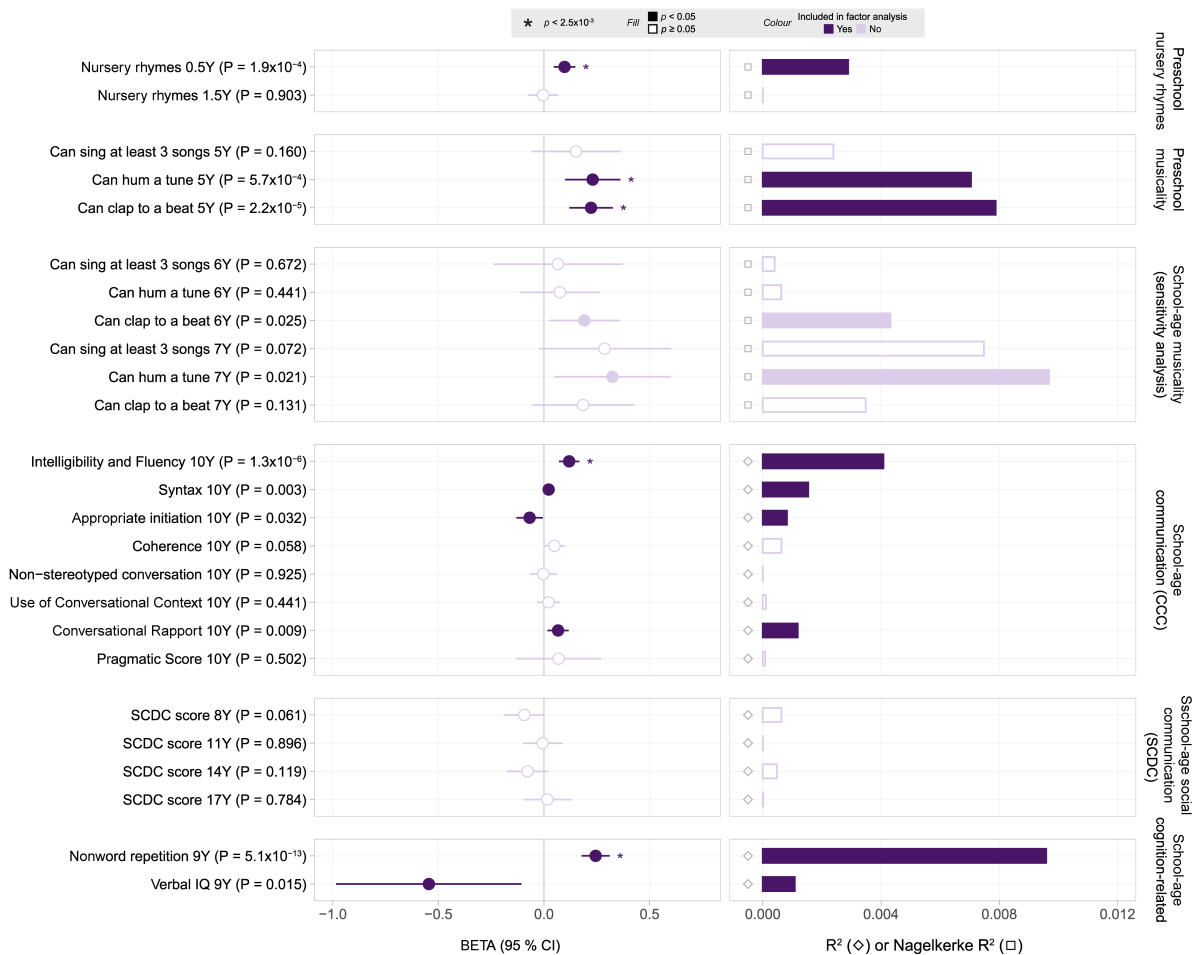
Figure 2. Effects of polygenic association with rhythmicity on ALSPAC measures. Beta estimates are shown as circles with their corresponding 95% confidence intervals. Variance explained for each phenotype is shown as bars and expressed as the regression R^2 for continuous traits (represented by an empty grey diamond) and, in analogy, by *Nagelkerke*-R^2 for binary traits (represented by an empty grey square). Filled circles/bars and empty circles/bars represent phenotypes with an association with PGS$_{rhythmicity}$ of p<0.05 and p≥0.05, respectively. Estimates are shown in dark purple if they were included in subsequent factor analysis and in light purple otherwise. If a phenotype passed multiple-testing threshold of 2.5x10^{-3} this was indicated with an asterisk in the beta coefficient. A full table with the values for this analysis is available in Supplementary Table 1. Abbreviations: SCDC (Social Communication Difficulties Checklist), CCC (Children's Communication Checklist).

