Individual Differences in Rhythm and Grammar Phenotypes and Potential Underlying Genetic Influences

By

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LIST OF ABBREVIATIONS

GWAS	Genome-Wide Association Study
GCTA	Genome-Wide Complex Trait Analysis
DLD	Developmental Language Disorder
ADHD	Attention Deficit Hyperactivity Disorder
SLI	Specific Language Impairment
SLP	Speech Language Pathologist
PTONI	Primary Test of Non-Verbal Intelligence
TOLD-P:4	Test of Language Development 4th Edition
TEGI	Test of Early Grammatical Impairment
SI	Sentence Imitation
PV	Picture Vocabulary
MC	Morphological Completion
SPELT-3	Structured Photographic Expressive Language Test-3
BBA	Beat Based Advantage
KABC-II	Kaufman Assessment Battery for Children 2nd Edition
SEM	Structured Equation Modelling
MES	Musical Experience Score
SES	Socio-economic Status
TD	Typically Developing
PGS	Polygenic Score
PGS-R	Rhythm Polygenic Score
VANTAGE	Vanderbilt Technologies for Advanced Genomics
QC	Quality Control
SNP	Single Nucleotide Polymorphism
PC	Principle Components
EHR	Electronic Health Record
APT-DLD	Automated Phenotyping Tool for identifying DLD
SD	Synthetic Derivative
GREML	Genome-based Restricted Maximum Likelihood
GRM	Genetic Relationship Matrix
ICD	International Classification of Diseases
eMERGE	Electronic Medical Records and Genomics

Chapter 1

Introduction

The Human Experience of Communication.

Communication provides an outlet for expressing what one has experienced and perceived, and is important for transmitting information between entities, especially within social animals like humans (Hauser, 1996). In human societies, language and music may utilize different symbols (speech vs notes), but they are both ubiquitous forms of acoustic communication (Ujfalussy, 1993). In the speaking world, we are familiar with using language as a mode of getting information across, much like this document! Similarly, music has also been central to several socio-cultural forms of communication like drummed languages and whistled languages (Meyer, 2015; Seifart et al., 2018; Tang, 2007); and has been shown to aid in several forms of therapy (Aalbers et al., 2017; Geist et al., 2008; R. L. Gordon, Fehd, et al., 2015).

Rhythm: The Intersection of Music and Language.

One parameter that plays a role in effective expression in both music and language is rhythm (Jackendoff, 2009; Molino, 2000; Patel, 2003). Rhythm is a pattern of sounds, that in music induces a regular pulse (Patel, 2003). The perception of regular beat and rhythm are important for both music and language (Besson & Schön, 2012; Slevc, 2012). It is the rhythm that distinguishes a waltz from a foxtrot, or a peppy dance number from a romantic ballad.

In spoken language, acoustic signals, like stress, intonation, loudness, phrasal pauses, and pitch are perceived as rhythmic and collectively contribute to what is known as prosody (Fitch, 2013; Kotz et al., 2018), though prosodic rhythm may not necessarily adhere to the isochronous meter we usually perceive in musical rhythms (Brown et al., 2017; Nolan & Jeon, 2014). These prosodic cues

in spoken language, (much like musical rhythm) help resolve ambiguities, and provide vital information such as context, emotion, and tone (Besson & Schön, 2012; Bryant, 2010; Hellbernd & Sammler, 2016; Slevc, 2012). Changes in prosody, conveys information about social context, tone, emphasis, and nuanced emotional states (Coutinho & Dibben, 2013; Tzeng et al., 2018). Awareness of the prosody of a language, has been shown to be present at birth (Nazzi et al., 1998) and used by children as young as 6 months old to distinguish between two languages that follow inherently different prosodic rules (Nazzi et al., 2000). Toddlers are sensitive to prosodic changes (Soderstrom et al., 2003), and altering the prosody of sentences affects grammatical processing (Schmidt-Kassow & Kotz, 2009). Moreover, prosodic cues have been shown to be important in helping toddlers acquire the meaning of novel words in relation to their syntactic use (de Carvalho et al., 2017, 2019), and sensitivity to prosody also predicts children's reading ability (Holliman et al., 2010). The reliance on prosodic cues is most evident when processing complex sentences (i.e., sentences with multiple clauses), since it is prosodic cues like pauses, lengthening of prosodic boundaries, and changes in intonation that aid our ability to parse information from such sentences (Frazier et al., 2006; Hawthorne & Gerken, 2014).

Given that 'rhythm' is a feature that can be perceived in both music and language, it is intriguing to consider whether there is a domain general effect of rhythm processing on both music and language. That is people who are sensitive to rhythm overall, show increased performance on both musical tasks and language tasks, indicating an overlap in processing of musical rhythms and complex syntax (Fedorenko et al., 2009). This ability to leverage rhythm would prove useful for effective processing of music and language, since both musical rhythm and grammar, particularly grammatical syntax, follow a temporal hierarchy that unfolds over time (Asano et al., 2021). By meta-analysing neural imaging studies Heard and Lee (2020) demonstrated that regions of the brain involved in hierarchical processing (the left supplementary motor area, left inferior frontal gyrus and

the bilateral insula), are utilised during musical rhythm and syntax processing tasks. Neural correlates of rhythm entrainment have also been shown to predict children's expressive grammar abilities (Persici et al., in revision), and conversely people with amusia were shown to struggle with grammatical syntax processing (Sun et al., 2018). Using behavioural approaches to fully explore the relationship between musical rhythm and grammar will provide much needed insight into the association between musical rhythm sensitivity and grammatical syntax processing, at the phenotypic level, which can then be leveraged to understand the underlying biology of this association.

Phenotypic Correlations between Musical Rhythm and Grammar.

There is growing evidence in the literature which shows that measures of music rhythm perception are correlated with individual differences in performance on linguistic tasks. Musicians and children with musical training have demonstrated heightened ability to distinguish similar sounding syllables in speech (Chobert et al., 2014; Strait et al., 2014, 2015), enhanced reading skills, and pitch discrimination (Moreno et al., 2009) compared to children without musical training. A study by Lagrois (2019) indicated that adults who exhibit less accurate musical synchronization also find it hard to identify beats in speech and song. Lundetræ and Thomson (2018) have also shown that literacy skills concerning reading and grammar at Grade 1 (6 years old) were positively correlated with their performance on a rhythmic tapping task. Another study from 2019 showed that performance on a rhythm perception task was positively correlated with performance on a sentence repetition task (Politimou et al., 2019). More accurate synchronization to beat in pre-schoolers (4-year-olds) was positively correlated to their reading skills (Woodruff Carr et al., 2014). Findings from our lab have further bolstered rhythm-grammar links by demonstrating robust associations between rhythm perception and grammar. Gordon, Shivers et al. (2015) showed that musical rhythm is positively correlated with expressive grammar, and this association is maintained even after

controlling for IQ and socio-economic status, and this finding was expanded with observations that musical rhythm sensitivity is correlated with expressive complex syntax (R. L. Gordon, Jacobs, et al., 2015).

Of note, studies have also found that actively listening to regular rhythms improves performance on tasks measuring phonological accuracy and grammatical judgement (Cason et al., 2015; Chern et al., 2018; Ladányi et al., 2021). Auditory stimulation with rhythmic patterns has also been shown to aid in speech production in adults (Falk et al., 2017; Zhang & Zhang, 2019). Rhythmic priming studies which involve temporary improvement grammar task performance, like the ones listed above, show rhythm-grammar correlations at the trait level, while cohort studies that look at individual differences in rhythm sensitivity and grammar abilities (Y. S. Lee et al., 2020; Swaminathan & Schellenberg, 2019), demonstrate stable, state-level correlations. Complementary evidence from both types of studies further proves that there is a deeper biological influence tying musical rhythm sensitivity and grammar together.

Genetic Influences Underlying Rhythm and Grammar Phenotypes.

Throughout plant, animal and insect evolution, phenotypic correlations have been proven to be markers of underlying genotypic correlations – that is when two phenotypes co-occur, there is a higher chance that the genes influencing those two phenotypes are also correlated (Cheverud, 1988). In the biological field this is known as Cheverud's conjecture and has been successfully demonstrated in the animal kingdom through an experimental study in grasshoppers (Roff, 1995), and also in plants using a meta-analytic approach (Waitt & Levin, 1998).

In humans, studying genetic correlations tends to involve sophisticated statistical approaches, because i. the human genome is large, and ii. most human traits are complex traits, i.e., they are influenced by several genes. It was only after the advent of statistical genetic methods like

genome wide association studies (GWAS), that research into common complex human traits was made possible. Briefly, GWAS involves analysis of the overall effect of > 100,000 commonly occurring genetic variants across the genome, to identify those variants that are associated with a phenotype of interest (Uffelmann et al., 2021). Over the past 15 years, thousands of GWAS' have been conducted on hundreds of phenotypes of interest, in millions of people. This collection of data is extremely valuable for meta-analytic approaches such as the one used by Sodini et al., (2018), to demonstrate the validity of Cheverud's conjecture in human traits. This study leveraged large-scale GWAS summary statistics for several traits from the UK Biobank, calculated genetic correlations between traits, and showed that these genetic correlations could predict phenotypic correlations of those same traits in an independent sample. Subsequent findings by Watanabe et al. (2019) confirm that substantial pleiotropy is common across a large number of complex traits.

With the understanding that music rhythm and grammar skills are phenotypically correlated, one possible reason for this observed association might lie in shared genetic architecture or pleiotropy between these two traits (Ladányi et al., 2020). Pleiotropy occurs when there is an overlap between genetic variants and genes that influence two traits, in our case musical rhythm and language phenotypes. That is and overlapping set of genes are responsible for driving two different phenotype and are the reason why the traits show phenotypic associations. The effect of the shared genetic architecture can be exerted via neural endophenotypes like neuro-biological signalling or developmental cascades, and neural pathways that are responsible for processing both language and musical rhythm (Nayak et al., under review). Thus, studying the underlying genetics of musical rhythm and language will better our understanding of how these skills are regulated and dependent on each other.

One way of demonstrating that a trait is influenced by genetic variation, is to study its heritability. Heritability of a trait is the amount of observed phenotypic variation in a trait that can

be explained by genetic variation within individuals. Twin and family-based studies have elucidated the heritability of musicality and language related traits. Musical accomplishment, ability to discriminate pitch, rhythm and melodies has shown moderate heritability (0.4-0.7) in twins (Drayna et al., 2001; Hambrick & Tucker-Drob, 2014; Seesjärvi et al., 2016; Ullén et al., 2014). Studies have also shown moderate heritability for musical skills, after adjusting for environmental factors (hours of practice, music exposure) indicating a role for genetics (Hambrick & Tucker-Drob, 2014; Mosing et al., 2014). Similar approaches for assessing language-related abilities point to heritability of phonology, semantics, pragmatics, grammar, and spelling, (Dale et al., 2010; Hayiou-Thomas et al., 2006; Rice et al., 2014) as well as heritability of reading, literacy and numeric skills between siblings and parents (Grasby et al., 2016; Luciano et al., 2013; Smith et al., 2019). So far, the work to elucidate the genetic architecture of musical and language traits has been sequestered within these individual fields. Recent twin-based research has started to consider cross-trait genetic approaches and has successfully demonstrated that musical aptitude and engagement are phenotypically correlated with verbal ability with results suggestive of shared familial influences (Gustavson et al., 2021; Wesseldijk et al., 2021).

Studies on the heritability of grammar and musical rhythm have not only established that there is indeed a substantial genetic component that influences individual variation in musicality traits (like rhythm) and language traits (like grammar), but also that these traits are polygenic/complex in nature (Gingras et al., 2015; Honing et al., 2015; Kornilov et al., 2016; Luciano et al., 2013). Evidence for the polygenicity of these traits also comes from the wide spectrum of individual variation observed in the phenotypes that measure musical rhythm and grammar. However, large scale, population-based GWASs that can be leveraged to explore polygenic architecture and pleiotropy; on musicality traits and language ability are hard to conduct and have started to pick up pace recently (Doust et al., 2021; Eising et al., 2021). Armed with GWAS

data, a way to seek answers to the shared polygenic architecture between musical rhythm and language is to conduct cross-trait genetic analyses like polygenic scoring, LD score regression and bivariate genome-wide complex trait analysis (GCTA), to name a few (Nayak et al., under review). I have used polygenic score methods in this dissertation to attempt to unravel the pleiotropic nature between musical rhythm and language skills. It is important to note, that language encompasses a whole array of components, which include morpho-syntax, phonology, semantics, and pragmatics. Grammar, vocabulary, reading skills, and speech are also essential aspects of language, that aid in appropriate usage of a given language for communication. While we may study each component individually, (for e.g., the focus in this dissertation is on expressive grammar), they are simply a way to access the roots of language as a neurobiological process.

Genetics of Rhythm and Grammar in the Context of a Communication Disorder.

The phenotypic variation in people's skills in musical rhythm and grammar abilities also comes into play when considering children with language impairments. Expanding on the phenotypic associations seen between musical rhythm sensitivity and grammar task performance, in a typically developing population, (R. L. Gordon, Shivers, et al., 2015; Y. S. Lee et al., 2020; Lundetræ & Thomson, 2018), when we consider that musical rhythm and grammar abilities lie on a continuous spectrum, these associations can also be expected to occur in the atypically developing population. The Atypical Rhythm Risk hypothesis (Ladányi et al., 2020) posits that children with atypical (impaired) music rhythm skills are more likely to have developmental speech and language disorders (R. L. Gordon, Jacobs, et al., 2015; Wieland et al., 2015). Evidence for the associations between impaired music rhythm skills and speech/language disorders has been well documented. Studies have found that impairments in beat synchronisation, musical rhythm perception and production co-occur in children with developmental dyslexia, stuttering, attention deficit hyperactive

disorder (ADHD), and Developmental Language Disorder (DLD) (Corriveau & Goswami, 2009; Flaugnacco et al., 2014; Puyjarinet et al., 2017; Wieland et al., 2015).

The Music Cognition Laboratory is particularly interested in Developmental Language Disorder (DLD), also known as Specific Language Impairment (SLI). DLD is a disorder that manifests itself as delays in grammar and vocabulary development and affects up to 7% of the population (Bishop et al., 2017; McLeod & Harrison, 2009; Tomblin et al., 1997). Symptoms include delay and difficulty in acquiring spoken language and issues with morpho-syntax, and receptive and/or expressive language, without the presence of other biological developmental or intellectual disabilities, cerebral trauma, or abuse (Bishop et al., 2016; Kamhi, 1998; Lancaster & Camarata, 2019; Simms & Jin, 2015; Stark & Tallal, 1981). Studies on children with DLD/SLI show less accurate music and beat perception and synchronization to a regular beat (tapping) (Cumming et al., 2015; Sallat & Jentschke, 2015). Further, studies have also demonstrated that children with DLD have impaired rhythm production (Corriveau & Goswami, 2009), auditory stress perception (Richards & Goswami, 2015), melodic perception (Sallat & Jentschke, 2015), and auditory working memory (Cumming et al., 2015). Of note, children with DLD demonstrated improved grammatical judgements after listening to regular rhythmic primes (Ladányi, et al., 2021; Przybylski et al., 2013), lending credence to the functional overlap of rhythm and grammar. These observations tie into the Atypical Rhythm Risk hypothesis, which also predicts that genetic markers of impaired musical rhythm are enriched in children with DLD versus typically developing peers.

Genetic studies of DLD have demonstrated that DLD is moderately heritable (0.4 – 0.7 concordance in twins) and tends to run in families (Kornilov et al., 2016; Kovac et al., 2001). Molecular studies DLD are ongoing and have uncovered several genes that might influence speech and language (Deriziotis & Fisher, 2017; Evans et al., 2015; Graham & Fisher, 2013; Newbury et al., 2002). A recent GWAS of language and reading traits on 34,000 people conducted by the Gen-Lang

Consortium, found 4 new potential candidate genes that could be related to reading abilities (Eising et al., 2021). Delving into the underlying genetics of language impairment and rhythm might explain the common biology that exerts important influences over these two abilities. Exploring the relationship between musical rhythm sensitivity and language abilities in an atypical population is key to understanding the developmental impact of musical rhythm processing on language acquisition. Such studies will also help lay the foundation for developing better screening and intervention for developmental language disorders.

Overview of Dissertation Studies

Music and language are two unique skills that help humans communicate. Evidence from the field points to the underlying role that rhythm plays in grammar abilities, and the heritability of both rhythm and grammatical skills. This dissertation aimed to use phenotypic and genotypic associations to probe the relationship between of musical rhythm sensitivity and grammar abilities. In **Chapter 2,** I used a phenotypic individual differences approach to study the relationship between musical rhythm and expressive grammar (Figure 1.1A). This study harnessed experimental measures for rhythm and grammatical task performance from a sample of 132 typically developing children to explore the associations and possible mediatory role of prosodic sensitivity or working memory, between the measures of rhythm and grammar. This approach was an extension of previous studies in the lab and is strengthened by the relatively substantial sample size for a developmental cohort. By examining the effects of mediation between variables, we hoped to advance the understanding of the underlying mechanism by which rhythm affects grammatical performance.

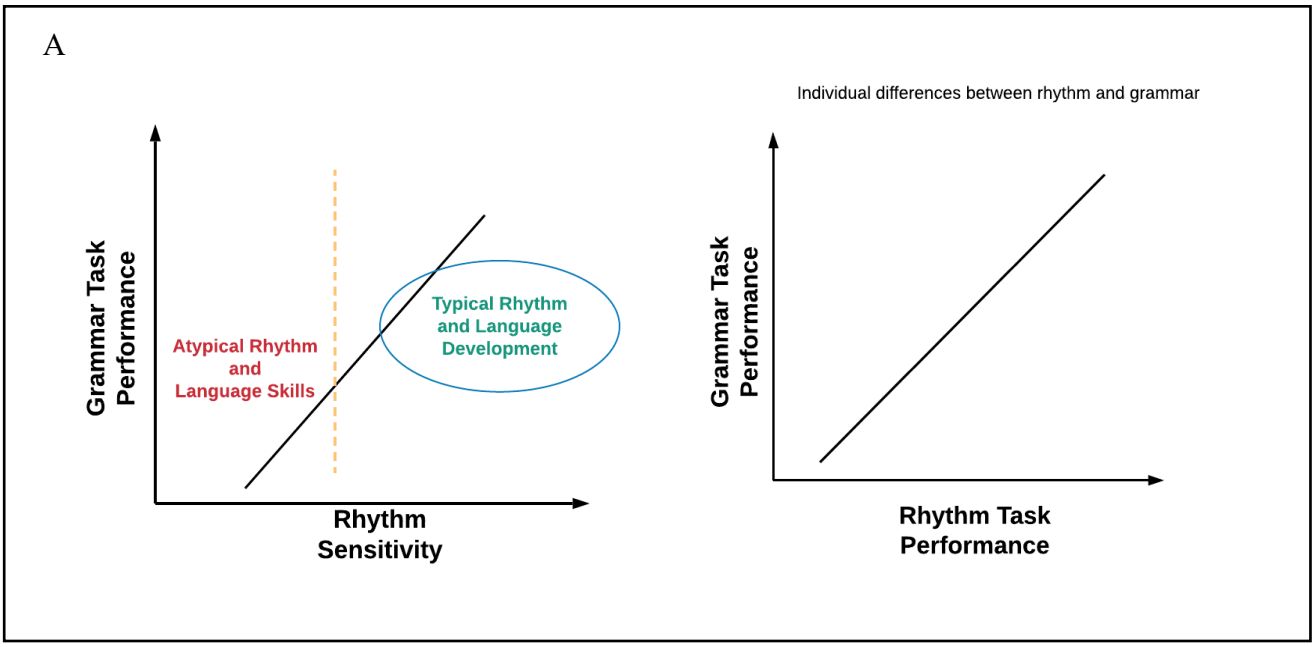
I also explored the rhythm-grammar dynamic from a genetic approach in **Chapter 3,** using the same cohort of typically developing children as in Chapter 2, and several children with DLD. This study attempted to understand if the polygenic scores of self-reported beat synchronisation,

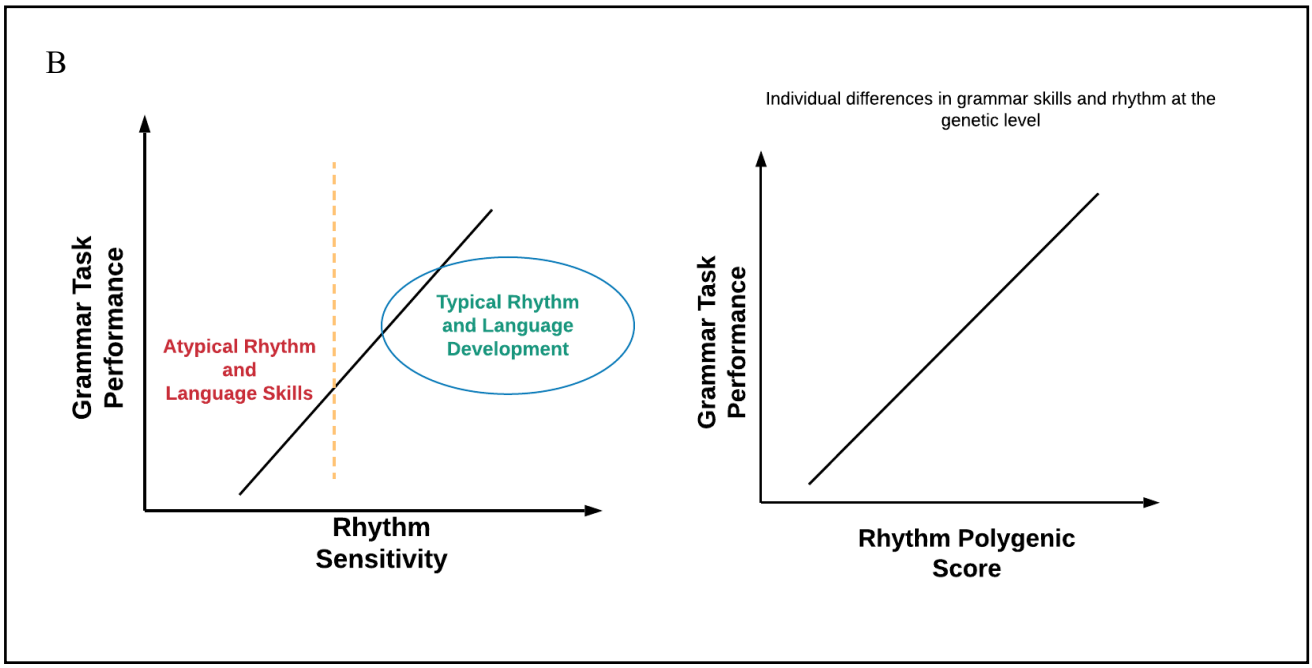
which represent one important dimension of rhythm sensitivity, are predictive of individual differences grammatical task performance (Figure 1.1B). We hypothesized that higher polygenic score for rhythm would be positively correlated with grammar task scores, and with musical rhythm task scores. This approach would yield valuable insight into the possible shared genetics and neurobiology of rhythm and grammar. By testing the phenotypic and genotypic associations between rhythm and grammar, this study will help us understand the landscape of language abilities and the factors that influence them.

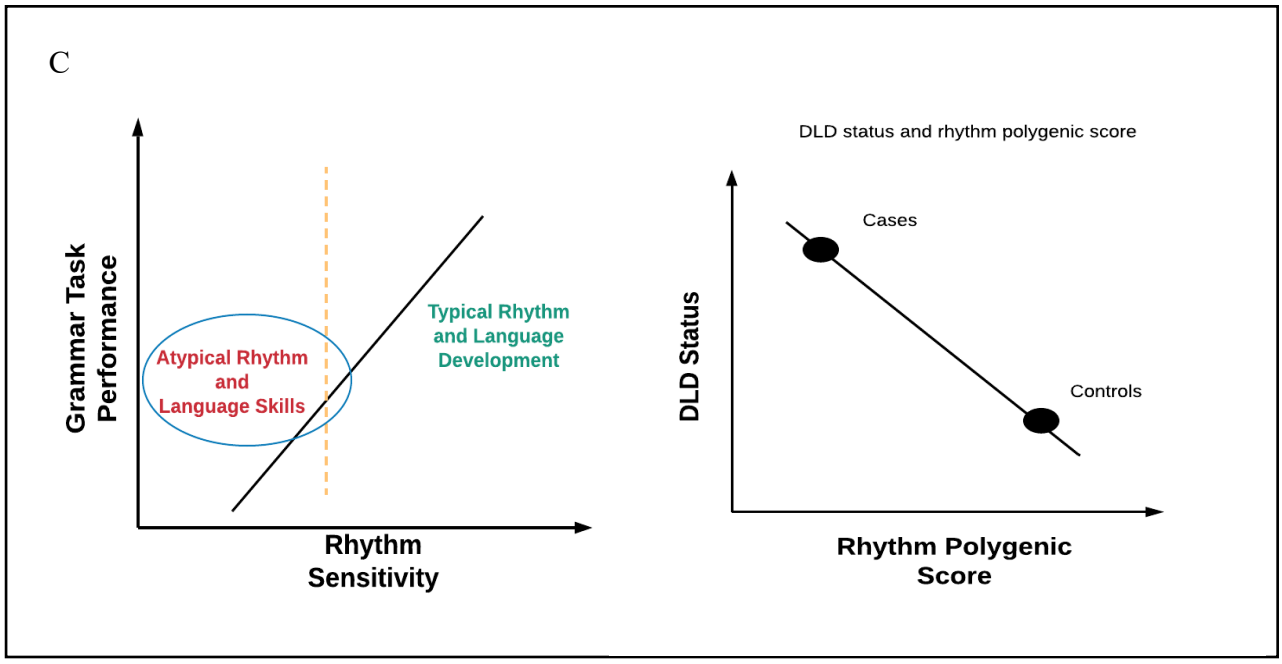
Finally, in **Chapter 4**, I considered the association between musical rhythm sensitivity and grammar through the lens of a communication disorder, to test the atypical rhythm risk hypothesis. I utilised a polygenic approach to explore whether the genetic risk of rhythm impairment can be used to predict developmental speech and language disorder status (Figure 1.1C). I hypothesized that lower polygenic scores for rhythm (higher risk for rhythm impairments) would be directly correlated with occurrence of DLD. This approach will help us in identifying high risk phenotypes indicative of language disorder before language emergence and will lay the framework for further studies aimed at studying the neuro-developmental pathways that influence rhythm and language acquisition especially in the context of language impairments.

In summary, expanding phenotypic and genetic studies into the individual differences in rhythm and grammar skills, using larger cohorts, could eventually lead to better understanding of the shared biology between these traits.

Figure 1.1: Schematic Depicting the Hypotheses and Expected Associations for Each Aim







Note. For Chapter 2 (aim 1), I will focus on the phenotypic correlations between rhythm and grammar phenotypes in a typically developing population (A), and we expect results to show that there is a direct correlation between the two phenotypes. Part (B) pertains to Chapter 3 (aim 2), where I will still look at individual differences in grammar task performance, and the *genetic* influences behind rhythm perception. Again, we expect a positive correlation between rhythm polygenic score and grammar task performance scores. Part (C) of the figure focuses on atypical language development in DLD and the correlation between DLD status and risk of rhythm impairments and is the focus of the work conducted in Chapter 4 (aim 3). We expect there to be a negative correlation between typical rhythm and DLD status.

Chapter 2

Individual Differences in Musical Rhythm and Grammar Skills in Typically Developing School Children.

Introduction

There are a growing number of studies showing a correlation between musical rhythm perception and speech/language skills, including grammar (R. L. Gordon, Shivers, et al., 2015; Y. S. Lee et al., 2020; Politimou et al., 2019; Swaminathan & Schellenberg, 2019). Gordon et al. (2015) demonstrated that children (primary school-aged) who were more accurate at distinguishing between musical rhythm sequences, also performed more accurately on tasks probing expressive grammar skills, despite the fact that the testing paradigms used differed from each other in their task demands and material. This finding was extended by Swaminathan and Schellenberg (Swaminathan & Schellenberg, 2019), who showed a strong association between musical beat perception and receptive grammar with a larger sample size of ~100 school-aged children and a grammatical comprehension task; and the Politimou et al. (2019). study which showed that rhythm perception was associated with performance on a sentence imitation task (which encompasses both the receptive and expressive nature of grammar) in pre-schoolers. Moreover, Lee et al. (2020) also found a correlation between rhythm discrimination and receptive grammar in a wider age range of participants (7–17-year-olds), while controlling for working memory, age, and musical training.

Further behavioural investigations into the rhythm-grammar relationship are important because such studies could provide insight into mediating mechanisms, which in turn can inform us about overlap between how music and language might be processed and decoded. This understanding of this relationship is also important in the context of atypical language development. Disorders that affect the use of language and hamper communication have long-term negative

impacts on quality of life, economic outcomes, and mental health (Conti-Ramsden et al., 2018; Eadie et al., 2018). Children with developmental disorders of reading and communication (e.g., developmental dyslexia, developmental language disorder, stuttering) are known to struggle with rhythmic tasks (like rhythm production, discrimination, and synchronization) (Corriveau & Goswami, 2009; Cumming et al., 2015; Sallat & Jentschke, 2015). Impaired sensitivity to musical rhythm perception also seems to be associated with atypical language development (Ladányi et al., 2020), and a better understanding of the role of rhythm in grammar might be instrumental in providing new perspectives into studying language disorders. It is interesting to note that rhythmic priming experiments, where participants actively listen to regular rhythmic sequences prior to a grammar-based task, have shown that listening to regular rhythms enhances the performance of the listener in a sentence imitation task that measures phonological accuracy (Cason et al., 2015), and also in grammaticality judgement tasks (Chern et al., 2018; Ladányi et al., 2021). This observation is valid for both typically developing participants and those with language disorders (Cason et al., 2015; Ladányi et al., 2021; Przybylski et al., 2013). The convergence of evidence of associations between rhythm and grammatical skills at both the trait (stable correlations over time) and state level (transient improvement in skills) provides further corroboration for overlapping processing of both rhythm and grammar.

This groundwork demonstrating the correlation between rhythm and grammar task performance, in the typical and atypical populations, has led to the question of what underlying cognitive and biological mechanisms might account for such a relationship. In order to dissect the relationship between rhythmic and grammatical skill, the current study had two goals: first, we evaluated the associations between music rhythm perception and expressive grammar; and second, we examined the role of working memory and prosodic sensitivity as potential mediators, with IQ as a covariate, of the association between rhythm and grammar, using a mediation model. In addition

to an overall measure of expressive language, we also used a complex syntax sub-score from the grammar test (R. L. Gordon, Jacobs, et al., 2015). Complex syntax refers to sentences constructed using multiple clauses, that can either be linked with connectors or be embedded (Frizelle et al., 2018). When parsing such sentences, children appear to use prosodic cues to process multiple clauses in the sentence. Since prosodic sensitivity is measured in our study, using complex syntax as an additional outcome would be another way to understand its specific role in mediating the rhythm-grammar link.

The first mediator we considered is thus prosodic sensitivity. In music, rhythm is represented by temporal patterns of sounds organized around the "beat" or pulse of a piece of music, while in language it is captured by speech prosody, i.e., intonational and stress patterns of syllables, the lengthening and pausing during and of phrases, and the loudness and pitch of speech (Boutsen, 2003; Bryant, 2010; Hellbernd & Sammler, 2016). These patterns are perceived as the rhythmic components of speech, though prosody may not necessarily adhere to the isochronous meter we usually experience in musical rhythm (Brown et al., 2017; Nolan & Jeon, 2014). Prosody plays a crucial role in early language acquisition and lexical development: for example, de Carvalho et al. (2017, 2019) demonstrated that prosodic boundaries, which in sentences generally reflect the sentences' syntactic structure, are leveraged by toddlers to learn the syntactic function of novel words. Five-month-old children can distinguish between their native and similar timed language, but not between two unknown languages which follow similar rhythmicity (Nazzi et al., 2000). Studies have also shown that the prosody of sentences affects grammatical processing (Schmidt-Kassow & Kotz, 2009) and facilitates word learning in toddlers (de Carvalho et al., 2019). Sensitivity to prosody is also important for syntactic parsing and lexical access in addition to decoding nuanced emotions, tone, context, emphasis, and semantics (Coutinho & Dibben, 2013; de Carvalho et al., 2017; Hellbernd & Sammler, 2016).

Prosody also interfaces with musicality, with musical training also associated with increased prosodic sensitivity (Moreno, 2009; Swaminathan & Schellenberg, 2019; Zioga et al., 2016). Torppa et al. (2019) found that children who are musically engaged also show improved performance on tasks that measure stress pattern awareness in speech. Because people who have higher sensitivity to musical rhythm also have enhanced sensitivity to prosodic cues (Hausen et al., 2013; Torppa et al., 2019), children's concomitant enhanced grammatical performance, could be attributed to their domain general rhythm perception ability. This attunement to rhythm might give these children an advantage in accessing the syntactical nature of grammar thus allowing prosody to play a mediatory role in how rhythm and grammar are processed (Heffner & Slevc, 2015).

The other mediator we explored is working memory. Working memory is a multi-component system that is primarily employed during task/goal-oriented activities and involves storage of relevant information (verbal or non-verbal), and cognitive manipulation and processing of the stored information to complete said task (Miyake et al., 2000). When required, it can also transfer information received during the task to long-term storage, and thus plays an important role in learning (Chai et al., 2018). Working memory ability is correlated with performance on rhythmic synchronization tasks (Ireland et al., 2019), prosodic sensitivity (Torppa et al., 2014), the ability to distinguish between prosodically deviant sentences (Stepanov et al., 2020), and also with sensitivity to morphosyntactic and grammatical violations (Marton et al., 2011; Zhou et al., 2017). Further, just as for prosody, musical ability and training have been shown to correlate with higher working memory spans (Bailey & Penhune, 2010; Hansen et al., 2013). Given that working memory interacts with rhythm, grammar, and prosodic abilities, we hypothesized that it could play a mediatory role between rhythm and grammar processing and is thus included in our mediation model.

Some of the paradigms from the original study of N=25, 6-year-old children (R. L. Gordon, Shivers, et al., 2015) were used here in a larger sample (N = 132) of typically developing children

between the ages of 5-7. We then used structured equation modelling (path model) to dissect the role of prosodic perception, working memory, and non-verbal IQ, as mediating cognitive mechanisms in how musical rhythm task performance correlates with grammar skills.

Methods

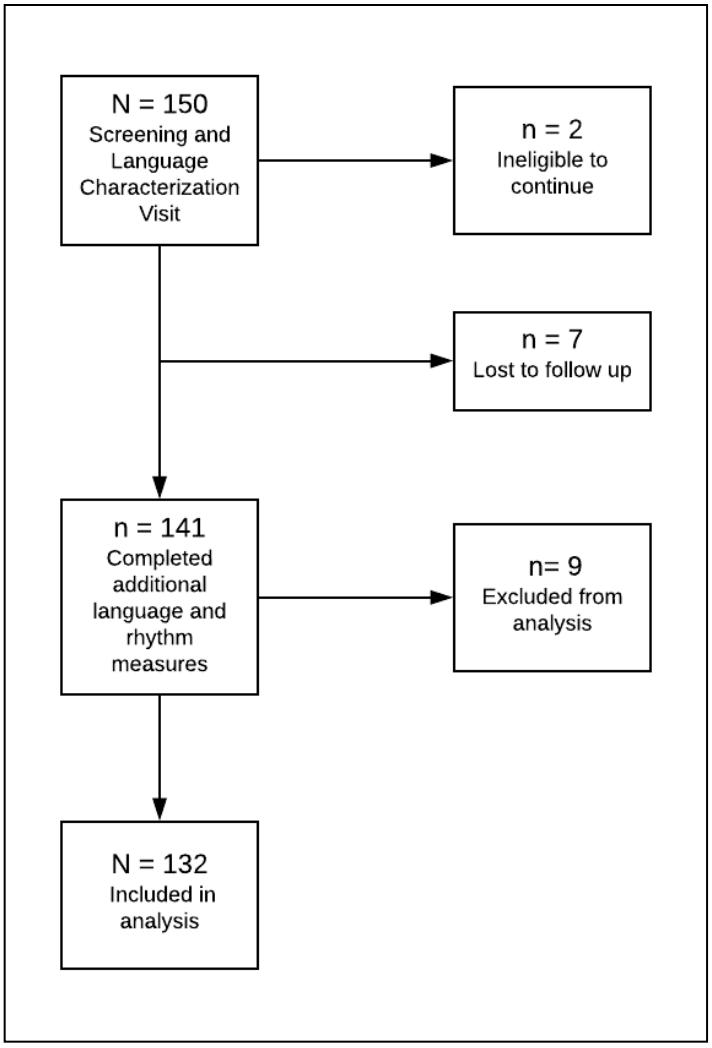
Participant Recruitment

Children (N = 150) between the ages of 5-7 were recruited from several sources in the Middle Tennessee community such as libraries, museums, research mailing lists through Vanderbilt University, and schools, and were screened for the study. The study protocol was approved by the Institutional Review Board of Vanderbilt University. All participants and their parents gave verbal assent and written informed consent respectively, in accordance with established protocols. Children were invited for one in-depth, on-campus screening visit, and those who were eligible were invited back for one-two additional study visits on-campus. Families were compensated with a gift card and small toy per visit. Details of screening measures and language characterisations used to determine eligibility for the study are detailed below. Screening took place by trained research staff under the supervision of Speech-Language Pathologist (SLP) staff.

From the 150 participants that were screened, 2 participants were considered ineligible due to repeated failed hearing screenings, while 7 were "lost-to-follow-up" and did not return for further testing; thus 141 participants completed the behavioural assessments of the study. A further 9 participants were excluded from analysis, due to the following reasons: speakers of dialects other than Standard American English (n=3), 2nd -language immersion program at school (n=1), difficulties in understanding and/or completing the tasks (n=1), failure to meet TD language criteria on assessments (n=3), and technical errors during administration of computer assessments (n=1). Thus N = 132 (aged 5;5 – 7;11, mean = 6;5 years, SD = 10 months, 76 females) qualified for the full

study. The review process from recruitment, screening and eligibility determination is visualized in below in Figure 2.1

Figure 2.1: Study Enrolment Pipeline for Participants



Note. This figure encapsulates the review pipeline for participant inclusion, from screening to final analysis. All decisions to exclude participants based on eligibility were made by SLPs after review of the participants' screening measurements and assessments.

Screening and Language Characterization

Hearing Screening

Using headphones, each child listened to a series of 20dB pure-tones presented 3 times at 1000, 2000 and 4000 Hz in each ear respectively (18 tones in total; 9 in each ear; 3 at each frequency). To pass, participants needed to correctly identify two out of three presentations at each frequency, in both ears. If a child failed a hearing screening due to allergies/infections, they were invited back for a second screening, which if they passed, allowed them to continue in the study.

Nonverbal IQ

To rule out cognitive disabilities in participants, the PTONI (Primary Test of Non-Verbal IQ Ehrler & McGhee, 2008) was administered to assess age-normed nonverbal IQ. In the PTONI participants are asked to determine which picture does not belong in a series of pictures. Participants needed a standardized score >= 78, which is indicative of absence of intellectual disabilities, to qualify for the study. Of the 132 total participants, n=8 participants had invalid administration for the PTONI, (due to incorrectly established basal scores, child shyness, or inattention); however, study eligibility was established through a combination of clinical judgments and above criterion performance on the pertinent subtests of the TOLD P-4 (see Language Screening for details). These scores rule out global intellectual disability, even when a PTONI score was not available (Camarata & Swisher, 1990).

Language Screening

The TOLD-P:4 (Test of Language Development - Primary, 4th edition; Newcomer & Hammill, 2008) and the TEGI (Test of Early Grammatical Impairment; Rice & Wexler, 2001) were used to assess language eligibility and rule out language disorders. To assess typical language

development, we used three subtests from the TOLD-P:4, namely Sentence Imitation (SI), Picture Vocabulary (PV) and Morphological Completion (MC). In the SI task, SLPs would read out a sentence, and participants were asked to repeat the sentence word for word. There were 38 sentences in this test with increasing syntactical complexity from first to last, with 2 practice sentences at the start. In the PV test, participants were shown 4 pictures, and asked to point to one of four pictures in response to a question. For example, they were shown a panel of pictures portraying a book, dog, ball, and a baby and asked to "point to baby". The final subtest is the MC test. It had 38 sentences in which children were asked to complete a sentence where the last word of the sentence is missing. The sentences are designed to elicit responses that require the use of particular expressive morphology in order to be considered correct. Because these subtests assess expressive and receptive syntax, receptive vocabulary, and expressive morphology respectively, they effectively capture language impairments, if present. We also used the phonological probe from the TEGI to rule out speech and/or phonological impairments that may interfere with accurate assessment of morphosyntax.

Children who failed the phonological probe of the TEGI (raw score of 12 or below) were excluded from study participation. Children with signs of language impairment indicated by below average scaled scores on any one of the specific TOLD subtests (scaled score < 8 for either SI, PV, or MC) were not eligible to continue, and were referred to another study for children with language impairment. One participant scored below criterion on the SI subtest for the TOLD P-4 due to non-compliance. However, their average performance on the PTONI, SLP expert opinion based on holistic review of other tests, and observations during the assessments verified normal language development allowed them to be included in the study. All standardized language testing and decisions to include or exclude participants based on scores were overseen by SLP research staff. Language characterization was performed for eligibility and group assignments, whereas expressive

grammar, the phenotype of interest for the individual differences analysis, was measured with the SPELT-3 (described below).