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Together, these findings suggest that genetic influences underlying rhythmicity are shared with preschool musicality and school-age cognition, working memory and speech-related communication abilities, consistent with overarching aetiological mechanisms.

Identification and genetic characterisation of phenotypic structures

During the second stage of our study design, we studied the phenotypic structure across measures sharing a polygenic load with rhythmicity ($PGS_{rhythmicity}$ $p<0.05$), conducting principal component and factor analyses (Figure 1). In particular, we aim to understand whether there is evidence for a developmental pathway linking preschool musicality to school-age communication through genes shared with rhythmicity. Note that we specifically selected preschool musicality measures, as school-age musicality measures showed ceiling effects and might be affected by reverse causation due to schooling[28].

Firstly, we modelled the relationships across $PGS_{rhythmicity}$-associated measures adopting a data-driven approach (Methods). We identified three phenotypic dimensions using principal component analysis, as reflected by three eigenvalues above one (Supplementary Figure 3). We, subsequently, fitted a three-factor EFA model with and without correlated factors and confirmed the identified structure in CFA using a split-halves approach (Figure 1). The identified three-factor CFA model, allowing for correlation between factors, showed a good model fit in the full sample (CFI=0.97, TLI=0.95, RMSEA=0.03, SRMR=0.02, Figure 3A). A preschool musicality factor (F1) described phenotypic variation of preschool ability to clap to a beat ($\lambda=0.55(SE=0.041)$) and hum a tune ($\lambda=0.52(SE=0.039)$) at 5 years. The school-age verbal cognition factor (F2) captured variation within nonword repetition

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(λ=0.61(SE=0.022)) and verbal IQ (λ=0.64(SE=0.022)) at 9 years. A school-age communication factor (F3) explained variation across three of the CCC subscales at 10 years: intelligibility and fluency (λ=0.57(SE=0.019)), syntax (λ=0.58(SE=0.019)) and conversational rapport (λ=0.39(SE=0.018)). Inter-factor correlations with F1 were modest ($r_{F1,F2}$=0.21(SE=0.028), $r_{F1,F3}$=0.27(SE=0.029)), while the correlation between F2 and F3 was strong ($r_{F2,F3}$=0.57(SE=0.024)). Thus, $PGS_{rhythmicity}$-associated measures are captured by three overarching phenotypic dimensions and, consequently, underlying association patterns might be shared across these dimensions, too.