Behavioural Assessments for Individual Differences Analyses

Grammar

Expressive grammar was measured with the Structured Photographic Expressive Language Test-3 (SPELT-3) (Dawson et al., 2003). Participants were shown a series of pictures and asked questions that elicit responses requiring specific grammatical construction (e.g., relative clauses, possessive pronouns). The raw scores from this assessment were used as the outcome measure of expressive grammar skills for the phenotypic correlations, while controlling for age.

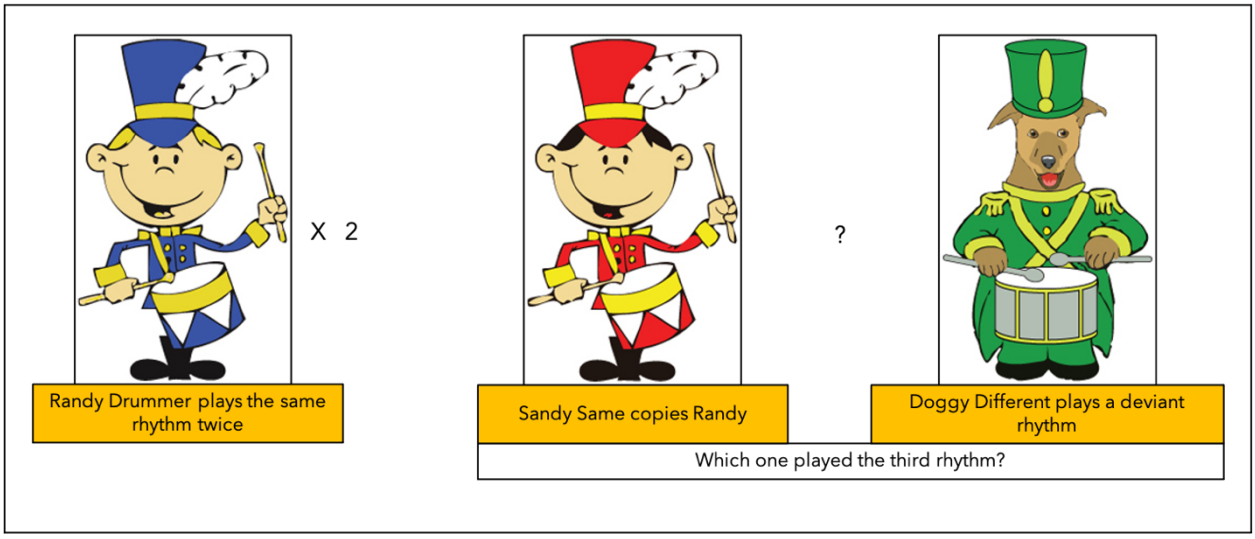
Rhythm Phenotypes

Musical Rhythm (BBA). Musical rhythm perception was measured using and the children's version of BBA (Beat-based Advantage) test (R. L. Gordon, Shivers, et al., 2015; Wieland et al., 2015), which has been adapted from the original adult version of the task implemented by Grahn and Brett (2009), both of which use auditory stimuli developed by Povel and Essens (1985). The children's BBA is a computer-based test developed and presented via E-Prime v2.0 Professional (Psychology Software Tools, Inc.) on a laptop. The sounds were presented over external speakers connected to the laptop and calibrated to 70dB. The BBA was presented as the "Drummer" game show in Figure 2.2 (where there are three parties involved – Randy-Drummer, Sandy-Same and Doggy-Different (R. L. Gordon, Shivers, et al., 2015). During the task, participants were asked to listen to 3 standard rhythms, played sequentially. The first two rhythms were identical and played by Randy-Drummer, while the third and final rhythm could be the same as the first two (thus played by Sandy-Same who copies Randy-Drummer), or different (played by Doggy-Different). Participants

were asked to determine with the third rhythm was played by Sandy-Same or by Doggy-Different and tested rhythm discrimination. This task employed simple and complex rhythms (half the trials each). The same stimulus corpus and visual representation was used here as in Gordon et al. (R. L. Gordon, Shivers, et al., 2015) such that rhythms were 25% faster than in the other work in adults (McAuley et al., 2006).

The BBA had four practice trials (2 simple and 2 complex – each with a same/different variation) followed by 28 test trials, divided into 14 simple and 14 complex rhythms, with each rhythm type further subdivided into 7 "same" and 7 "different" trials. The rhythms heard in the practice trials were excluded from the test trials. Correct/incorrect feedback was provided only in the practice stage. For analyses, we calculated the d' separately for simple and complex rhythms, and then averaged them for an overall BBA d' score.

Figure 2.2: Illustration of the Drummer Game: BBA Task and Visual Stimuli Shown to Participants



Note. For each trial, children heard a standard rhythm repeated 2 times, followed by a third rhythm which would either be the same as the first, or different. Participants were asked to choose between "Sandy Same" and "Doggy Different" with a clicker to indicate if they thought the third rhythm was the same as the first two or different.

Prosody Perception. Prosodic sensitivity was measured with the Prosody-Matching task (adapted from Soman, 2017), which tests sensitivity to intonational fluctuations in speech. The task was presented through the "Astronaut" game, via E-Prime using the same computer and speaker setup as for the BBA. The task was a forced-choice ABX discrimination task that required children to match the prosody of a low-pass speech filtered sentence to one of two non-filtered, normal speech sentences. The unfiltered sentences were spoken by either the red astronaut or the blue astronaut in the visual (Figure 2.3), while the low-pass (400Hz) filtered speech was attributed to their green alien friend. Children were told that the astronauts and their green alien friend were playing a copycat game. The alien was trying to copy what one of the astronauts was saying, but "it's hard to hear in outer space"; and it was the child's job to determine which astronaut the alien was copying.

The children were presented with the first unfiltered sentence (Stimulus A), and then a second sentence (Stimulus B). Stimulus A was spoken by one of the astronauts – either red or blue (the order is switched for successive participants), and then a second sentence spoken by the other astronaut. Stimulus A is always a declarative sentence, and the second utterance (Stimulus B) is a modified version of Stimulus A – it is either a shorter version of the first declarative sentence, has an alternative pausing schema, or adds interrogative intonation to the sentence. Both Stimulus A and B are presented in normal, unaltered speech. An example of the stimuli is provided below:

Stimulus A - Declarative sentence: "The boy is pouring juice in the glass."

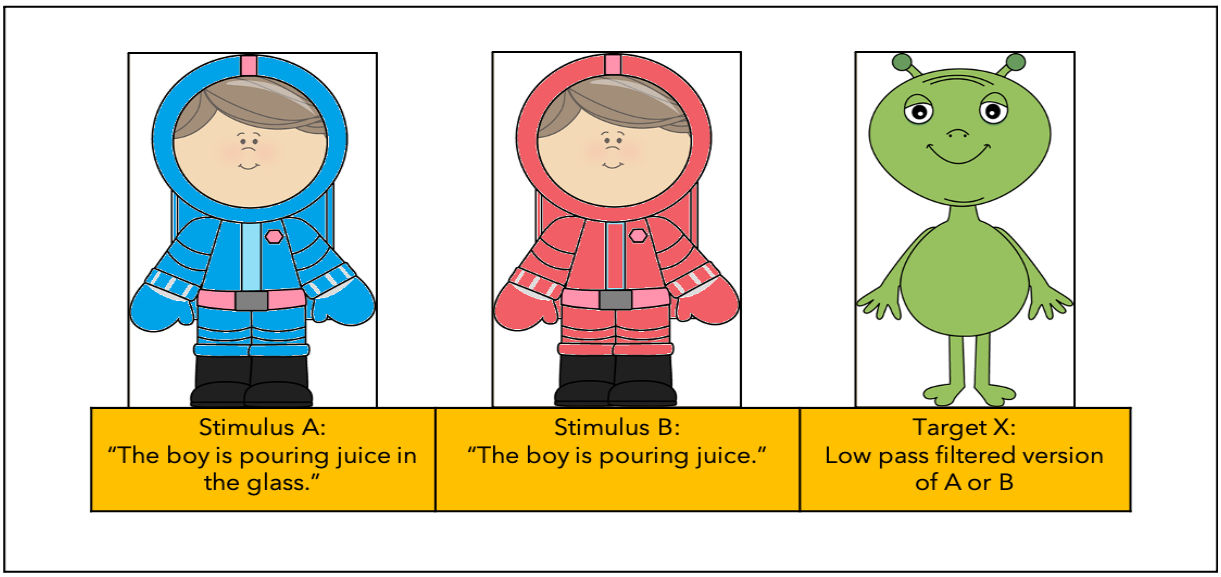
Stimulus B - One of the following modified conditions:

1. Short version: "The boy is pouring juice."
2. Alternative pausing: The boy is pouring // juice in the glass."
3. Interrogative intonation: "The boy is pouring juice in the glass?"

The third phrase the participants heard (Target X), is the voice of the green alien, and is the 400 Hz filtered version of either Stimulus A or B. Thus, Target X (the green alien) is mimicking either Stimulus A or B (one of the astronauts).

The task had a total of 24 trials (12 trials mimicking one of the normal speech sentences, and 12 trials the second) which were presented to the participants in random order. Similar signal detection theory analysis was used to calculate the d', which was then z-scored and used as a measure of prosodic sensitivity.

Figure 2.3: Illustration of the Astronaut Game: Prosody Matching Task and Visual Stimuli



Note. For each trial, two normal-speech stimuli A and B (astronauts) were presented, followed by one of those two sentences low-pass filtered through 400 Hz (Target X). Participants were asked to identify which astronaut the alien was imitating

Verbal Working Memory

The forward digit span subtest of the KABC-II (Kaufman Assessment Battery for Children, second edition) (Singer et al., 2012), was used to measure verbal working memory, which was positively correlated with rhythm perception and with grammar task performance in earlier work

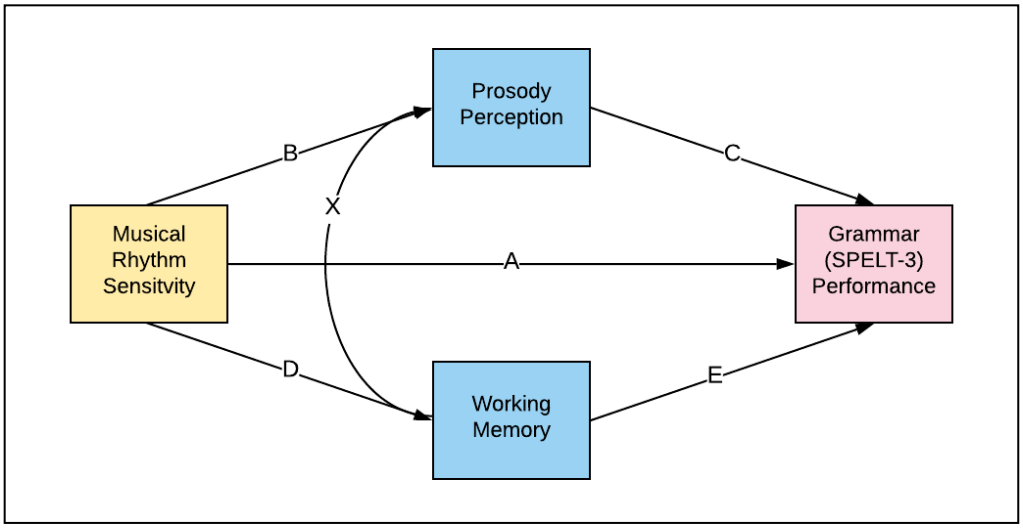
(Meinz & Hambrick, 2010; Talamini et al., 2017). The raw scores from the test were z-scored and used for analysis.

Analysis Plan

All data were analysed using R software environment (R Core Team, 2021), the tidyverse R package (Wickham et al., 2019), and the lavaan package (Rosseel, 2012). Using lavaan, a structured equation model (SEM)/path model was used to examine the possible mediation of the music rhythm – grammar relationship through prosodic perception or working memory, with missing values excluded in a list-wise manner. Prosodic perception and working memory served as possible mediators, with IQ and age as covariates. As shown in Figure 2.4, we evaluated two possible mechanisms of mediation – one through prosodic perception (path BC), and the other through working memory (path DE). This path model was fully identified, hence model fit indices were not considered.

For both the path model and correlation analyses, we used raw scores for all our measures (SPELT-3, KABC-II, Prosody Matching, BBA), except for non-verbal IQ, where we used the age-normed PTONI scores. For the measures which used raw scores, we first z-scored, then regressed the z-scores on age, and used the residuals as the final input values in the analyses. For the PTONI standard scores, we z-scored the available scores, and then used these z-scores in our analyses. Though the SPELT-3 is a standardised test, with age normed scores available, since we used the SPELT-3 scores as an outcome measure of expressive grammar ability within our sample rather than as a measure of ranking/standing within the general age group of the participants, we used raw scores (age-controlled) in our analysis. However, we used PTONI standard scores, since the PTONI was used to control for possible effects of non-verbal IQ in our models, while the SPELT-3 was an outcome measure.

Figure 2.4: Path Model for Mediation Analysis of Rhythm Sensitivity and Grammar Performance



Note. This path model examines the relationship between musical rhythm sensitivity (predictor) and grammar performance (outcome), and the possible mediators (working memory capacity and prosody perception) that might play a role in this correlation. Path A is the direct effect from rhythm to grammar, while paths BC and DE constitute the mediation effects through prosody perception and working memory respectively. Path X depicts the residual correlation between prosody perception and working memory.

Results

Sample Characteristics

We screened 150 participants for this study from which, n=132 (aged 5;5 – 7;11, mean = 6;5 years, SD = 10 months, 76 females) met the complete eligibility criteria for our study based on their various assessment scores and holistic review of screening measures by Speech-Language Pathologists (SLPs) and constitute the final dataset. Eligibility for the current study was dependent on participants having normal hearing, typical non-verbal cognitive ability, typical language development, an absence of major neurodevelopmental disorders or conditions (e.g., autism spectrum disorder, brain injury, cerebral palsy), and English being the primary language spoken at home. We also assessed children's musical experience (MES) using the same parent questionnaire as

Gordon et al. 2015 (R. L. Gordon, Shivers, et al., 2015). The descriptive statistics of all the eligible participants (N = 132) including age, socioeconomic status, and musical experience score is tabulated in Table 2.1 below. During the screening visit, parents were also asked to fill in a demographic questionnaire, from which we used mother's highest level of education as a proxy for socioeconomic status (SES).

Table 2.1: Demographics and Assessment Scores of the Cohort

Sample Characteristics	N	Mean	SD	SE	Range	Skew	Kurtosis
Age (years)	132	6.53	0.84	0.07	5.07 - 8.17	0.21	-1.20
PTONI standard score	124	120.55	19.36	1.74	80 - 150	-0.36	-1.02
Picture vocabulary (scaled score)	132	12.89	2.18	0.19	5 - 17	-0.94	1.25
Sentence Imitation (scaled score)	131	12.65	2.12	0.19	8 - 17	-0.03	-0.74
Morphological completion (scaled score)	132	12.86	1.84	0.16	6 - 17	-0.63	0.57
Socioeconomic status (SES)	132	7.50	1.00	0.09	5 - 9	-0.02	-0.72
Musical experience (MES)	131	1.09	1.01	0.09	0 - 4	0.79	0.10

Note. This table summarises the demographic characteristics and scores of the screening measures employed in the study. The picture vocabulary, sentence imitation and morphological completion scores provide age-normed scaled scores for the cohort. A questionnaire was used to assess the musical engagement and calculate a musical experience score, and the highest level of maternal education was used as a proxy for socioeconomic status. The age-normed standard scores of the PTONI are reported for the non-verbal IQ measure. PTONI = Primary Test of Non-Verbal IQ.

Individual differences analysis.

We used an expressive grammar test, a rhythm task, a prosody sensitivity task, and a verbal working memory test as the behavioural assessments for the individual differences analyses. Expressive grammar was measured with the Structured Photographic Expressive Language Test-3 (SPELT-3, Dawson et al., 2003), while verbal working memory was assessed with the forward digit span of the KABC-II(Kaufman Assessment Battery for Children, second edition, Singer et al., 2012). Musical rhythm perception was measured using the children's version of BBA test (Beat-based Advantage, R. L. Gordon, Shivers, et al., 2015; Wieland et al., 2015). The BBA is a computer-based

task, in which participants are asked to identify which rhythms are same and which are different from a pair of rhythms presented over speakers. Finally, the computer-based Prosody-Matching task which is a forced choice ABX sentence prosody matching test was used to probe prosodic perception, in which participants had to match a low-pass filtered speech sentence to one of two non-filtered sentences.

The descriptive statistics of the outcome measures (viz. SPELT-3, KABC-II, BBA, and Prosody Matching) are summarized in Table 2.2. From the 132 participants that completed all study visits and assessments, n = 103 participants had valid and complete data for all the tasks and assessments. For the computer-based assessments (BBA and Prosody Matching), n = 23 participants (individual test missingness is: n = 11 for BBA, n = 14 for Prosody Matching) did not have useable data for one or more of the tests either due to technical errors, program malfunctions, or participant's inability to understand or attend to the behavioural task.

Table 2.2: Descriptive Statistics of Behavioural Outcome Measures

Variable Name	N	Mean	SD	SE	Range	Skew	Kurtosis
SPELT-3 standard score	132	113.13	6.66	0.58	90 - 126	-0.78	1.06
SPELT-3 raw score	132	46.06	3.80	0.33	35 - 53	-0.77	0.22
SPELT-3 complex syntax sub-score	132	0.79	0.13	0.01	0.42 - 1	-0.63	-0.004
BBA d'	121	0.99	0.85	0.08	-1.20 - 2.73	0.12	-0.64
Prosody Matching d'	118	1.79	0.78	0.07	0.13 - 3.28	-0.40	-0.39
KABC-II number recall raw score	132	9.36	2.02	0.18	5 - 16	0.06	0.37

Note. Descriptive statistics for behavioural outcome measures show the age-normed standard scores and the raw scores for the expressive language test. The complex syntax sub-score is a non-scaled raw score. The d' calculated using signal detection is reported for the BBA and Prosody Matching tests. The non-scaled raw score of the forward digit span subtest of the KABC-II is used. SPELT-3 = Structured Photographic Expressive Language Test-3; BBA = Beat-Based Advantage; KABC = Kaufman Assessment Battery for Children.

Correlations

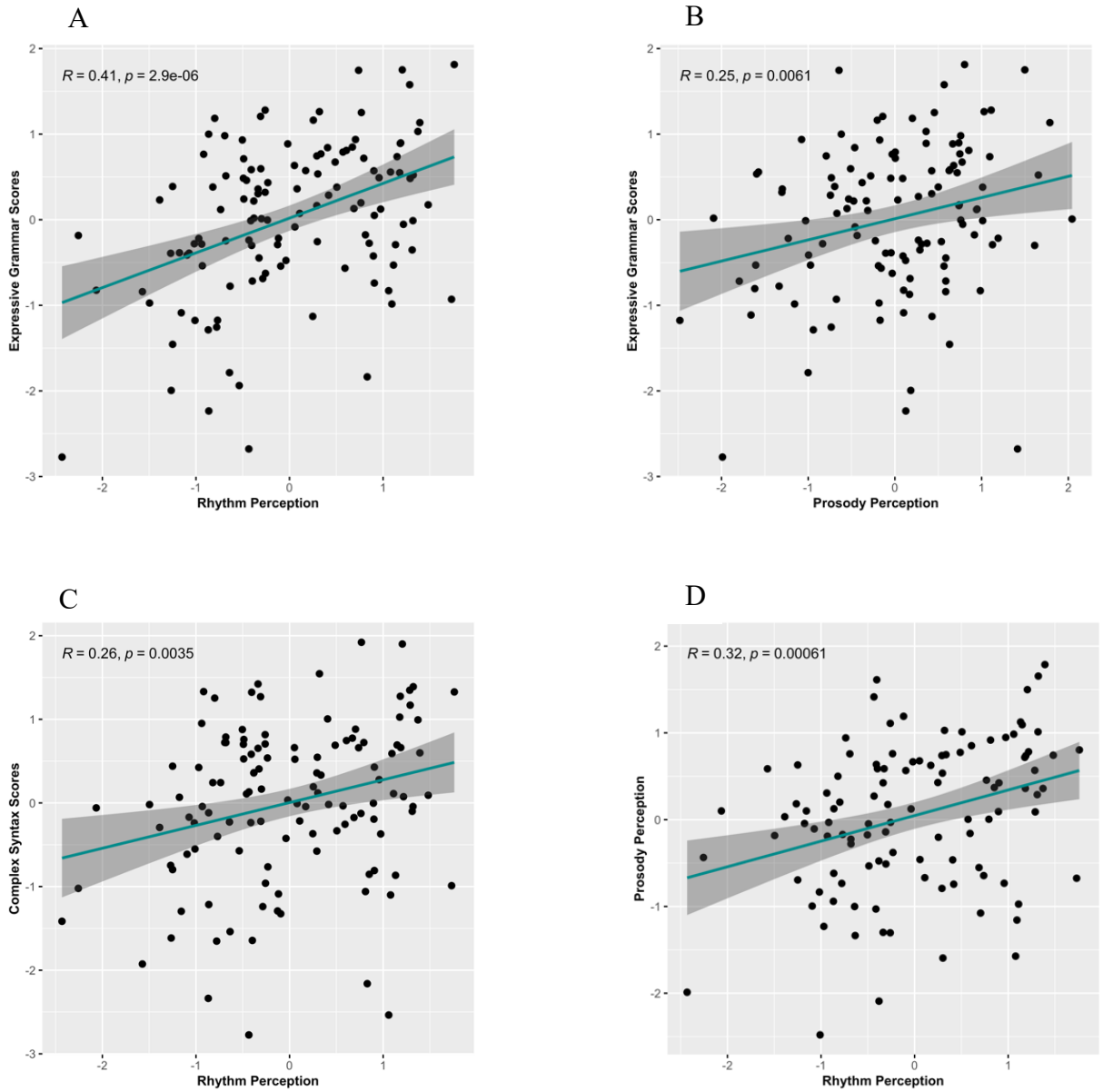
Correlations between all measures (controlling for age) are displayed in Table 2.3. For the correlation we first z-scored the raw scores for SPELT-3, BBA, Prosody Matching, KABC-II, Musical experience score (MES), and socio-economic status score (SES), then regressed age from all the variables, and used the residuals from the age-controlled regression for pairwise correlation. For IQ we used z-scored standard scores of the PTONI and used these in the correlation. Since musical MES and SES did not correlate significantly with the prosodic perception, grammar, or rhythm measures, they were not included in further analyses. Individual BBA ($r = 0.41$, $p < 0.001$) and Prosody Matching ($r = 0.25$, $p = 0.006$) scores were both significantly and positively correlated with expressive grammar (SPELT-3) scores. Prosody Matching scores were also positively correlated with rhythm perception BBA scores ($r = 0.32$, $p < 0.001$). Further, we also computed a complex syntax sub-score from the SPELT-3 using the items groupings as described in Gordon et al. (2015). Since complex syntactical ability has been demonstrated to be strongly correlated with musical rhythm sensitivity in their studies and parsing musical rhythm sequences and linguistic sentences both might tap into domain-general perception abilities, this metric was explored in the associations. In our sample, BBA scores are also positively correlated with complex syntax sub-scores ($r = 0.26$, $p = 0.003$). Scatter plots for the relevant individual correlations are shown in Figure 2.5 A-D.

Table 2.3: Pearson Correlation Matrix of all Variables Used in the Correlation and Path Model Analysis

Variable	1	2	3	4	5	6	7	8
1. SPELT-3 raw score	-							
2. SPELT-3 complex syntax sub-score	0.72**	-						
3. BBA	0.41**	0.26*	-					
4. Prosody Matching	0.25*	0.15	0.32**	-				
5. PTONI standard score	0.27*	0.21*	0.33**	0.24*	-			
6. KABC-II number recall raw score	0.21*	0.10	0.33**	0.27*	0.30**	-		
7. SES	0.08	-0.01	0.03	0.11	0.10	0.21*	-	
8. MES	0.01	-0.19*	-0.06	0.07	-0.10	0.05	0.18*	-

Note. This table summarises the Pearson correlation matrix of all variables used in the correlation and path model analysis. Except for the PTONI age-normed standard scores (which are the z-scored standard scores), the raw scores of all other variables were z-scored and then regressed on age, and the residuals were used in the correlation matrix. Values are correlation r values for each pair of variables. Missing values were excluded in a pair-wise manner. SPELT-3 = Structured Photographic Expressive Language Test; BBA = Beat-Based Advantage; PTONI = Primary Measure of Non-Verbal IQ; KABC = Kaufman Assessment Battery for Children; SES = Socioeconomic Status; MES = Musical Experience Score.
* indicates $p < 0.05$, and ** indicates $p < 0.001$

Figure 2.5: Scatterplots for Outcome Measures



Note. Scatterplots showing the correlations between (A) expressive grammar (SPELT-3) scores and musical rhythm perception (BBA) scores (n = 121); (B) expressive grammar and prosody perception (Prosody Matching) scores (n = 118); (C) Complex Syntax (CS) scores and musical rhythm perception (n = 121); and (D) musical rhythm perception and prosody perception (n = 109). Age is controlled for in all plots.

Mediation Analysis

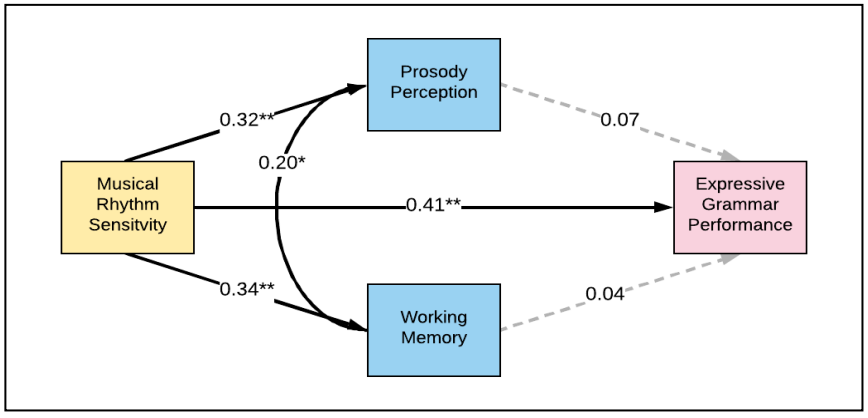
We used a fully identified path model to investigate the possible mediation of prosodic perception or working memory in the rhythm-grammar correlation, displayed in Figure 2.6 (n = 109). In this model, we controlled for age by using residualised variables for all measures (i.e., regressing all z-scored raw measure scores on age and saving residualised scores prior to analysis, as described for the simple correlations above). As shown in Figure 2.6, the direct path from musical rhythm perception to expressive grammar task performance was significant (Path A; $\beta = 0.41$, $p < 0.001$), even when accounting for prosodic perception and working memory. The indirect effects of musical rhythm perception on grammar through prosodic perception (Path BC; $\beta = 0.02$) and working memory (Path DE; $\beta = 0.01$) were small and non-significant. Thus, musical rhythm perception was correlated significantly with expressive grammar skills, and this correlation was not mediated by either prosodic perception or working memory. The residual correlation between prosodic perception and working memory was also significant (Path X, $\beta = 0.20$, $p = 0.037$).

We also conducted the same path analysis by covarying for non-verbal IQ from all measures in the model (n = 103). We used the z-scored standard scores from the PTONI as the measure for IQ, while all other variables were the age-residualised raw scores. As shown in Figure 2.7 although IQ was significantly correlated with musical rhythm perception and working memory, the primary results of the model remain unchanged. That is, the direct path between musical rhythm perception and expressive grammar remained significant ($\beta = 0.38$, $p < 0.001$), while the indirect paths through prosodic perception and working memory were non-significant.

We also performed similar path analyses (controlling for age, as previously described), to investigate the association between musical rhythm perception as the predictor and complex syntax task performance as the outcome, displayed in Figure 2.8. We hypothesized that since complex

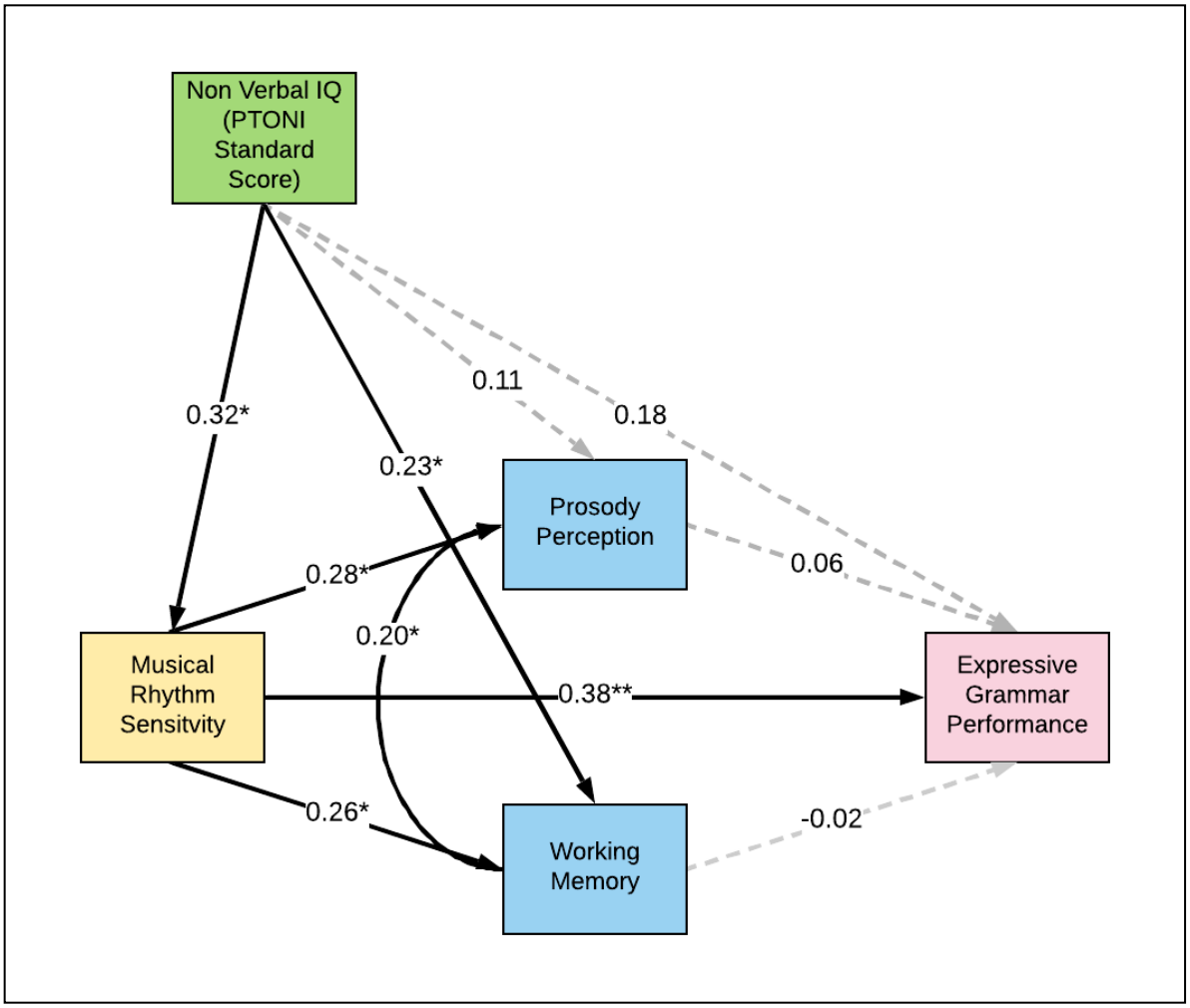
syntax and musical rhythm follow an inherent hierarchy that unfolds over time, processing both complex syntax and rhythm might employ shared processing pathways evident in their behavioural output. Our analysis showed that the association between rhythm perception and complex syntax was positive and significant ($\beta = 0.27$, $p = 0.007$) in our path model (Fig 2.8 A). Further, in Figure 2.8 A, the direct association between rhythm perception and complex syntax, remained significant, and the indirect mediating pathways through prosodic perception ($\beta = 0.02$) and working memory ($\beta = 0.06$) were non-significant. Similar results were observed when we included non-verbal IQ as a covariate in the path model (Figure 2.8 B), showing that complex syntax, much like expressive grammar in the previous path model (Fig 2.8A), was positively and significantly correlated with performance on the musical rhythm task ($\beta = 0.25$, $p = 0.018$), and this correlation was not mediated either by prosody perception or working memory, and neither explained by non-verbal IQ.

Figure 2.6: Path Analysis Model of Associations between Musical Rhythm Perception and Expressive Grammar



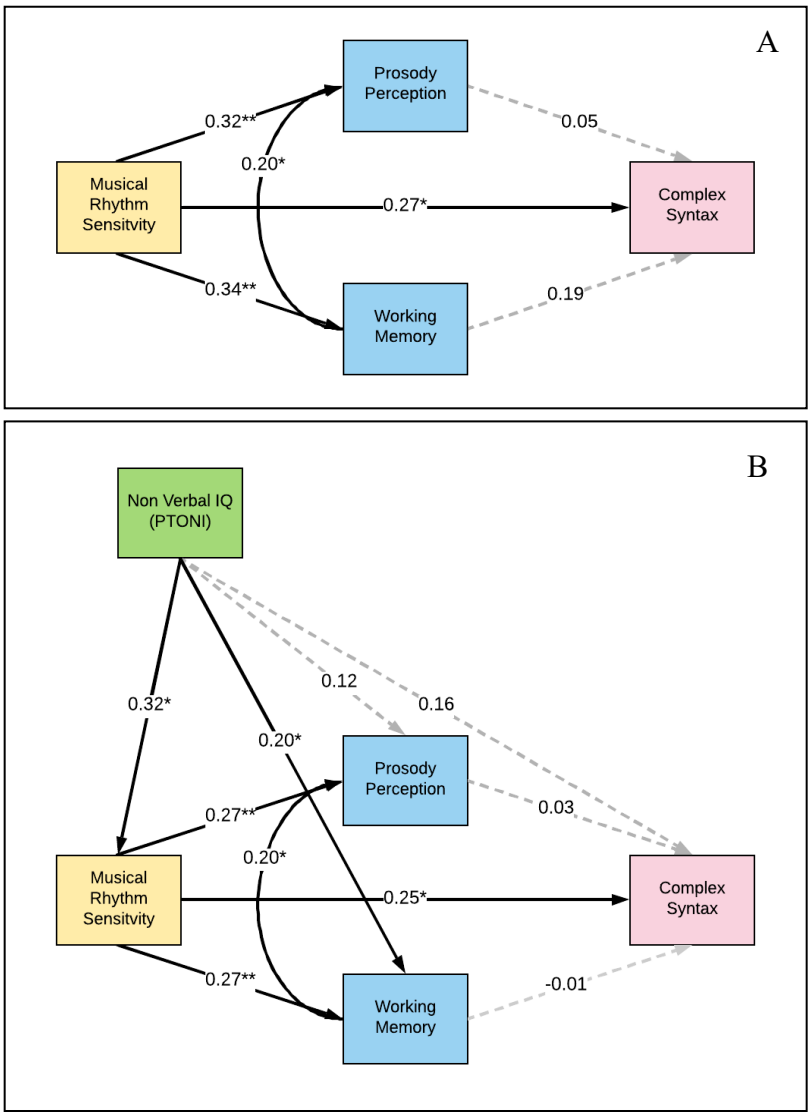
Note. The path analysis model shows the associations between musical rhythm perception, expressive grammar task performance, prosody perception and working memory, while controlling for age (n = 109). Age-regressed residuals of the z-scored raw scores were used for all measures. We found that though the relationship between musical rhythm sensitivity and expressive grammar task performance is positive and significant, it is not explained by prosodic sensitivity or working memory. The model uses list-wise exclusion for missing values. The β for each pair of variables is indicated on the path. Solid lines indicate a significant relationship.
* signifies $p < 0.05$, while ** signifies $p < 0.001$.

Figure 2.7: Path Analysis Model for Musical Rhythm Perception and Expressive Grammar, Controlling for Non-Verbal IQ



Note. This figure depicts the path model for music rhythm perception and expressive grammar, prosody perception and working memory as mediators, with IQ as a covariate (n = 103). Age was partialled out from all variables (except IQ), by creating residualised scores of age against the z-scored, raw scores of variables. Z-scored standard PTONI scores were used as the measure of IQ. Missing values were excluded in a list-wise fashion. The β for each pair of variables is indicated on the path. Solid lines indicate a significant relationship.
* signifies $p < 0.05$, while ** signifies $p < 0.001$.

Figure 2.8: Path Analysis Model for Musical Rhythm Perception and Complex Syntax



Note. (A)This figure (n = 109) depicts the path model for musical rhythm perception and complex syntax, prosody perception and working memory as mediators. Residualised scores were created by partialling age from z-scored raw scores of all variables. The age-residualised scores were used in the path model. We find that the relationship between musical rhythm sensitivity and complex syntax task performance is non-significant. Solid lines indicate a significant relationship. * signifies $p < 0.05$, while ** signifies $p < 0.001$.

(B) Path analysis model for musical rhythm perception and complex syntax, controlling for IQ (n = 103). Residualised scores were created by partialling age from the z-scores of all variables, except for IQ. For IQ we used z-scored standard PTONI scores. The age-regressed residual scores, and z-scored PTONI standard scores were used in the path model. The β for each pair of variables is indicated on the path. Even by controlling for IQ, the relationship between musical rhythm and complex syntax remains non-significant. Solid lines indicate a significant relationship. * signifies $p < 0.05$, while ** signifies $p < 0.001$.

Discussion

In light of prior findings of associations between rhythm and grammatical task performance (R. L. Gordon, Shivers, et al., 2015; Y. S. Lee et al., 2020; Politimou et al., 2019; Swaminathan & Schellenberg, 2019), we explored the behavioural correlation between musical rhythm perception and expressive grammar and investigated potential mediating factors that might be influencing and directing this relationship. Extending findings from prior work (R. L. Gordon, Shivers, et al., 2015; Swaminathan & Schellenberg, 2019), we demonstrated a positive correlation between musical rhythm perception and expressive grammar skills here in a sizeable sample of 132 school-aged (5–7-year-old) children. We also found that prosodic perception is positively correlated with musical rhythm perception ($r = 0.32$, $p < 0.001$), and with expressive grammar ($r = 0.25$, $p = 0.006$). The importance of prosodic sensitivity in the context of language has been elaborated in studies which showed that prosodic cues play an important role in early language acquisition (Langus et al., 2017), and impact literacy skills in children (Holliman et al., 2010). Changing the prosodic cues evident in a sentence also affects neural processing of grammatical structure (Schmidt-Kassow & Kotz, 2009), again indicating that prosodic skills are important for spoken language development and literacy (François et al., 2013; Moreno et al., 2009).

We then explored the possibility that sensitivity to prosody is the factor that is mediating the associations between rhythm and grammatical skills. Prosodic cues mark phrasal boundaries, and these cues are used by adult listeners to parse complex sentences and comprehend them (Frazier et al., 2006; Speer & Ito, 2009), and leveraged by children in parsing syntax but also to learn the meaning of novel words (de Carvalho et al., 2017, 2019). Previous studies have explored the correlation between prosodic sensitivity and reading and literacy skills (Groen et al., 2019) as well as musical rhythm sensitivity (Hausen et al., 2013), showing that there is a direct correlation between performance on prosodic tasks, reading comprehension, and music rhythm perception skills. Given

the interaction between prosody and rhythm perception and prosody and language comprehension, we proposed that prosodic perception acts as the intermediary process that ties together musical rhythm perception and grammar.

To study this, we used a path model that factored in prosodic perception as a mediator. We used working memory as a second mediator, since working memory also plays a role in performance on music and grammar tasks (D'Souza et al., 2018; Ireland et al., 2019; Zhou et al., 2017). The associations between rhythm and grammar skills could simply be driven by variable memory capacity (language and rhythm tasks could be confounded by working memory demands), or because processing the hierarchy of rhythm in music and syntax in language might rely on similar working memory functionality. Using working memory as another mediator, would thus also help us gain some insight into the behavioural mechanisms that drive the rhythm-grammar link.

From our mediation analyses, in the path models (Figures 1.6 and 1.7) we see that the associations between music rhythm and grammar measures remained significant and are not accounted for by sensitivity to prosody, nor by working memory. Both prosodic perception and working memory were independently and significantly correlated with musical rhythm perception, but not with expressive grammar. Using non-verbal IQ and age as covariates did not impact these associations, indicating that the rhythm-grammar link is not driven by prosodic sensitivity, working memory, or IQ.

Furthermore, in our study, path modelling with complex syntax sub-scores demonstrated similar results as for overall grammatical skill as the outcome: there was a significant direct effect of rhythm discrimination on complex syntax, and this relationship was not mediated by prosody perception nor working memory. In line with previous findings of musical rhythm variables predicting children's individual differences in complex syntax skill (R. L. Gordon, Jacobs, et al., 2015; Persici et al., in revision) and adults' years of musical experience predicting attainment of long-

distance syntactic dependencies in an artificial language learning paradigm (Brod & Opitz, 2012), we thus found converging evidence for an association between mastery of complex multiclausal syntactic structure and musicality variables.