Secondly, following the identification of phenotypic structure across these $PGS_{rhythmicity}$-associated measures, we examined whether polygenic load for $PGS_{rhythmicity}$ can capture overarching factor relationships, accounting for overlap with verbal cognition and phonological working memory (Supplementary Table 1, Figure 2). Adopting an analytical framework analogous to mediation analysis (Methods), we dissected the relationships between the three phenotypic factors (F1, F2 and F3) and modelled association effects shared with and without $PGS_{rhythmicity}$. Specifically, we dissected the association of preschool musicality (F1) with both school-age verbal cognition (F2) and school-age communication (F3), as captured by polygenic influences underlying rhythmicity (Figure 3B). After adding $PGS_{rhythmicity}$ to the CFA model structure, the model fitted the data similarly well (CFI=0.94, TLI=0.90, RMSEA=0.03, SRMR=0.02). Note that the factor structure of the model remained otherwise unchanged, such that estimates of the correlation between school-age verbal cognition (F2) and school-age communication (F3), as well as all other factor loadings, were virtually identical (Figure 3A vs Figure 3B).
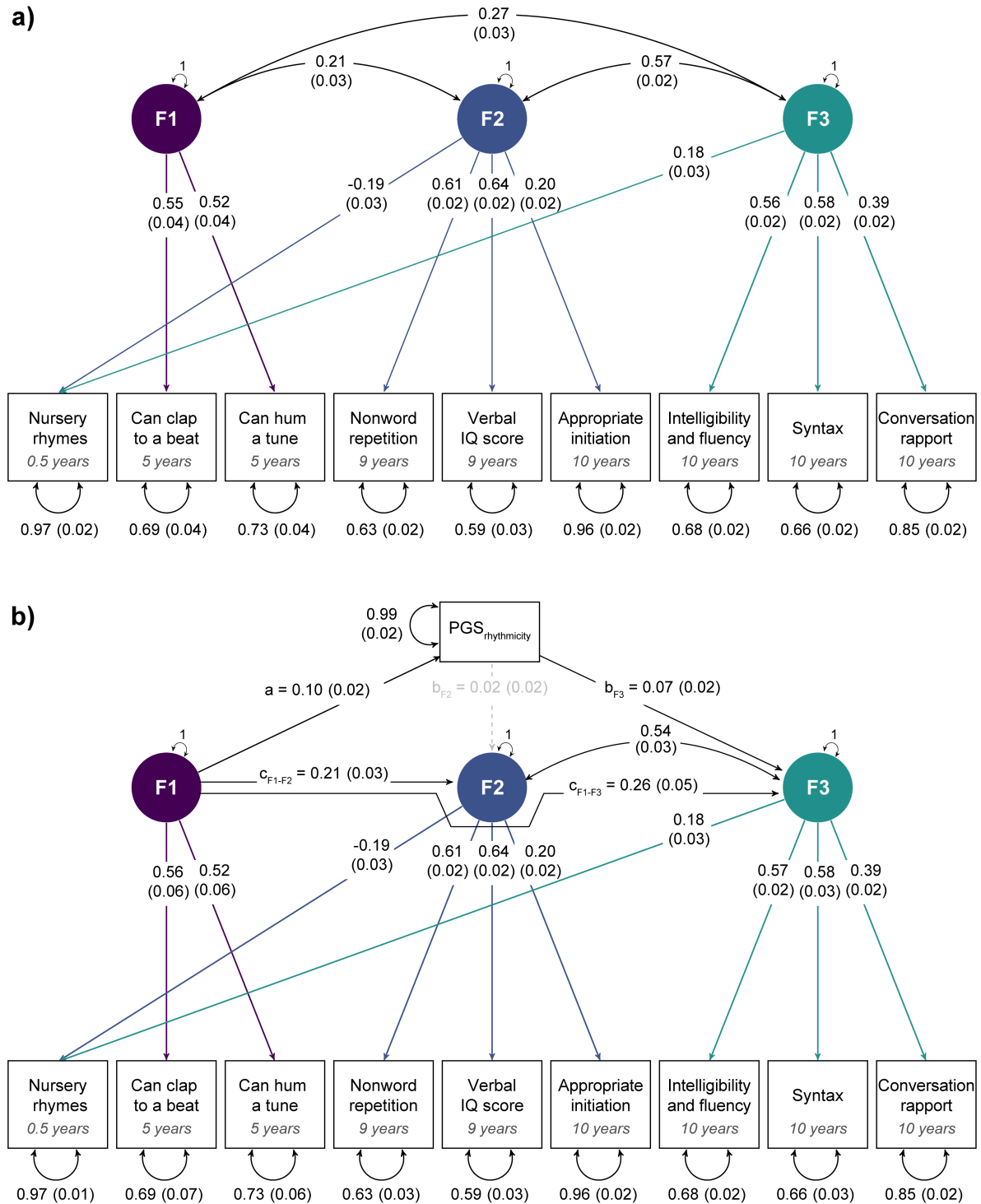
Figure 3. Phenotypic relationships between preschool musicality, school-age cognition-related skills and communication skills. a) Confirmatory factor model of phenotypes sharing genetic links with $PGS_{rhythmicity}$. Estimates are shown with their corresponding SEs. Observed measures are represented by squares and latent variables by circles. Coloured single-headed arrows define factor loadings with