These cross-sectional results should not be interpreted as a causal role of musical rhythm on grammar. While our study upholds previous observations that rhythm and grammar performance are indeed correlated, we do not delve into the neural, biological, or genetic mechanisms that are responsible for this association. The path model employed here included grammar as the dependent variable to parse its covariance with musical rhythm into 3 paths (one direct association and 2 indirect associations). Although our findings suggest that working memory, prosodic perception, and IQ do not drive the association between music rhythm and grammar, other study designs will be necessary to unpack any potential longitudinal or (bi)directional associations between them.

A particular limitation is that in our application of the structural model to our data, we could not construct latent variables for our measures. Inclusion of latent variables would have reduced the measurement errors present in the study measures and allowed us to create variables that capture individual differences with reduced error margins. Future studies should include multiple correlated measures for each construct that test various aspects, like testing rhythm production, perception, and imitation for a "rhythm" construct. This will likely tap into the abilities of participants on the broader construct, rather than focussing on performance on a single task.

Furthermore, our Prosody Matching task investigates the sensitivity of participants to prosodic cues signifying syntactic structure, like intonations that signify when a question is being asked or phrasal lengthening to indicate pauses. This test thus may not capture speech-rhythm, but rather capture prosodically directed sentence-level syntactic processing that affects the relationship of the constituents of the phrase. Including measures of speech-rhythm (tasks concerning identification of stressed syllables, or repetition of nonsense syllable rhythms) will help us better

parse the effects of prosodic sensitivity on the associations between rhythm-grammar task performance. Similarly for the outcome measure, we have used expressive grammar abilities, though prior research has shown similar results with receptive grammar measures as well. In children aged 7-17 years, Lee et al (Y. S. Lee et al., 2020) demonstrated that participants with better performance on the rhythm task also had higher scores on the receptive grammar test. Grammatical syntactic processing is a complex, multi-layered neurobiological function, and studying various facets will help specify the role of rhythmic perception in the various aspects of grammar performance.

Another caveat is that our study only looked at monolingual speakers of American English. Studies have shown that bilingual participants also show associations between musicality and language skills (Y. S. Lee et al., 2020; Liu & Kager, 2017; Stepanov et al., 2018), and studies going forward will have more inclusive criteria with bilingualism as a covariate (Swaminathan & Schellenberg, 2019).

From the literature and from our study we observe that musical rhythm sensitivity has significant implications for development of grammatical skills, such that children who are more sensitive to rhythm have an advantage during language learning, though the processes underlying this relationship are not well understood. Rhythm and language are often studied as two separate domains(Kotz et al., 2018), though they share several similarities including but not limited to structure (presence of phrasing), timing (pauses and rests) and stress (duration of beats and syllables) (Boll-Avetisyan et al., 2017; Patel, 2003). However, empirical studies provide evidence that considering music and language as separately as we do, might not be reflective of their developmental or cognitive origin. Of note, new-born children can successfully distinguish between languages that follow separate rhythmic rules. Even though their 'language' as an ability cannot be tested, they are able to tell apart English (stress-timed) from Japanese (mora-timed), but not English and Dutch, both of which are stress-timed (Nazzi et al., 1998), showing a dependence on the

'rhythm' of the language even at such an early age. At 6 months, this ability to use their prosodic sensitivity to discriminate becomes nuanced, with children being able to distinguish between British-accented English and the American-accent, when one of these dialectical accents is native to them, though they still cannot distinguish between two syllable-timed languages or two stress-timed languages, if both are foreign to their ears (Nazzi et al., 2000). This inherent speech prosody is also leveraged by infants during language and especially syntactical learning (de Carvalho et al., 2019; Soderstrom et al., 2003). The association between rhythm perception and language becomes more directly measurable in older children. In the Politimou et al.(2019) study, pre-schoolers who had better rhythm perception and production skills also performed better at a sentence imitation task (which taps into both receptive and expressive grammar and syntax). In addition, Lundetræ and Thompson (2018) demonstrated in their study of school aged children that performance on a task that required participants to tap to a rhythm was positively associated the children's reading and spelling performance in school. Taken together these observations suggest that early language and music development might be entangled, language development to some extent utilizes rhythmic perception, and the domain specificity and nuanced processing of these stimuli develops over time (Brandt et al., 2012).

While neural processing of language and music shows some lateralisation, evidence from neuroimaging studies indicate that there is marked overlap in neural regions responsible for generation and processing of rhythm and speech (Brown et al., 2006; Heard & Lee, 2020; Peretz et al., 2015). Both musical rhythm and grammar are ordered in a temporally progressing hierarchy (Brennan & Hale, 2019; Frank et al., 2012; Lerdahl, 2015; Lerdahl & Jackendoff, 1983). Considering these parallels in organization, there could be shared mechanisms at play that are responsible for processing both music and grammar (Patel, 2012; Patel & Iversen, 2007).

The standardised tests and behavioural tests used in our dataset have been validated by several other studies in various populations, giving credence to their ability to measure the constructs they were intended to capture. I believe that our dataset has been deeply phenotyped for rhythmic sensitivity (both musical and prosodic), expressive grammar and working memory. Further, our sample of 132 children is a sizeable sample, that would be effective at capturing individual differences, whereas previous studies used smaller samples. The robust significant correlations seen between our individual outcome and predictive measures are in line with previous literature and provide further evidence that our measured constructs are defensible and rational measures. Bearing this in mind, the lack of mediation by prosodic sensitivity or working memory, can be a signal of underlying mediating mechanisms that were not measured, but influence the association between musical rhythm and grammar.

Because prosodic perception, working memory, and IQ did not account for the associations between musical rhythm perception and expressive grammar, the question then arises: what other mechanisms might drive this effect? One cognitive pathway that might feature in this relationship is hierarchical processing. Hierarchical processing helps to break down a complex, stratified system into its individual components (Fitch & Martins, 2014). With hierarchical processing the higher complex action or sentence can modulate the process in the lower levels of sentence structure/action over time. Hierarchical structures are applicable to both music rhythm and grammar (in our case syntax). Like rhythm, the grammatical structure of language, especially syntax, follows a hierarchical structure that unfolds over time (Brennan & Hale, 2019; Fitch & Martins, 2014; Patel, 2003). Disruptions in the underlying rhythmic patterns of music cause expectancy violations in the hierarchy of the music, just like how violation of the syntactic rules may ambiguate the listener's grammatical expectancy of the sentence. Studies have shown that there is a hierarchy of processing when listening to spoken language, with different regions being responsible for different

levels of processing the parts of grammar (like phrasal syntax or morphemes) within a sentence to parse and process what we are hearing (Davis & Johnsrude, 2003; Gaskell & Marslen-Wilson, 1997). Further, imaging studies have indicated that certain brain regions like the Broca's and Wernicke's (which are typically involved in language processing) and BA44, 41 and 47, inferior frontal gyrus and bilateral insula (Bidelman et al., 2013; Davis & Johnsrude, 2003; Jeon, 2014; Koelsch et al., 2002) are activated not only during grammar tasks like sentence processing, but also during music tasks like rhythm, beat, and pitch perception, with some of these regions also observed to be involved in processing hierarchical information (R. L. Gordon, Jacobs, et al., 2015; Heard & Lee, 2020; Jeon, 2014).

Another possible answer to the cross-trait relationship between rhythmic perception and grammatical skills could lie in shared genetics (Peretz, 2009; Wesseldijk et al., 2021). Studies have shown that traits that are linked phenotypically are influenced by genes that are correlated, i.e., an overlapping set of genes (Cheverud, 1988; Sodini et al., 2018). Pleiotropy, where the same set of genes influence both phenotypes, usually through a common neural pathway, or through a common neural molecular signalling pathway (neural endophenotypes), can be explored through several different types of genetic analyses (like genome-wide studies and cross-trait polygenic risk scores; see Ladányi et al., 2020). Developmental observations in music and language further support the case for common genetic influences on these traits. Both rhythm and language are perceived acoustically first, and though as adults we consider them dichotomous modules, as children this difference might not be as evident (McMullen & Saffran, 2004). Studies with infants have demonstrated that infants as young as 7-months-old, show a preference for previously heard passages of music and words as compared to novel words (Saffran et al., 2000). Infants also show enhanced rhythmic processing and speech tracking when infant directed conversation is more song-like (sing-song) as compared to speech-like (Kalashnikova et al., 2018; Leong et al., 2014). Interestingly, rate of language acquisition

in children can be predicted by the "melodic complexity" of their cries. Infants whose cries show lower complexity than their peers, have delayed language skills as toddlers (Wermke et al., 2007, 2021; Wermke & Mende, 2009). Put together with evidence from studies in infants on language discrimination, development of rhythm and grammar might be concomitant rather than sequential (Brandt et al., 2012).

Our study in school-aged children study adds to the growing literature in music cognition that demonstrates the association between individual differences in musical rhythm perception and expressive grammatical skill. This study replicates the finding that there is a positive correlation between rhythm and grammar performance, but interestingly this relationship is independent of working memory and IQ, is not simply driven by sensitivity to prosody but rather is truly a cross-domain interaction. These results could indicate interesting underlying common biological and genetic mechanisms that drive the rhythm-grammar links, and future studies could focus on studying these cryptic underlying causes for this relationship either through behavioural or genetic methods.

Chapter 3

Genetic Associations Between Musical Rhythm Perception and Grammar Performance in Typically Developing Children Using Polygenic Approaches.

Introduction

The evolution of language in the human species sets us uniquely apart from our non-human primate cousins. We see that communication and the use of language as a tool for communication are an innate part of human activity and might even have a deep-rooted genetic component. Studies have shown that even when speaking is not a possibility (i.e., in very young infants), there still exists a mode of verbal communication, through cooing and babbling, with differences in complexity of cries being indicative of future language development (Brandt et al., 2012). Children are able to readily learn languages they are exposed to without formal direction and training (Graham & Fisher, 2013), and also show spontaneous creation of structured language (sign languages), when there are no other modes of communication available (Nicaraguan sign language, see Maclaughlin et al., 1995). This evidence may point to the use and development of language to be an essential part of the human experience.

The first evidence for the genetic basis of language came from the study that showed mutations in *FOXP2* to be singularly responsible for a particular type of familial speech/language disorders (Lai et al., 2001). This landmark study was followed by several others, which showed the involvement of genes in varied inherited speech and language disorders like *ROBO1, CNTNAP2, DCDC2, KIAA0319* to name a few (Graham & Fisher, 2015). The clear observation that came from these studies was that language is not a mono-genic trait but is a complex trait with several genes that contribute to the development of language. With the advent of population-wide genetic methods like GWASs, the same efforts were made to identify genes contributing to common

language disorders, as well as unravelling the underlying genetic architecture of language. A GWAS is a study used to probe the effect of millions of common variants or single nucleotide polymorphisms across several thousand genomes to identify those common variants which contribute to the most to the observed phenotypic variability of the trait. Results from these population-based studies have further strengthened the fact that language is highly polygenic, with a complex genetic make-up. Two recent language-related GWAS', one of 51,800 people with developmental dyslexia (Doust et al., 2021) and the other of 34,000 people that looked at reading and language traits (Eising et al., 2021), have demonstrated the polygenic nature of language. Eising et al. (2021) found evidence of shared genetic architecture between language and reading traits, and other cognitive abilities – in line with previous research. Similarly, the dyslexia study found 42 significantly associated loci, 17 of which showed pleiotropy with cognitive traits as well, again indicative of the polygenic architecture of language and language-related abilities.

Much like language, musicality, and rhythm (the phenotype under consideration here), are also complex genetic traits. Evidence for the genetic basis of musicality and rhythm comes from several twin studies which have demonstrated that varied aspects of music like sensitivity rhythm, pitch and melodies is moderately heritable (0.4-0.8)(Drayna et al., 2001; Seesjärvi et al., 2016; Ullén et al., 2014). Further, Mosing et al (2014) and Hambrick & Tucker-Drob (2014) found that hours of practice is not the only contributing factor to musical skills, and there is a gene x environment interaction that not only drives music skills, but also other behaviours (like music engagement and propensity to practice) that might contribute to increased heritability of musicality. In recent years population and medical record-based studies have played a role in identifying the genetic and phenotypic architecture of beat/rhythm perception in humans (Niarchou et al., in press; Niarchou et al., 2021).

The Niarchou et al., (2021) study is the largest GWAS of a musicality trait and queries the trait of "beat synchronization," with the results (69 genome-wide significant loci) highlighting the polygenic architecture of rhythm. I used this well-powered GWAS as the study that informed the polygenic score model. This study had 606,825 individuals of European ancestry who participated in research with personal genomics company 23andMe, Inc, and answered the question 'Can you clap in time with a musical beat?' Because the trait under study was a self-reported trait, the authors also conducted validation studies in an independent sample to verify the sensitivity of the self-report. They showed that self-reported ability to clap to a musical beat is positively and significantly correlated with a beat perception measure (higher sensitivity to musical rhythm), a beat synchronisation test (lower asynchrony in beat synchronisation), and a musical sophistication questionnaire. These validation studies showed that generally, people who responded 'yes' to the question 'can you clap in time with a musical beat', do not have rhythm impairment, thus indicating that the self-report beat synchronisation trait is a believable measure of beat ability.

Taking a step back, in Chapter 1 we demonstrated phenotypic correlations between musical rhythm sensitivity and expressive grammar ability. Based on these observations we can hypothesize that the behavioural links we see between musical rhythm sensitivity and grammar ability might be explained by genetic pleiotropy (Ladányi et al., 2020; Nayak et al., under review). Often in the animal and plant kingdoms, when phenotypes/traits are correlated, there is a greater chance that the genotypes associated with the traits are also associated (Cheverud, 1988; Sodini et al., 2018) Given that there is a robust and replicable correlation between music rhythm perception and grammar phenotypes, we can possibly investigate the genetic correlations between these traits using cross trait approaches.

Because both rhythm and grammar are polygenic traits, the genetic variants that drive these phenotypes are widely distributed across the genome. When considering such traits, family-based or

gene-based studies do not sufficiently capture the variability both genetic and phenotypic, and more sophisticated population-based approaches are required. However, it may be a considerable challenge to acquire the extensive sample sizes (sometimes in the millions) required to carry out these genome wide studies. Cross-trait genetic approaches are another way to leverage available population data on one trait to query the genetic influences behind a related or co-morbid trait. For several psychiatric traits, cross trait approaches have been instrumental in unearthing overlapping comorbidities and yielding unexpected insights into how much shared genetic architecture lies beneath commonly co-occurring neural traits (Amare et al., 2018; Bulik-Sullivan & Neale, 2015) Such polygenic approaches are thus also well suited to probing the possible genetic overlap between music rhythm and grammar abilities.

In this study we used polygenic score (PGS) analysis to investigate the genetic influences which might influence in part both music rhythm perception and grammar performance. We used a recently published population wide study of beat synchronisation (Niarchou et al., in press) to generate rhythm polygenic scores (PGS-R) for our sample of school-aged children.

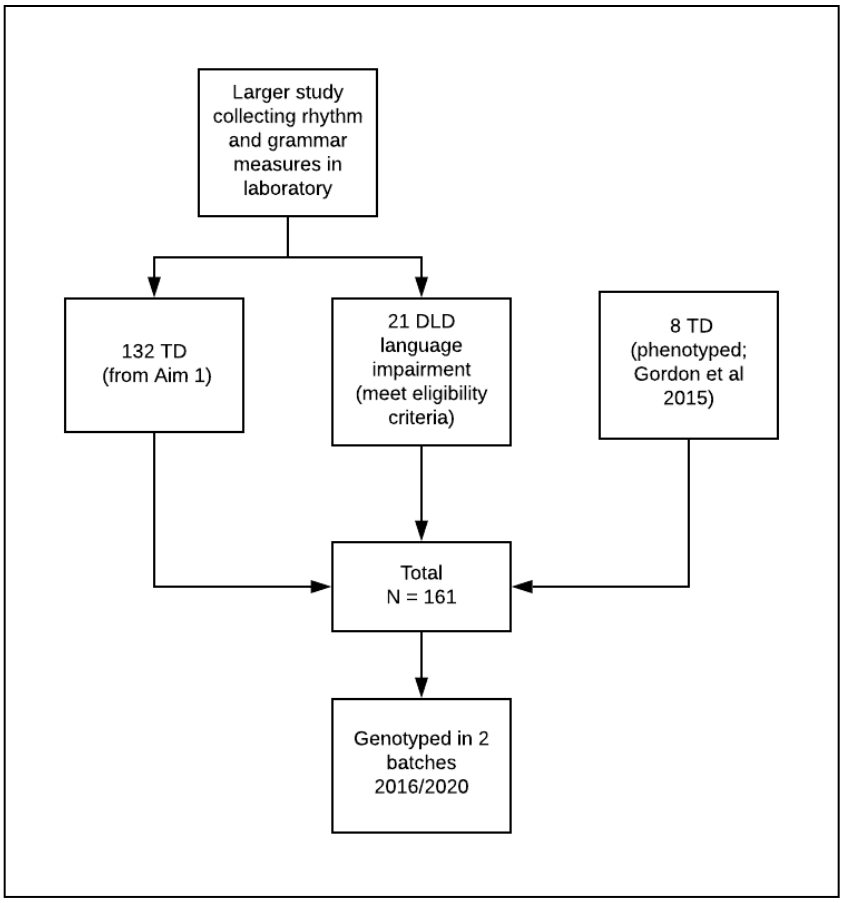
Methods

Participants

The participant cohort for this analysis is made up of children with typical language development and atypical language development, particularly developmental language disorder (DLD). Children with typical language development came from two separate studies. n = 132 were the same participants whose phenotypic data was used in the path analysis in Chapter 2. As part of our IRB approved data collection protocols, we also collected genetic data from these 132 participants during one of their two study visits. A further n = 25 typically developing (TD) participants who were part of a previously published study (R. L. Gordon, Shivers, et al., 2015) were

recontacted and requested to schedule a visit so that we could collect their genetic data and increase our pool of participants for genetic analyses. Of the 25, 8 participants were willing to participate, and submitted their genetic samples. DLD participants were recruited as part of a larger study conducted in our lab, that explored similar associations between rhythm and grammar, but in children with DLD. Again, as part of IRB approved protocols, we collected genetic data from n = 21 DLD participants during their planned study visits. Thus, we had a total of N = 161 participants with genetic data that are included in this aim. Figure 3.1 encapsulates the various cohorts from which the participants were drawn

Figure 3.1: Pipeline of Participants used in Chapter 3



Note. This figure illustrates the various studies from which the participants for Chapter 3 were drawn from. TD = Typically developing, DLD = Developmental Language Disorder

Screening and language characterisation of participants for group assignment (TD vs DLD) was carried out by SLP research staff. Language characterisation to identify impairments and assess language development was performed using the TOLD-P:4 and the phonological probe of the TEGI as described in Chapter 2. PTONI scores were used to rule out cognitive impairments in participants (see Chapter 2). All group assignments were determined by SLP staff, based on a combination of participant scores, and SLP opinion based on review of other assessments used in the various studies from which the participants were drawn. Although we have classified participants as TD and DLD, this study is not a between group study, but a study of individual differences of the genetic influences of rhythm and grammar, since we have continuous phenotypic scores on each individual. By using both TD and DLD participants we aimed to capture the widest range of individual differences across the spectrum of rhythm and grammar task performance abilities.

Phenotypes

Grammar

For both grammar phenotypes, based on observations from studies in the lab (R. L. Gordon, Shivers, et al., 2015), external studies (Politimou et al., 2019; Swaminathan & Schellenberg, 2019), and results presented in this dissertation (Chapter 2), I hypothesized that higher PGS-R would be associated with better scores on the grammar tasks.

SPELT-3. Expressive grammar was measured with the Structured Photographic Expressive Language Test-3 (SPELT-3, Dawson et al., 2003). Participants were shown a series of pictures and asked questions that elicit responses requiring specific grammatical construction (e.g., relative clauses, possessive pronouns). The raw scores from this assessment were used as the outcome measure of expressive grammar skills. We used raw SPELT-3 scores since we are using age as a

covariate in the regression model and are using the SPELT-3 scores as an outcome measure and not as a diagnostic measure for language characterisation.

TOLD-P:4 Sentence Imitation (SI) Subtest. In the SI task, SLPs would read out a sentence, and participants were asked to repeat the sentence word for word. There were 38 sentences in this test with increasing syntactical complexity from first to last, with 2 practice sentences at the start. Since SI requires both the understanding (receptive) and production (expressive) of syntax, SI scores were used as on outcome measure in this analysis.