366 p≤0.05. Double-headed black arrows represent the variance of each phenotype and

367 factor correlations. The CFA model provided an optimal model fit (CFI=0.97, TLI=0.95,

368 RMSEA=0.03, SRMR=0.02). **b)** Genetic characterisation of phenotypic relationships

369 between F1 on F2 and F3 explained by shared genetic links with $PGS_{rhythmicity}$.

370 Estimates are shown with their corresponding SEs. Observed measures are

371 represented by squares and latent variables by circles. Coloured single-headed

372 arrows define factor loadings with p≤0.05. Double-headed black arrows represent the

373 variance of each phenotype and factor correlations. Grey dotted and black solid single-

374 headed arrows define relationships between factors and with $PGS_{rhythmicity}$ with p>0.05

375 and p≤0.05, respectively. The shared genetic effect between F1 and F3, as captured

376 by $PGS_{rhythmicity}$, is estimated as $a*b_{F3}$ and the total effect between F1 and F3 as $a*b_{F3}$

377 + c_{F1-F3}. The shared genetic effect between F1 and F2, as captured by $PGS_{rhythmicity}$, is

378 estimated as $a* b_{F2}$ and the total effect as $a* b_{F2} + c_{F1-F2}$.

379 Our analyses demonstrated that the association between preschool musicality skills

380 (F1) and school-age communication skills (F3) (total effect:

381 β=0.27(SE=0.047),p=1.59x10^{-9}) was partially accounted for by $PGS_{rhythmicity}$ (shared

382 effect: β=0.0065(SE=0.0021),p=1.58x10^{-3}, Supplementary Table 2). In contrast, there

383 was little evidence that genetic variation shared with $PGS_{rhythmicity}$ contributes to the

384 association between preschool musicality (F1) and school-age verbal cognition (F2)

385 (shared effect: β=0.0015 (SE=0.0022), p=0.49; total effect: β=0.21(SE=0.033),

386 p=2.35x10^{-11}). Within the structural model, all analyses were adjusted for each other.

387 These association patterns show that preschool musicality is linked to the

388 development of cognition- versus communication-related abilities, as captured by

389 genetic load contributing to rhythmicity in large genome-wide studies[18]. As the

390 proportion of explained phenotypic variation by $PGS_{rhythmicity}$ for each phenotype,

391 consistent with other studies[44], was small (Figure 2), investigating the phenotypic

structure across $PGS_{rhythmicity}$-associated measures using structural models increases the power of our study.

Adjustment for genetic confounding

Families with higher socioeconomic status (SES) may have easier access to music training, and there is evidence for an association between musicality and EA[45], a proxy of SES with genetic contributions[40]. Consequently, we performed additional analyses to rule out genetic confounding by EA that may, potentially, affect links between preschool musicality and school-age social communication. We applied GWAS-by-subtraction techniques[41] to create $PGS_{rhythmicity-EA}$ (Methods, Supplementary Figure 2), thereby removing genetic variance from the rhythmicity GWAS shared with the EA, and repeated the PGS and structural equation modelling analyses as described above.

Association analysis using $PGS_{rhythmicity-EA}$ (Stage 1, Figure 1) identified a similar pattern of genetic overlap across the studied measures, compared to analyses using $PGS_{rhythmicity}$, especially for associations passing the multiple-testing threshold (Supplementary Figure 4, Supplementary Table 3). In addition, the phenotypic factor structures and association patterns remained robust (Supplementary Figure 5, Supplementary Table 4), suggesting that our findings are unlikely to reflect genetic effects shared with educational attainment, consistent with previous findings[18].

Thus, genetic links between latent preschool musicality (F1) and school-age communication (F3), but not verbal cognition (F2), are partially attributable to genetic variation underlying rhythmicity(beat synchronisation)[18], independent of genetic variation contributing to EA.

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Discussion

Investigating a UK population-based sample of unrelated children, this study showed that (i) preschool musicality and school-age communication abilities share genetic links with polygenic load for rhythmicity and that (ii) this overlap can partially explain phenotypic links between preschool musicality and school-age communication in population-based cohorts. These findings are in support of aetiological mechanisms, where preschool musical engagement, as captured by genes underlying rhythmicity, contributes to children's school-age communication abilities during mid-childhood, above and beyond influences underlying general cognition.

The association of $PGS_{rhythmicity}$ with early musicality measures spanning 6 months to 5 years (based on parent reports), including playing nursery rhymes at 6 months, clapping to a beat and humming a tune at 5 years, demonstrates that the genetic underpinnings of being able to clap to a beat in adulthood are transferable across the lifespan. Moreover, the association with $PGS_{rhythmicity}$ validates these ALSPAC measures phenotypically, given the previous link of $PGS_{rhythmicity}$ with objective tests of rhythm ability[23].

The observed associations between $PGS_{rhythmicity}$ and language- and communication-related phenotypes converge with previous studies reporting a phenotypic association between spoken language and rhythmic abilities in children[14], extending them to communication abilities. Rhythm perception and production have been previously identified as predictors of phonological awareness, while melody perception has been linked to grammar acquisition[46]. Thus, our results are in line with two postulated frameworks the *Musical Abilities, Pleiotropy, Language, and*

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Environment (MAPLE) framework[14] and the *Atypical Rhythm Risk Hypothesis*[25], which discuss the potential role of rhythmicity in language- and communication-related traits.

The correlation between the factors of preschool musicality and school-age communication was partially accounted for by shared genetic effects with $PGS_{rhythmicity}$. Consistently, impaired rhythmic skills and timing have been highlighted as an early predictor of atypical developmental cascades[47] that may contribute to later language and communication difficulties. Given that phenotypic relationships are largely similar to genetic relationships[48], our findings also strengthen the support for musical, and in particular rhythm, training during early childhood as an intervention to improve school-age speech- and syntactic language abilities[49,50]. This might be particularly relevant for children with fluency-related disorders, characterised by speech-flow interruptions[2].

The factor for preschool musicality was also correlated with a school-age cognition-related factor. However, in contrast to school-age communication, there was little evidence for an association through shared genetic effects with $PGS_{rhythmicity}$. Given comparable power (i.e. similar sample numbers) and cohort design, aetiological links between preschool musicality and school-age communication skills might be distinct from processes shaping working memory and cognitive development. However, larger samples are required to show a difference in effect, based on non-overlapping 95% confidence intervals.

This study has multiple strengths. First, we introduced a multivariate modelling framework combining PGS analyses with mediation and factor analytic techniques. This approach allows us to compare and combine $PGS_{rhythmicity}$-related associations across a wide range of communication abilities. Hence, our findings based on

structural models enhance the understanding of relationships across large phenotypic dimensions beyond individual PGS association analyses. Second, we characterise and validate the covariance structure between identified phenotypic factors by disentangling shared polygenic load with rhythmicity. In particular, this PGS-based study draws power from the large rhythmicity GWAS analysis[18], increasing evidence for the specificity of the identified association between preschool musicality and school-age speech-related communication abilities. Still, the presented PGS association analyses need replication in an independent population-based cohort, which is challenging given the scarcity of longitudinal birth cohorts with genomic data and both (social) communication and musicality phenotypes, especially for individuals of non-European ancestry. Third, the longitudinal order phenotypes, split across preschool and school-age developmental windows, makes reverse causation unlikely. Fourth, genetic links between preschool musicality and school-age speech-related communication are robust to genetic confounding and independent of genetic effects related to EA. Thus, the link between preschool musicality and school-age speech-related communication is highly consistent with underlying causal mechanisms.