Rhythm

Entrainment Region (ER). Entrainment Region is defined the range of tempi to which someone can show attentional entrainment (McAuley et al., 2006). We used a Tapping (rhythm production) task with participants to estimate their ER (See Ladányi et al., in revision). The task was presented using an iPad and children were instructed to tap on the iPad with just one finger, first at the speed that is 'just right' for them, then as slowly as they can like a snail, and finally as fast as they can like a race car. Entrainment region was estimated using the difference between a participant's slowest speed of tapping and fastest speed of tapping divided by their 'just right' speed of tapping. Entrainment region hypothesis from McAuley et al (2006), posits that the width of the ER is narrower earlier in life, widens until adulthood and narrows during the later stages of life. If we were to consider, individual differences in ER, a wider entrainment region (higher ER score) would indicate that a person is able to recognise regularly presented auditory information in very slow frequency tempi and in very fast tempi as well. A recent study has shown that children with wider ER have better performance on a rhythm perception task that requires children to identify rhythms as being 'same' or 'different' from each other (Ladányi et al., in revision). For entrainment region, I

hypothesized that higher PGS-R would be associated with wider entrainment regions, and thus with higher ER scores.

BBA. Musical rhythm perception was measured using and the children's version of BBA (Beat-based Advantage) test (R. L. Gordon, Shivers, et al., 2015; Wieland et al., 2015). For analyses, we calculated the d' separately for simple and complex rhythms, and then averaged them for an overall BBA d' score, which was used in the analysis. See chapter 2 for details regarding the BBA experiment and d' calculations. As with ER, I again hypothesized a positive correlation between BBA d' and PGS-R.

Genetic Data Collection

We collected 2ml of saliva from N = 161 TD and DLD children using DNA Genotek's Oragene-Discover OGR-500 kits. During one of the two study visits, we asked the children to carefully salivate into the collection tube, after ensuring that they had not eaten food, or had a drink of water for at least an hour before saliva collection. A similar protocol was followed for the children who were invited back only for saliva collection. On collection of saliva, the kits were submitted to Vanderbilt's VANTAGE (Vanderbilt Technologies for Advanced Genomics) genotyping and biobanking core.

Genotyping

At VANTAGE, DNA was extracted from the saliva samples, and genotyped using the Illumina Infinium® MEGA^{EX}. The Expanded Multi-Ethnic Genotyping Array was developed to provide comprehensive coverage of single nucleotide polymorphisms (SNPs) across European, East Asian, and South Asian populations. During participant recruitment we strived to include participants from a wide range of genetic ancestries and socioeconomic statuses to capture the

widest possible phenotypic variation of the measures under study. The ability to retain and use data across as many genetic ancestries as possible was a goal during my genetic analyses. The data for this study was genotyped in two batches; going forward referred to as Batch2020 and Batch2016. Post genotyping, the VANTAGE lab conducted primary quality control (QC) on the data, biobanked the DNA, and securely transferred the raw files and well as the plink compatible data to us.

Quality Control

The data received from VANTAGE underwent stringent quality control to prune variants and samples with low quality data. The data was subject to QC, then imputed and analysed in two ways – one that included only those participants of European ancestry, and the second with participants of European and non-European ancestry together.

Twenty-nine of the participants were genotyped in Batch2016, while the remaining 132 participants were genotyped in Batch2020 along with N = 208 samples from another study (discussed in Chapter 4). Batch2020 was subject to the following first pass QC in PLINK (Batch2016 underwent the same QC, and differences are noted in parentheses): removal of duplicate variants and indels, SNP filtering at a call rate of < 0.90 (< 0.80 for Batch2016), individual filtering at a call rate of < 0.80 (< 0.80 for Batch2016) updating ids to rsID names using VANTAGE's documentation, removal of rsID duplicates using plink2, filtering for heterozygous samples |FHet| > 0.2 (samples that did not meet heterozygosity constraints in Batch2016 were simply flagged at this stage), flagging sex discrepancies (at this stage sex discrepant participants were not omitted from either batch), and finally SNP filtering for Hardy-Weinberg Equilibrium violations at $p < 10^{-20}$. Next, I used PRIMUS to perform a principal component analysis (PCA) to calculate principal components (PC) and assign genetic ancestries to the participants, and further split both the batches based on these PCs and assigned them to one of three ancestral groups (viz. European, African-American,

Hispanic, South Asian, and East Asian). Since the populations of East-Asian and South-Asian ancestries was very small in number in both the batches (n = 1 each of South-Asian and East Asian in Batch2016, and n = 1of South Asian ancestry, no East Asian ancestry in Batch2020) these samples were dropped from further analyses. For each ancestral group, I performed MAF filtering to remove SNPs with minor allele frequencies < 0.05, and SNP filtering for Hardy-Weinberg Equilibrium violations at $p < 10^{-10}$.

After performing preliminary SNP and sample level quality control and filtering, I merged the study participants that remained from Batch2016 (n = 24) and the study-relevant samples from Batch2020 (n = 129). To do this, I merged Batch2020 with Batch2016, first with just the participants with European ancestry (combined n = 130), and then with participants of European, African-American, and Hispanic ancestry (combined n = 153). Since the two batches, Batch2016 and Batch2020, for the participants were so disparate in numbers (n = 24 and 129 respectively), I did not check for batch effects at this stage. After merging the batches, for both the European ancestry and mixed ancestry analyses, I conducted stringent QC on the complete dataset that involved SNP and individual sample filtering at < 0.95, MAF filtering for the complete dataset at > 0.05, heterozygosity filtering at |FHet| > 0.2, and clarifying sex discrepancies, where samples with inconsistent or indeterminate sex classification were pruned out. I further pruned for relatedness by removing individuals with IBD pihat >= 0.125 (i.e., excluding third-degree relatives), and a final SNP filtering was conducted based on Hardy-Weinberg Equilibrium violations of $p > 10^{-6}$, leaving a combined n = 135, in the dataset with combined ancestries, and n = 116 in the European-only sub-set.

After stringent QC, the data was imputed to the HRC hg19 panel using Minimac 4 on the Michigan Imputation Server. The array build for my dataset was on the hg19 panel. For both the mixed-ancestry and European-only ancestry datasets I used the following parameters for imputation: HRC r1.1 2016 (GRCh37/hg19) as the reference panel, R^2 filtering > 0.001, Eagle 2.4 phased

output. Post-imputation filtering of MAF <= 0.05, R^2 >= 0.7 was conducted, and finally conversion of dosage to hard calls was done using default PLINK settings. The plink binary files were used for generation of polygenic scores.

Rhythm Polygenic Score

For the rhythm polygenic analysis, I used a well-powered genome-wide association study (GWAS) which had 606,825 individuals of European ancestry who participated in research with personal genomics company 23andMe, Inc. (Niarchou et al., in press). Participants who had consented to participant in research with 23andMe, answered the question "Can you clap in time with a musical beat"? All participants provided informed consent in accordance with 23andMe's protocol, which was reviewed by an external IRB, the Ethical & Independent Review Services. It is the largest GWAS of a musicality trait and queries the trait of "beat synchronization," with the results (69 genome-wide significant loci) highlighting the polygenic architecture of rhythm. Though this GWAS was conducted on a self-reported trait, the authors conducted several validation studies to show that self-reported evaluations of beat synchronisation are correlated with (measured) ability to tap to a musical beat, rhythm perception task performance, a multi-item rhythm questionnaire, and with Goldsmith's musical sophistication scale, thus successfully demonstrating that the self-report is indeed capturing rhythm abilities.

Using the Beat synchronization (rhythm) GWAS summary statistics as the primary trait GWAS, I used the PRS-CS software (Ge et al., 2019) to generate a polygenic model of rhythm. PRS-CS is a python-based software that uses continuous shrinkage to estimate SNP effect sizes based on GWAS summary statistics and an external reference panel that accounts for linkage disequilibrium. Application of PRS-CS requires three separate inputs: i. the GWAS summary statistics of the trait of interest ii. the external LD reference panel matched to the ancestry of the trait GWAS (since the

Rhythm GWAS was conducted in a European-only population, I used the European LD reference panel built based on the 1000 Genomes Phase 3 samples available on the PRS-CS GitHub), and iii. the target sample for which polygenic scores are to be assigned (imputed plink files of the n = 135 mixed ancestry samples or n = 116 European ancestry samples collected in our lab with rhythm and grammar phenotypes).

To build the polygenic rhythm model for my target, sample I used the default parameters for PRS-CS. Once the polygenic model was constructed, I applied this model to my sample and generated a rhythm polygenic score (PGS-R) for each of the participants in my target sample. Polygenic scores are the weighted sum of each individual's SNPs, based on the effect size of those SNPs in a primary GWAS. Since the GWAS is a measure of ability of beat synchronisation, the PGS-R is a score of 'good rhythm', i.e., a higher polygenic score corresponds to increased ability of beat synchronisation and vice-versa.

Linear Regressions of PGS-R with Measured Rhythm and Grammar Phenotypes

I performed linear regression analysis using the PGS-R as the independent variable and the rhythm and grammar phenotypes (viz. BBA, Entrainment Region, expressive grammar (SPELT-3), and SI) as the dependent variables to test the associations between genetic rhythm ability and measured rhythm and grammar task performance. Sex, age, and the first 10 PCs were used as covariates. For this analysis, I z-scored (standardised) all variables: the PGS-R scores, PC values, age, raw SPELT-3 scores, raw SI scores, BBA d' and entrainment region scores, prior to building the regression models. Of the 135 samples that survived QC, we had complete SPELT-3 (expressive grammar outcome measure) for N = 131 samples (aged 5;5 – 7;11, mean = 6;5 years, SD = 10.2 months, 70 females) which were then used in the PGS analysis. Sample characteristics of the

grammar and rhythm phenotypes and demographics of the participants are described in Table 3.1

Table 3.1: Demographics, Sample Characteristics, and Descriptive Statistics of Behavioural Outcomes for PGS analysis

Variable Name	N	Mean	SD	SE	Range	Skew	Kurtosis
Age	131	6.49	0.85	0.07	5.07 – 8.17	0.29	-1.17
PTONI standard scores	124	117.10	20.26	1.82	78 - 150	-0.19	-1.19
SPELT-3 standard scores	131	110.66	11.05	0.97	65 – 126	-1.97	4.86
SI scaled scores	121	12.03	2.68	0.24	5 - 17	-0.50	-0.17
SPELT-3 raw scores	131	44.72	6.28	0.55	15 - 53	-2.18	6.39
SI raw scores	121	22.60	7.26	0.66	6 - 36	-0.30	-0.64
BBA d'	115	0.92	0.84	0.08	-1.20 - 2.73	0.17	-0.66
Entrainment Region scores	102	3.21	2.55	0.23	0.32 – 16.53	2.45	7.64

Note. Demographics, sample characteristics, and descriptive statistics for behavioural outcome measures for the polygenic analysis are shown in this table. SPELT-3 = Structured Photographic Expressive Language Test-3; BBA = Beat-Based Advantage; PTONI = Primary Test of Non-Verbal Intelligence; SI = Sentence Imitation.

Results

Our hypothesis for these analyses is based on the positive associations between musical rhythm perception and grammar performance observed in Chapter 2, and in several other studies. We predicted that PGS-R would be positively associated with BBA scores, ER scores, and with the grammar measures. However, as seen in Table 3.2 and 3.3 we observed non-significant correlations between our outcome measures and the rhythm PGS, for both the European-only subset (n =116) and for all genetic ancestries combined (n = 135). We believe that though our data is richly phenotyped, we did not have the power to detect the genetic effect of rhythm, simply due to our small sample size.

Table 3.2: Linear Regression Results for Rhythm PGS and Outcome Measures, in Participants of European Ancestry

Measure	β	p value	95% Confidence Interval
SPELT-3 Raw score	-0.02	0.85	[-0.19 0.16]
Sentence Imitation score	0.06	0.51	[-0.13 0.25]
BBA d'	0.09	0.34	[-0.10 0.28]
Entrainment Region	-0.13	0.22	[-0.33 0.08]

Note. This table summarises the results of the linear regressions to test the association of polygenic rhythm score with various rhythm and grammar outcome measures, while using age, gender, and 12 principal components as covariates in the regression model, in all participants of European ancestry (n = 116). The outcome measures and PGS were normalized prior to analyses. BBA = Beat-Based Advantage; SPELT = Structured Photographic Expressive Language Test.

Table 3.3: Linear Regression Results for Rhythm PGS and Outcome Measures in Participants of European and Non-European Ancestry

Measure	β	p value	95% Confidence Interval
SPELT-3 Raw score	0.04	0.66	[-0.78 0.31]
Sentence Imitation score	0.04	0.68	[-0.14 0.22]
BBA d'	0.11	0.25	[-0.08 0.30]
Entrainment Region	-0.10	0.27	[-0.29 0.08]

Note. This table summarises the results of the linear regressions to test the association of polygenic rhythm score with various rhythm and grammar outcome measures, while controlling for age, gender, and 12 principal components as covariates in the regression model, in participants of European and non-European ancestry (n = 135). The outcome measures and PGS were normalized prior to analyses. BBA = Beat-Based Advantage; SPELT = Structured Photographic Expressive Language Test.

Discussion

In our current sample we have observed phenotypic correlations between music rhythm perception and grammar task performance. However, we did not find significant associations between musical rhythm perception polygenic score and grammar task performance, which would have helped start to unpack the complex nature of the genetics of language. While we do see trends in the expected direction with higher rhythm polygenic scores corresponding with higher performance on grammar tasks, these correlations are not statistically significant.

One major contributing factor in this analysis might be the small sample size of the tested cohort. While the language variables of the sample were extensively phenotyped and characterised, the effective sample size might prevent detection of the expected correlation between the genetic contribution to rhythm and grammar task performance phenotype. Even in the rhythm perception GWAS which was used to generate the polygenic scores in our target sample, the heritability in a large sample of over half a million people was estimated to be 13 - 16% (Niarchou et al., in press). Twin and family-based studies have estimated the heritability of music related phenotypes to be between 0.2 – 0.8 (Nayak et al., under review). Similarly, language-based traits have also been shown to be moderately heritable – between 0.2 – 0.8 (Bishop & Hayiou-Thomas, 2008; Rice et al., 2018). When investigating cross trait associations between rhythm and grammar, it is thus likely that the moderate heritability of both these traits is not captured by small sample sizes such as in this study, given their extensive polygenic architecture.

Another possible reason why our analyses were not significant could be because the trait used in the GWAS, 'beat synchronisation', overlaps with but is not identical to rhythm perception. Though the rhythm perception test was used to validate the beat synchronisation self-reported trait, the GWAS and the validation studies were conducted in adults. Our target population consists of school-aged children between 5-8 years, and the overlap between the cognitive processes involved in

beat synchronisation and rhythm perception might not be as similar in developing children. As a result, the shared genetic architecture of the traits might not be as evident.

Moving forward, work should focus on building larger sample sizes for each individual trait – rhythm perception (including other music related traits), as well as grammar (and other language related traits). Larger sample sizes would not only enable the parsing of the complex genetic architecture of each individual trait under study but will also aid cross-trait genetic discoveries, like the one hypothesized in this chapter. Such studies will also help unravel the genetic influences driving the co-occurrence of traits by using a heritability and LD-score regression approach. Having deeply genotyped and sequenced genetic information would also be advantageous for considering fine-mapping and functional genomic approaches, which will yield further insight into the possible biological mechanisms driving the associations between musical rhythm perception and grammar task performance.

Chapter 4

Exploring Cross-Trait Genetic Associations between Atypical Speech and Language Phenotypes, Rhythm Impairments, and Other Comorbidities.

Introduction

Developmental Language Disorder (DLD) is a commonly occurring (up to 7% prevalence) paediatric communication disorder characterised by difficulty in effectively learning and utilizing language, especially grammar, with males being at a slightly higher risk than females (1.33:1 ratio of males to females diagnosed with DLD) (Norbury et al., 2016; Simms & Jin, 2015; Tomblin et al., 1997). Weaknesses in language development in children with DLD include difficulty in syntax use, vocabulary, word finding, semantics, immature grammar formation, poor lexicon, inability to effectively follow ideas and tasks, and slower verbal learning and memory in receptive and/or expressive language domains (Bishop et al., 2016; Lancaster & Camarata, 2019). DLD is said to occur independent of external trauma, neurodegeneration, abuse or brain damage, and children with DLD are phenotypically distinguishable from patients whose language capabilities are affected by alternative phenotypes, including, but not limited to, hearing loss, autism, cerebral palsy, and other known neurodevelopmental disorders(Bartak et al., 1975; Bishop, 2017; Kamhi, 1998; Stark & Tallal, 1981).

DLD is primarily a disorder that affects language, and the associations between musical rhythm and language are also applicable to DLD, such that with evidence from literature points to impairments in rhythm production and perception being prominent in DLD (Corriveau & Goswami, 2009; Przybylski et al., 2013). Studies have demonstrated that children with DLD perform below children with typically developing language on several tasks that test musical rhythm such as tapping to a beat, recognising rhythm in music and speech, and rhythm discrimination. It is also

important to note that such rhythm impairments are also commonly seen in other disorders that affect language like dyslexia, thus strengthening the link between rhythm and grammar (for a detailed review see Ladányi et al., 2020).

The complexity of DLD is evidenced by how varied the overall DLD phenotype, trajectory and outcomes are in the clinical population. Based on developmental criteria, language and speech usually develops during the toddler/pre-school stage (Feldman, 2005), and identification of delayed/impaired language can be conducted at this age. Longitudinal studies of DLD, in the past and present, have demonstrated that from a cohort of preschool-aged late talkers (ages 3 ½ - 4), some children will show some resolution of their reading and oral skills by the age of 5 ½ - 6 (Bishop & Adams, 1990; Bishop & Edmundson, 1987; Law et al., 2008; Miniscalco et al., 2007; Snowling et al., 2016). In contrast, those who still struggled with language at age 5.5 continued to show hampered linguistic capabilities including but not limited to oral grammar and vocabulary well into their adolescence (Snowling et al., 2016; Stothard et al., 1998), thus resulting in a consistently impaired language and literacy trajectory across their lifespan (Elbro et al., 2011; Whitehouse et al., 2009).

To complicate matters further, DLD diagnoses are often accompanied by several other comorbidities. Children diagnosed with DLD showed 61% of exhibited comorbidities within the domain of psychiatric and neurodevelopmental disorders (Westerlund et al., 2002). Attention deficit hyperactivity is a commonly co-occurring disorder that affects children with language impairment, and further impacts educational trajectories (Beitchman et al., 1996; Helland et al., 2014; Mueller & Tomblin, 2012; Sciberras et al., 2014). Other studies have also found that children with DLD face issues with mathematical and reading tasks, indicating an overlap with developmental dyslexia and dyscalculia (Manor et al., 2001; Morsanyi et al., 2018; Newbury et al., 2011; Pennington & Bishop, 2009). On the social side of the scale, children with DLD find it difficult to initiate and maintain

friendships, due to social reticence as a result of inability to communicate with peers, as evidenced by increased co-occurrence of conduct and mood disorders with DLD, stunting social development, (Beitchman et al., 1996; Fujiki et al., 2001; Van Daal et al., 2007), further demonstrating that DLD is not limited to its language phenotype. The negative outcomes associated with DLD can extend well beyond childhood. Adults who were diagnosed with DLD as children will often show continued impairments in their cognitive profiles (including higher rates of schizotypal features) well into adulthood which contribute to including low verbal IQ, persistent literacy delays, higher rates of unemployment, poor social adaptability (Clegg et al., 2005; Elbro et al., 2011; Snowling et al., 2006).

Given this broad psycho-social profile of DLD and its associated comorbidities which result in life-long socio-economic pitfalls, the timely identification and provision of intervention for DLD is critical and essential. Although a prevalent disorder, DLD is often underdiagnosed with only ¼ of the clinical population receiving a formal diagnosis (McGregor, 2020; Tomblin et al., 1997). The CATALISE (Bishop et al., 2016, 2017) study noted that it has been difficult to successfully identify key risk factors for DLD, since previous studies focussed only on the language impairment phenotype (Volkers, 2018b, 2018a) with highly specific selection criteria resulting in very small sample sizes. The restriction to identifying only the language related impairments does not allow for the proper overall characterization of the risk factors and comorbidities associated with this disorder, and a broader definition would aid in identifying at-risk children who would benefit from language intervention (Bishop, 2017; McGregor, 2020).

One approach to better understand the medical phenotype of DLD is to take a population-based approach (Raghavan et al., 2018; The National Academies of Sciences, Engineering, and Medicine, 2016). Data mining algorithms using electronic health records (EHRs) are useful in large-scale population-wide studies to classify aetiology and comorbidities (Casey et al., 2016). Identifying DLD cases in existing epidemiological data sets and medical records permits us to capitalise on the

broader definition of DLD and explore associated comorbidities, thus enabling us to tap into the underlying biology of DLD in clinically relevant manner. Using comorbidities to create a phenotypic profile of DLD in electronic data can help identify an "at risk" population, that should then receive high priority in terms of diagnosis, intervention, and attention from clinicians.

We created a phenotyping algorithm called, "Automated Phenotyping Tool for identifying DLD" (APT-DLD) cases in health systems data, to classify DLD cases within Vanderbilt University Medical Center's (VUMC's) de-identified EHR database (Walters et al., 2020). While efficient and holistic diagnosis of DLD by SLPs is valuable for diagnosis and provision of intervention and therapies to patients, APT-DLD is primarily a research tool that enables the quick classification of DLD cases in EHR databases. This algorithm allows for identification of DLD patients with a positive predictive value (PPV) of 95%. Additionally, since APT-DLD does not utilize language processing or key-terms and only relies on ICD codes (International Classification of Diseases) and dates of these ICD codes, access to diagnostic notes and laboratory results are not required, making it easy to deploy in any EHR with ICD code data. ICD codes are a set of alpha-numeric codes that are used by medical professionals to document the health concerns in EHRs.

We applied APT-DLD to two research databased housed at Vanderbilt University Medical Center's - Synthetic Derivative (SD) which consists of de-identified EHRs, and the SD's biobank system (BioVU). EHRs in the SD are associated with their de-identified medical records that include ICD codes, notes, lab reports and relevant demographic information, while EHRs in BioVU have an additional layer of information in the form of their biological data. With APT-DLD we can mine EHR databases, giving us access to a larger sample of people who have a profile that is convergent with DLD. These types of data – phenotype only (as found in the SD) and genetic data (found in biorepositories like BioVU) can be used to conduct enrichment analyses to identify the medical profiles of complex disorders and how they differ from controls as well as genetic analyses to

explore within-trait and cross-trait associations to better understand the genetic architecture of DLD.

Using the DLD cases classified from BioVU using APT-DLD, we sought to understand DLD's polygenic nature using cross-trait genetic analyses, for Aim 3a of this chapter. Generally, traits that show phenotypic association can be influenced by underlying shared genetics – a phenomenon known as pleiotropy (Solovieff et al., 2013; Watanabe et al., 2019). In the case of musical rhythm and language, we first tested the predictions of the Atypical Rhythm Risk Hypothesis via a polygenic approach. We used a rhythm polygenic score (PGS-R) derived from the beat synchronization GWAS (see Chapter 3 for details) to ascertain if risk for rhythm impairments would be associated with the presence of DLD. That is, when comparing PGS-R of DLD cases and their matched controls, the cases would have lower PGS-R (i.e., impaired beat synchronization abilities) as compared to the controls.

Further, with the DLD cases identified from the SD, which only have phenotype information, we employed a phenotype enrichment algorithm to identify related comorbidities that are enriched in the DLD population as compared to matched controls (Shaw et al., in preparation). The most significantly associated groups were language and developmental phenotypes, auditory phenotypes, weight and nutrition phecodes, colorectal phenotypes, conduct and social disorders, motor co-ordination errors, atopic disorders, and pulmonary phenotypes. Using these phenotypically associated comorbidities we created a list of curated traits, identified existing large-scale GWAS' of these traits, and investigated possible cross-trait genetic associations for Aim 3b. This strategy helps us bring together complementary methods to paint a clearer picture of the complex genetic aetiology of DLD.

Finally, we tested the Atypical Rhythm Risk Hypothesis in a third cohort that captured a broader spectrum of speech and language symptoms, for Aim 3c. Given that atypical rhythm is

observed in several other developmental disorders as well including dyslexia, stuttering, ADHD, and developmental co-ordination disorder (Ladányi et al., 2020), we used a broader definition to identify possible instances of developmental speech and language problems from the eMERGE database. Using EHRs from emerge that meet out criteria for speech-language disorder symptoms and their matched controls, we used a polygenic approach to test the correlation between genetic risk of rhythm impairment and presence of speech and language symptoms. We expect higher risk of rhythm impairment (lower PGS-R) to be predictive of speech-language symptoms.

The current study thus has 3 sub-aims: 3a. testing the predictions of the Atypical Rhythm Risk Hypothesis with DLD, 3b. investigating cross-trait polygenic associations between DLD and associated comorbidities and 3c. testing the predictions of the Atypical Rhythm Risk hypothesis in a sample of EHRs with indications of speech and language symptoms.

Methods

Aim 3a. Testing the Atypical Rhythm Risk Hypothesis in a DLD cohort

Cohort Selection using APT-DLD

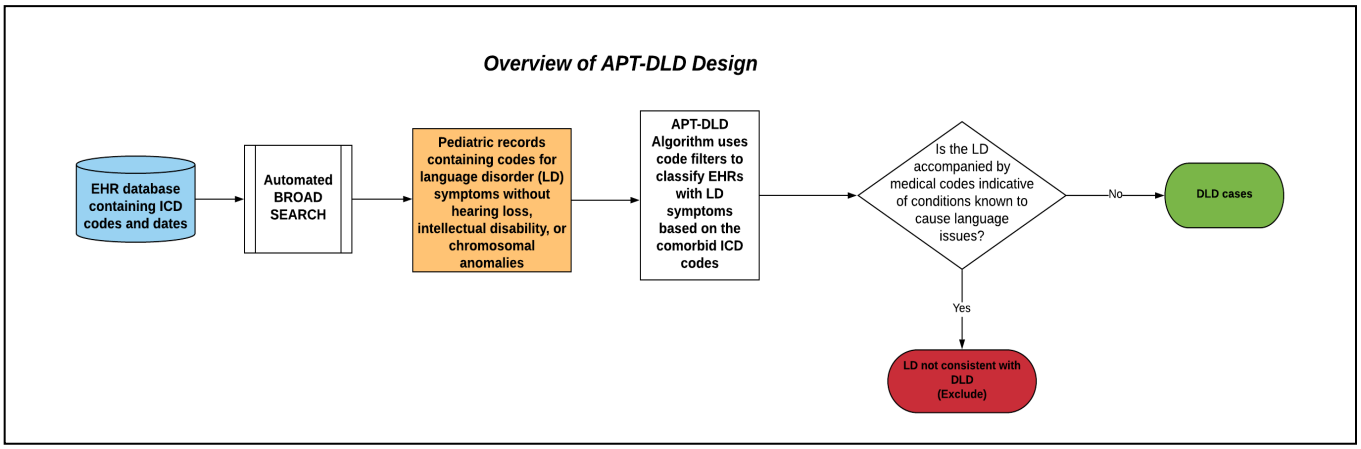
We created an automated phenotyping algorithm called APT-DLD (Automated Phenotyping Tool for identifying DLD), which is an electronic health record (EHR) data mining algorithm which relies on six language disorder ICD codes, a small set of exclusion criteria, and the dates of these codes to classify the DLD status for a patient (Walters et al., 2020). APT-DLD uses both ICD-9 and ICD-10 codes to inform its classification system. The algorithm was developed to mimic the classification results that the manual chart review of these EHRs, by an SLP clinician would yield. The target population for this technique includes paediatric records from EHR systems with ICD 9 and 10 indicators of DLD. Because we proposed exploring the genetic architecture of DLD via polygenic score analysis, we focused on identifying EHRs with available genetic data, and applied

APT-DLD to BioVU, Vanderbilt University Medical Centre's biobank. Ethical use of the genetic and EHR data reported in the current dissertation in Chapter 4 is covered by an approved institutional review board exemption (application no. 150643), and all users working with these data filed data use agreements with the institution that set forth policies and procedures that protect the integrity and confidentiality of the data.

Cases. The application of APT-DLD to an EHR system involves two steps. The first is a 'Broad Search' which uses a combination of six speech and language related ICD 9 and 10 codes as primary inclusion criteria, another set of ICD codes relating to hearing loss, intellectual disabilities, and chromosomal abnormalities as the exclusion criteria, and an age filter to identify a paediatric sample of EHRs. This broad search identified 973 paediatric EHRs that met all the criteria.

The second step involves the application of code filters that use the presence of certain ICD codes in the EHRs to classify them into 2 major categories: DLD cases and cases with language symptoms not consistent with DLD. From the 973 EHRs identified as potential DLD cases, 469 EHRs were classified by APT-DLD as DLD cases. An overview of APT-DLD is presented in Figure 4.1.

Figure 4.1: Overview of the Phenotyping Algorithm APT-DLD



Note. This figure summarises the major components and processes of applying the APT-DLD algorithm to an EHR database.

Controls. Up to 5 controls were selected for each case from a pool of 80,000 genotyped BioVU EHRs, for a total of 2065 controls (number of cases available for control selection is 413; see section on genotyping for details). Controls were matched to the identified case-set based on genetic similarities derived from PCs from ancestry assignment, sex, and age (within 5 years of the matched case). Control matching was conducted using a python-based control matching software developed by D. Shaw. Table 4.1 tabulates the self-reported demographics of the 413 DLD cases and 2065 matching controls.

Table 4.1: Demographic Characteristics of the DLD Cases and Matched Controls from BioVU

Variable	Category	Cases	Controls
Race			
	Caucasian	219 (53%)	1,198 (58%)
	African American	97 (23%)	420 (20%)
	Asian	13 (3%)	62 (3%)
	American Indian	0 (0%)	6 (0.3%)
	Unknown	5 (1%)	341 (17%)
	Other	5 (1%)	34 (2%)
	Multiple Race	0 (0%)	4 (0.1%)
Ethnicity			
	Hispanic/Latino	74	276 (13%)
	Non-Hispanic	339	1,549 (75%)
	Unknown	0	240 (12%)
Gender			
	Male	280	1,400 (68%)
	Female	133	665 (32%)
Total N		413	2,065

Note. The table shows the number of EHRs from BioVU per self-reported race, ethnicity and gender group in the cases and controls. Percentages are denoted in parentheses.

Genotyping

Of the 469 EHRs classified as DLD cases, 413 had useable genetic data as determined by BioVU. 205 of these 413 samples were previously genotyped at BioVU as part of a larger genetic effort. The Music Cognition Lab further requested genotyping of the remaining 208 DLD EHR samples. These 208 samples were genotyped in Batch2020 along with the 132 samples from Chapter 3. All genotyping efforts at Vanderbilt are carried out by VANTAGE, where the biobanked DNA of the EHRs is genotyped using the Illumina Infinium® MEGA^{EX}. The Expanded Multi-Ethnic Genotyping Array was developed to provide comprehensive coverage of SNPs across European, East Asian, and South Asian populations. As a result, we can include multiple genetic ancestries in our analysis. Post genotyping, the VANTAGE lab conducted primary quality control (QC) on the data and securely transferred the raw files and well as the plink compatible data to us.

Quality Control of Genetic Data

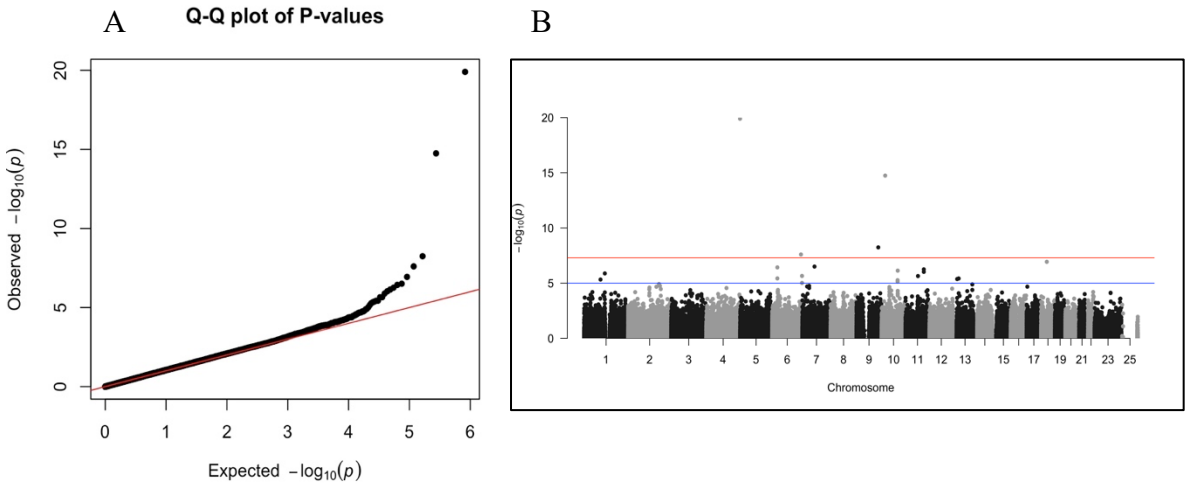
The data received from VANTAGE underwent stringent quality control to prune variants and samples with low quality data. The data was subject to QC, then imputed and analysed in two ways – one that included only those participants of European ancestry, and the second with participants of European and non-European ancestry together.

As with the QC for Chapter 3, the QC for the DLD EHRs was also carried out in two batches, Batch2020 and BatchVGI. Batch2020 contained the 208 DLD EHRs that were additionally genotyped, while BatchVGI which contained the remaining 205 DLD cases and the matching 2065 controls for the entire DLD case-set (n = 2270), was genotyped previously as part of a larger effort at the Vanderbilt Genetic Institute to spearhead genetic discoveries in BioVU. The thresholds used for the QC of Batch2020 are described in Chapter 3, and for ease of reference are included in parentheses in this description. BatchVGI was subject to the following first pass QC in PLINK: removal of duplicate variants and indels, SNP filtering and individual filtering at a call rate of < 0.90 (SNP filtering call rate < 0.90, and sample missingness threshold < 0.80 for Batch2020), updating ids to rsID names using VANTAGE's documentation, removal of rsID duplicates, flagging heterozygous samples (|FHet| > 0.2 filtering for Batch2020), flagging sex discrepancies (at this stage sex discrepant participants were not omitted from either batch), and finally SNP filtering for Hardy-Weinberg Equilibrium violations at $p < 10^{-20}$. Next, I used PRIMUS to perform a PCA, calculate PCs, and assign genetic ancestries to the participants. I further split both the batches into their ancestral groups based on these PCs (viz. European, African-American, Hispanic, South Asian, and East Asian). From BatchVGI, there were n = 1294 samples of European ancestry (106 from Batch2020), 542 of African American (56 in Batch2020), 191 of Hispanic (28 in Batch2020), 197 of South-Asian (15 in Batch2020) and 46 of East Asian ancestry (2 in Batch2020). Since the population of East-Asian ancestry was small in both the batches, these samples, and their matched controls

were dropped from further analyses. For each ancestral group I performed ancestry specific MAF filtering to remove SNPs with minor allele frequencies < 0.05, and SNP filtering for Hardy-Weinberg Equilibrium violations at $p < 10^{-10}$. Finally, I removed the participants relevant to Chapter 3 analyses (n = 130) from Batch2020 and kept only the 205 DLD EHRs. Similarly, after primary QC on the BatchVGI sample I had n = 2224 DLD EHRs that were included for further analyses.

Prior to merging the DLD EHRs from Batch2020 and BatchVGI, I ran a small GWAS using genotyping batch as the 'trait' of study to identify any batch related effects in only the cases from the two batches. Batch2020 had all 205 DLD cases, while BatchVGI had retained 200 DLD cases after first pass QC. I merged only the case-set from both the batches, filtered for variant and sample missingness at a call rate of < 0.95, an additional MAF filtering to remove SNPs with minor allele frequencies < 0.05, removal of sex discrepancies, removal of related samples (IBD pruning for pihat >= 0.125) and a final SNP filtering conducted based on Hardy-Weinberg Equilibrium violations of $p > 10^{-10}$. I performed a GWAS on these 398 remaining samples, with batch as the phenotype (Fig. 4.2 shows the qq-plot and the Manhattan plot for the batch GWAS), and identified SNPs with a p value $< 10^{-5}$, since these SNPs might be associated with the genotyping batch.

Figure 4.2: QQ Plot and Manhattan Plot for Testing the Effect of Genotyping Batch



Note. This figure highlights the results of the GWAS' conducted to test for genotyping batch effects. The QQ plot in (A) shows the deviation from the expected p values of the significant SNPs and the Manhattan plot (B) shows the chromosomes with the SNPs most significantly associated with genotyping batch. The red line in Fig 4.2 (B) indicates genome-wide significance after Bonferroni correction, which is set at 5 x 10^{-8}, while the black line indicates genome-wide significance of 5 x 10^{-5}

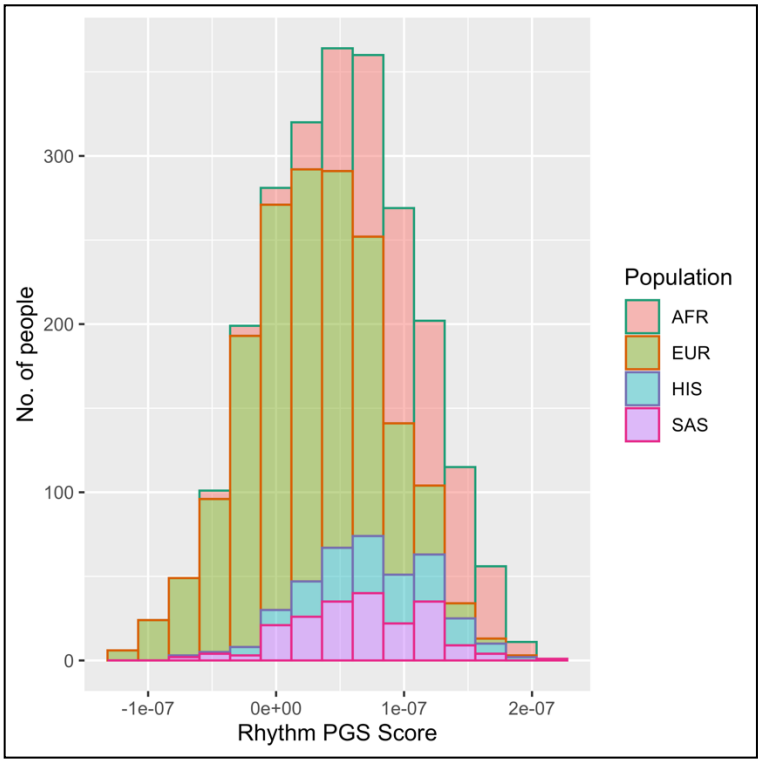
I then merged the study participants that remained from Batch2020 (n = 205) and the study relevant participants from BatchVGI (n = 2224), for a combined sample size of 2429. After merging, I filtered the batch-associated SNPs from the merged files since we wanted to be certain to include only those SNPs that will not be influenced by variation in genotyping. This was followed by a stringent variant and sample filtering at a call rate of < 0.95, MAF filtering at a call rate < 0.95, filtering for heterozygous samples |FHet| > 0.2, pruning samples with discrepant sex, filtering for relatedness (pihat >= 0.125), and a final SNP filtering to remove variants with Hardy-Weinberg Equilibrium violations of p > 10^{-10}. Next, I matched the controls to the remaining cases, and removed those controls that did not have a matching case in the sample. There were no unmatched cases, and each case had at least 1 matched control. This final sample had 398 cases (of the original 413 DLD cases) and 1960 matched controls (of the 2065 matched controls).

After stringent QC, the data was imputed to the HRC hg19 panel using Minimac 4 on the Michigan Imputation Server. The array build for my dataset was on the hg19 panel. I used the following parameters for imputation: HRC r1.1 2016 (GRCh37/hg19) as the reference panel, R^2 filtering > 0.001, Eagle 2.4 phased output. Post-imputation filtering of MAF <= 0.05, R^2 >= 0.6 was conducted, and finally conversion of dosage to hard calls was done using default PLINK settings. The plink binary files were used for generation of polygenic scores.

Polygenic Score Generation

Using the 'Rhythm' GWAS summary statistics as the primary trait GWAS, I used the PRS-CS software (Ge et al., 2019) to generate a polygenic model of rhythm. I then applied this polygenic model to the DLD cases and controls, to generate a PGS-R for each sample. For details of the PGS generation please refer to Chapter 3. The distribution of the PGS-R of the sample separated by the ancestries shows that the distributions are similar, and there are no outlier groups by ancestry. The PGS-R distributions are plotted in Figure 4.3.

Figure 4.3: Distribution of Rhythm Polygenic Scores of DLD Cases and Controls



Note. Figure 4.3 depicts the distribution of rhythm polygenic scores of all the DLD cases and controls in our cohort, grouped by ancestry. AFR = African-American ancestry, EUR = European ancestry, HIS = Hispanic ancestry, SAS = South Asian ancestry.

Logistic Regression to test the association of PGS-R with DLD status

I performed a logistic regression analysis using the PGS-R as the independent variable and the DLD status (case vs control) as the dependent variable to test the associations between genetic risk of rhythm impairment and DLD status. Sex and the first 10 PCs were used as covariates. For this analysis, I z-scored (standardised) the following variables: the PGS-R scores (z-scored within each ancestry group), and the PC values, prior to building the regression model. Based on the observation that children with DLD have rhythm impairments, we hypothesized that genetic risk of rhythm impairments would be associated with DLD cases, rather than with controls. That is, DLD cases would have lower PGS-R as compared to the controls.