Nonetheless, our work has several limitations. First, ALSPAC, like other longitudinal cohorts, is plagued by loss to follow-up, and, consequently, findings might be affected by attrition bias. However, as presented findings are independent of genetic factors contributing to EA in the studied children, such bias is less likely. Second, association analyses of individual measures with $PGS_{rhythmicity}$ were conducted using untransformed phenotypes as outcomes, while factor analytic approaches were carried out with transformed measures (adjusting different outcomes for different covariates). Consequently, we cannot exclude transformation bias, although findings were highly consistent across both stages. Third, the lack of association between

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$PGS_{rhythmicity}$ and social-communication phenotypes may reflect a lack of power. However, speech-related and social communication phenotypes were both investigated with a comparable study design and, for CCC measures, also questionnaire design, rendering power an unlikely explanation. Instead, differences in genetic association profiles may pinpoint differences in aetiological mechanisms. Nonetheless, given the broad scope of human musicality[8], there might be genetic links between social communication and musicality beyond rhythm production and perception (as captured by beat synchronisation). Likewise, other aspects of human social behaviour (such as social engagement or social reward, not included in this study) may reveal different association patterns. Fourth, in contrast to preschool scores, analyses of comparable school-age musicality measures revealed effect attenuation. This is consistent with lower study power due to ceiling effects, attrition and/or an increase of non-genetic influences due to a shared school environment. The GWAS of rhythmicity that we investigated in this work is, to date, the largest genetic study of a musicality phenotype. There are ongoing GWAS efforts within the Musicality Genomics Consortium (https://www.mcg.uva.nl/musicgens/), studying other musicality phenotypes, that will become available during the next years. Future research should consider the longitudinal collection of a wide range of musicality and communication phenotypes in powerful multi-ancestry samples to refine and characterise the biological processes underlying the reported findings.

In conclusion, we show that preschool musicality and school-age speech- and syntax-related communication abilities (i) can be predicted by polygenic load for rhythmicity and that, within a developmental context, preschool musicality and speech- and syntax-related communication are linked through shared genetic influences that are (ii) partially attributable to rhythmicity and (iii) independent of cognition and working

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memory. Consequently, preschool musical engagement involving rhythmic skills may represent a genetic precursor of school-age speech-related communication skills above and beyond general cognition. Our findings strengthen the support for music-related preschool intervention programmes for children with intelligibility-, fluency- and syntax-related communication problems.

Data availability

The data used are available through a fully searchable data dictionary (http://www.bristol.ac.uk/alspac/researchers/our-data/). Access to ALSPAC data can be obtained as described within the ALSPAC data access policy (http://www.bristol.ac.uk/alspac/researchers/access/).

Code availability

This study used openly available software. Specifically, PLINK (PLINK v1.9, https://www.cog-genomics.org/plink/1.9/), PRScs (https://github.com/getian107/PRScs). Analyses were mainly performed in R (version 4.1.1) using the following R packages: lavaan (v0.6-14), genomicSEM (v0.0.5), rcompanion (v2.4.30), dplyr (v1.0.8), nFactors (v2.4.1), Matrix (v1.4-1). Requests for scripts or other analysis details can be sent via email to the corresponding authors

Acknowledgements

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Author contributions

LDH performed the main analysis and BSP supervised the research. BSP. developed the study concept and, LDH contributed to the study design. LDH, EV, JRV and CF analysed the genetic and phenotypic data. LDH and BSP wrote the manuscript. LDH, EV, AO, JRV, CF, ML, SEF, RLG and BSP read and commented on the manuscript.

Competing interests

The authors declare no competing interests.

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