Heritability of DLD in EHRs classified by APT-DLD.

Though the sample size of DLD EHRs determined from BioVU by APT-DLD is quite small to conduct a well-powered GWAS to study identify genetic variants associated with DLD, we used the Genome-based restricted maximum likelihood (GREML) analysis from the Genome-wide Complex Trait Analysis Tool (GCTA) to calculate the SNP-based heritability of DLD in BioVU (Yang et al., 2011). SNP-based heritability is the proportion of variance in the phenotype that is explained by all the SNPs. Estimating heritability can help us better understand the extent to which genetic variation influences the measured phenotype. GREML analysis occurs in two steps – the first is the calculation of a genetic relationship matrix (GRM) which estimates the relatedness between in the individuals based on the SNPs. The second step is the calculation of the SNP-based heritability from the GRM. Thus, the SNPs used to calculate the GRM are used to inform the genetic variance. I used a 7% DLD prevalence (Tomblin et al., 1997), sex, and the top 3 PCs as covariates during the GREML analysis.

Aim 3b. Testing Cross-Trait Genetic Correlations using Results from Phenotype Enrichment Analysis

Phecode Enrichment Analysis to Identify Comorbid Phenotypes

Cohort Selection Using APT-DLD. In addition to applying APT-DLD to BioVU, we also classified a cohort of DLD cases that contained exclusively phenotypic data by applying APT-DLD to the Synthetic Derivative (SD). The SD is the EHR system at Vanderbilt University Medical Centre which contains over 3.1 million records. EHR information in the SD includes a de-identified patient ID, demographic information like age, sex, ethnicity, and clinical information including medications, lab values, test results, procedural and surgical codes, and ICD9 and 10 diagnostic and billing codes.

Cases. Application of the Broad Search of the APT-DLD algorithm helped select a pool of 13,652 paediatric EHRs, that met all the Broad Search criteria. Application of the APT-DLD code-filters finally classified 6013 EHRs as DLD cases. This case set of 6013 patients were then mapped to their phecodes exclusively from the ICD-9 codes in their EHR (excluding ICD-10 records).

Controls. We selected controls from a pool of 700,000 patients with available demographic and phecode record sets (phecode records were similarly only mapped from ICD-9 records) randomly selected from the SD. Controls were selected to match the identified case-set, based on ethnicity, race, age (within 5 years of matched case), and number of clinical visits (control clinical visit count must be within 20 visits of matched case). Up to five controls were selected for each case. Cases unable to be matched to a single control based on above criteria were removed from this study. Following control selection, 5273 cases and 26,353 controls were selected for the phecodes enrichment analysis. Control selection was conducted using the python-based control matching software developed by D. Shaw.

Phenotype Enrichment Results. Using the Phecode-enrichment algorithm (Pruett et al., 2021) developed by the Below Lab, we ran a large-scale comorbidity analysis in this large sample of classified DLD cases and controls from the SD, to assess phecodes/phenotypes that are more enriched in the DLD population as compared to matched controls. This methodology is useful for exploring replication of previously described DLD comorbidities and as well as identification of novel phenotypic associations. Through the comorbidity analysis, we identified 37 unique phecodes enriched in our DLD cohort as compared to their matched controls. The phecode enrichment analyses were conducted by D. Shaw, and the manuscript elucidating the results from this study is under preparation (Shaw et al., in preparation).

GWAS Selection

Using the phecodes identified via the phenotype-enrichment analysis, and through a literature survey of comorbidities associated with DLD, I curated list of traits that are known comorbidities of DLD. Using this list of traits, I identified well-powered, publicly available GWAS summary statistics related to these traits in order to conduct cross-trait PGS analyses with our DLD cohort identified from BioVU. This method is designed to explore the possibility of shared genetic variation between DLD and other traits. The traits used for this analysis are tabulated below in Table 4.2.

Table 4.2: Details of the GWAS' Used in the Cross-Trait Analysis

GWAS name	Phenotype Measured	N (GWAS)	PMID/Link	Phenotype coding in primary GWAS
Depressive symptoms	Depressive Symptoms	1,067,913	30643256	Higher score indicates increased depressive symptoms
Anxiety/tension	Anxiety (or anxious symptoms)	270,059	30867560	Higher score indicates more anxiety
ADHD	Attention Deficit Hyperactivity Disorder	55,374	30478444	Positive score indicates presence of ADHD
Insomnia	Insomnia	386,533	30804565	Positive score indicates presence of insomnia
Educational attainment (EA)	Number of years of schooling	766,345	30038396	Higher score stands for more years of schooling
Processing speed	Reaction time (perceptual motor speed)	330,024	32895543	Higher score indicates worse performance
Usual Walking Pace	Usual walking pace	384,081	31427789	Higher score signifies faster walking pace
Musculoskeletal strength	Grip strength of right hand	359,729	http://www.nealelab.is/uk-biobank	Higher score signifies greater grip strength

Genotyping and QC

The genotyping and QC for the DLD cases and matched controls is described in the methods for Aim 3a.

Polygenic Score Generation

Using the GWAS summary statistics for each of the traits in Table YYY above as the primary trait GWAS', I used the PRS-CS software (Ge et al., 2019) to generate a polygenic model of each individual trait. I applied the polygenic models of each trait to the DLD cases and controls, to generate a separate PGS for each sample for each trait. For details of the PGS generation please refer to Chapter 3. I also ensured that the distributions of each of the PGSs for the sample are not affected by outliers.

Analysis

I performed a series of logistic regression analysis using the various PGSs as the independent variable and DLD status (case vs control) as the dependent variable to test the associations between genetic risk of DLD-associated comorbidities and presence of DLD. Sex and the first 10 PCs were used as covariates. For this analysis, I z-scored (standardised) the following variables: the PGS scores (z-scored within each ancestry group) and the PC values, prior to building the regression model. After generation of the PGSs for each trait, I plotted the distribution of the scores grouped by genetic ancestry to ensure there were no ancestry-dependent outliers. These exploratory cross-trait analyses could yield insight into the overlapping genetic architecture between the comorbidities of DLD and DLD itself.

Aim 3c. Using the Atypical Rhythm Risk Hypothesis to Predict Prevalence of Speech-Language Symptoms

Cohort Selection in eMERGE using ICD inclusion and exclusion codes.

The eMERGE (Electronic Medical Records and Genomics) network is a consortium organized and funded by the National Human Research Institute, between the EHR and

biorepositories of 12 medical and academic research across the United States. This network was founded for the express purpose of combining EHR and biorepository resources to allow collaborating researchers to conduct high-throughput genetic and phenotype-based studies. eMERGE Phase III data grants access to the de-identified medical records and genetic information of 105,008 participants. Collaborators receive eMERGE samples with imputed genotyped variants in VCF files by chromosomes (imputed to HRC 1.1 b37/hg19), PCA results with ancestry assignment, IBD results, imputed R^2 metrics, demographic files, and medical records in the form of ICD 9 and 10 codes for every eMERGE participant. We applied APT-DLD to the eMERGE database and sought to increase the size of our DLD sample. However, there is an abundance of adult EHRs as compared to paediatric EHRs in eMERGE and further, several eMERGE paediatric records are genotyped for disorders that were part of our exclusion criteria. As a result, we could not classify sufficient DLD EHRs from eMERGE. We decided to expand our definition to include paediatric EHRs that have symptoms of all types of speech and language disorders and explore the polygenic architecture of speech-language symptomology.

Cases. We used a combination of 25 ICD codes as inclusion criteria and 94 ICD codes as exclusion criteria to select a pool of possible cases to which I then applied an age filter to exclude non-paediatric records who received an inclusion code after the age of 18. Thus, we identified a set of 3241 paediatric cases that met the broadest definition of developmental speech language symptoms. Table 4.3 lists the complete inclusion and exclusion criteria for cases.

Table 4.3: List of ICD 9 and 10 Codes used as Inclusion and Exclusion Criteria for eMERGE Cases

ICD Code	ICD Flag	Code Description
315.0	9	Developmental reading disorder
315.00	9	Developmental reading disorder, unspecified
315.01	9	Alexia
315.02	9	Developmental dyslexia
315.09	9	Other specific developmental reading disorder
315.2	9	Other specific developmental learning difficulties
315.3	9	Developmental speech or language disorder
315.31	9	Expressive language disorder
315.32	9	Mixed receptive-expressive language disorder
315.34	9	Speech and language developmental delay due to hearing loss
315.35	9	Childhood onset fluency disorder
315.39	9	Other developmental speech or language disorder
315.4	9	Developmental coordination disorder
F81.0	10	Specific reading disorder
F81.89	10	Other developmental disorders of scholastic skills
F81.81	10	Disorder of written expression
F80.1	10	Expressive language disorder
F80.2	10	Mixed receptive-expressive language disorder
F80.4	10	Speech and language development delay due to hearing loss
F80.81	10	Childhood onset fluency disorder
F80.0	10	Phonological disorder
F80.89	10	Other developmental disorders of speech and language
F82	10	Specific developmental disorder of motor function
H93.25	10	Central auditory processing disorder
R48.0	10	Dyslexia and alexia
Q90	10	Down syndrome
Q90.0	10	Trisomy 21, nonmosaicism (meiotic nondisjunction)
Q90.1	10	Trisomy 21, mosaicism (mitotic nondisjunction)
Q90.2	10	Trisomy 21, translocation
Q90.9	10	Down syndrome, unspecified
Q91	10	Trisomy 18 and Trisomy 13
Q91.0	10	Trisomy 18, nonmosaicism (meiotic nondisjunction)
Q91.1	10	Trisomy 18, mosaicism (mitotic nondisjunction)
Q91.2	10	Trisomy 18, translocation
Q91.3	10	Trisomy 18, unspecified
Q91.4	10	Trisomy 13, nonmosaicism (meiotic nondisjunction)
Q91.5	10	Trisomy 13, mosaicism (mitotic nondisjunction)

Q91.6	10	Trisomy 13, translocation
Q91.7	10	Trisomy 13, unspecified
Q92	10	Other trisomies and partial trisomies of the autosomes, not elsewhere classified
Q92.0	10	Whole chromosome trisomy, nonmosaicism (meiotic nondisjunction)
Q92.1	10	Whole chromosome trisomy, mosaicism (mitotic nondisjunction)
Q92.2	10	Partial trisomy
Q92.5	10	Duplications with other complex rearrangements
Q92.6	10	Marker chromosomes
Q92.61	10	Marker chromosomes in normal individual
Q92.62	10	Marker chromosomes in abnormal individual
Q92.7	10	Triploidy and polyploidy
Q92.8	10	Other specified trisomies and partial trisomies of autosomes
Q92.9	10	Trisomy and partial trisomy of autosomes, unspecified
Q93	10	Monosomies and deletions from the autosomes, not elsewhere classified
Q93.0	10	Whole chromosome monosomy, nonmosaicism (meiotic nondisjunction)
Q93.1	10	Whole chromosome monosomy, mosaicism (mitotic nondisjunction)
Q93.2	10	Chromosome replaced with ring, dicentric or isochromosome
Q93.3	10	Deletion of short arm of chromosome 4
Q93.4	10	Deletion of short arm of chromosome 5
Q93.5	10	Other deletions of part of a chromosome
Q93.7	10	Deletions with other complex rearrangements
Q93.8	10	Other deletions from the autosomes
Q93.81	10	Velo-cardio-facial syndrome
Q93.88	10	Other microdeletions
Q93.89	10	Other deletions from the autosomes
Q93.9	10	Deletion from autosomes, unspecified
Q95	10	Balanced rearrangements and structural markers, not elsewhere classified
Q95.0	10	Balanced translocation and insertion in normal individual
Q95.1	10	Chromosome inversion in normal individual
Q95.2	10	Balanced autosomal rearrangement in abnormal individual
Q95.3	10	Balanced sex/autosomal rearrangement in abnormal individual
Q95.5	10	Individual with autosomal fragile site
Q95.8	10	Other balanced rearrangements and structural markers
Q95.9	10	Balanced rearrangement and structural marker, unspecified
Q96	10	Turner's syndrome
Q96.0	10	Karyotype 45, X

Q96.1	10	Karyotype 46, X iso (Xq)
Q96.2	10	Karyotype 46, X with abnormal sex chromosome, except iso (Xq)
Q96.3	10	Mosaicism, 45, X/46, XX or XY
Q96.4	10	Mosaicism, 45, X/other cell line(s) with abnormal sex chromosome
Q96.8	10	Other variants of Turner's syndrome
Q96.9	10	Turner's syndrome, unspecified
Q97	10	Other sex chromosome abnormalities, female phenotype, not elsewhere classified
Q97.0	10	Karyotype 47, XXX
Q97.1	10	Female with more than three X chromosomes
Q97.2	10	Mosaicism, lines with various numbers of X chromosomes
Q97.3	10	Female with 46, XY karyotype
Q97.8	10	Other specified sex chromosome abnormalities, female phenotype
Q97.9	10	Sex chromosome abnormality, female phenotype, unspecified
Q98	10	Other sex chromosome abnormalities, male phenotype, not elsewhere classified
Q98.0	10	Klinefelter syndrome karyotype 47, XXY
Q98.1	10	Klinefelter syndrome, male with more than two X chromosomes
Q98.3	10	Other male with 46, XX karyotype
Q98.4	10	Klinefelter syndrome, unspecified
Q98.5	10	Karyotype 47, XYY
Q98.6	10	Male with structurally abnormal sex chromosome
Q98.7	10	Male with sex chromosome mosaicism
Q98.8	10	Other specified sex chromosome abnormalities, male phenotype
Q98.9	10	Sex chromosome abnormality, male phenotype, unspecified
Q99	10	Other chromosome abnormalities, not elsewhere classified
Q99.0	10	Chimera 46, XX/46, XY
Q99.1	10	46, XX true hermaphrodite
Q99.2	10	Fragile X chromosome
Q99.8	10	Other specified chromosome abnormalities
Q99.9	10	Chromosomal abnormality, unspecified
758	9	Chromosomal anomalies
758	9	Down's syndrome
758.1	9	Patau's syndrome
758.2	9	Edwards' syndrome
758.3	9	Autosomal deletion syndromes
758.31	9	Cri-du-chat syndrome
758.32	9	Velo-cardio-facial syndrome
758.33	9	Other microdeletions
758.39	9	Other autosomal deletions

758.4	9	Balanced autosomal translocation in normal individual
758.5	9	Other conditions due to autosomal anomalies
758.6	9	Gonadal dysgenesis
758.7	9	Klinefelter's syndrome
758.8	9	Other conditions due to chromosome anomalies
758.81	9	Other conditions due to sex chromosome anomalies
758.89	9	Other conditions due to chromosome anomalies
758.9	9	Conditions due to anomaly of unspecified chromosome

Note. ICD = International Classification of Diseases

Controls. To select controls, we first identified a large cohort of possible controls which met the following criteria: i. absence of speech and language symptoms, ii. absence of the 94 ICD exclusion codes iii. absence of a secondary list of 87 ICD exclusion codes (Table 4.4). We ascertained a cohort of 82617 EHRs from which we selected matched controls for our cases. Control matching was performed using a python-based software developed by D. Shaw from the Below Laboratory. Controls were matched on assigned sex, assigned genetic ancestry, and site of genotyping. We identified 9307 matched controls, with 44 cases that could not be matched to controls. Demographic information for the cases and controls is shows in Table 4.5

Table 4.4: List of ICD 9 and 10 Codes used as Control Specific Exclusion Criteria for eMERGE Cases

ICD Code	ICD Flag	Code Description
F70	10	Mild intellectual disabilities
F71	10	Moderate intellectual disabilities
F72	10	Severe intellectual disabilities
F73	10	Profound intellectual disabilities
F78	10	Other intellectual disabilities
F79	10	Unspecified intellectual disabilities
H90	10	Conductive and sensorineural hearing loss
H90.0	10	Conductive hearing loss, bilateral
H90.1	10	Conductive hearing loss, unilateral with unrestricted hearing on the contralateral side
H90.11	10	Conductive hearing loss, unilateral, right ear, with unrestricted hearing on the contralateral side
H90.12	10	Conductive hearing loss, unilateral, left ear, with unrestricted hearing on the contralateral side
H90.2	10	Conductive hearing loss, unspecified
H90.3	10	Sensorineural hearing loss, bilateral
H90.4	10	Sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side
H90.41	10	Sensorineural hearing loss, unilateral, right ear, with unrestricted hearing on the contralateral side
H90.42	10	Sensorineural hearing loss, unilateral, left ear, with unrestricted hearing on the contralateral side
H90.5	10	Unspecified sensorineural hearing loss
H90.6	10	Mixed conductive and sensorineural hearing loss, bilateral
H90.7	10	Mixed conductive and sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side
H90.71	10	Mixed conductive and sensorineural hearing loss, unilateral, right ear, with unrestricted hearing on the contralateral side
H90.72	10	Mixed conductive and sensorineural hearing loss, unilateral, left ear, with unrestricted hearing on the contralateral side
H90.8	10	Mixed conductive and sensorineural hearing loss, unspecified
H90.A	10	Conductive and sensorineural hearing loss with restricted hearing on the contralateral side
H90.A1	10	Conductive hearing loss, unilateral, with restricted hearing on the contralateral side
H90.A2	10	Sensorineural hearing loss, unilateral, with restricted hearing on the contralateral side
H90.A3	10	Mixed conductive and sensorineural hearing loss, unilateral with restricted hearing on the contralateral side
H91	10	Other and unspecified hearing loss
H91.0	10	Ototoxic hearing loss

H91.01	10	Ototoxic hearing loss, right ear
H91.02	10	Ototoxic hearing loss, left ear
H91.03	10	Ototoxic hearing loss, bilateral
H91.09	10	Ototoxic hearing loss, unspecified ear
H91.1	10	Presbycusis
H91.10	10	Presbycusis, unspecified ear
H91.11	10	Presbycusis, right ear
H91.12	10	Presbycusis, left ear
H91.13	10	Presbycusis, bilateral
H91.2	10	Sudden idiopathic hearing loss
H91.20	10	Sudden idiopathic hearing loss, unspecified ear
H91.21	10	Sudden idiopathic hearing loss, right ear
H91.22	10	Sudden idiopathic hearing loss, left ear
H91.23	10	Sudden idiopathic hearing loss, bilateral
H91.3	10	Deaf nonspeaking, not elsewhere classified
H91.8	10	Other specified hearing loss
H91.8X	10	Other specified hearing loss
H91.8X1	10	Other specified hearing loss, right ear
H91.8X2	10	Other specified hearing loss, left ear
H91.8X3	10	Other specified hearing loss, bilateral
H91.8X9	10	Other specified hearing loss, unspecified ear
H91.9	10	Unspecified hearing loss
H91.90	10	Unspecified hearing loss, unspecified ear
H91.91	10	Unspecified hearing loss, right ear
H91.92	10	Unspecified hearing loss, left ear
H91.93	10	Unspecified hearing loss, bilateral
317	9	Mild intellectual disabilities
318	9	Other specified intellectual disabilities
318	9	Moderate intellectual disabilities
318.1	9	Severe intellectual disabilities
318.2	9	Profound intellectual disabilities
319	9	Unspecified intellectual disabilities
389	9	Hearing loss
389	9	Conductive hearing loss
389	9	Conductive hearing loss, unspecified
389.01	9	Conductive hearing loss, external ear
389.02	9	Conductive hearing loss, tympanic membrane
389.03	9	Conductive hearing loss, middle ear
389.04	9	Conductive hearing loss, inner ear
389.05	9	Conductive hearing loss, unilateral

389.06	9	Conductive hearing loss, bilateral
389.08	9	Conductive hearing loss of combined types
389.1	9	Sensorineural hearing loss
389.1	9	Sensorineural hearing loss, unspecified
389.11	9	Sensory hearing loss, bilateral
389.12	9	Neural hearing loss, bilateral
389.13	9	Neural hearing loss, unilateral
389.14	9	Central hearing loss
389.15	9	Sensorineural hearing loss, unilateral
389.16	9	Sensorineural hearing loss, asymmetrical
389.17	9	Sensory hearing loss, unilateral
389.18	9	Sensorineural hearing loss, bilateral
389.2	9	Mixed conductive and sensorineural hearing loss
389.2	9	Mixed hearing loss, unspecified
389.21	9	Mixed hearing loss, unilateral
389.22	9	Mixed hearing loss, bilateral
389.7	9	Deaf, nonspeaking, not elsewhere classifiable
389.8	9	Other specified forms of hearing loss
389.9	9	Unspecified hearing loss

Note. ICD = International Classification of Diseases.

Table 4.5: Demographic Characteristics of the Cases and Controls from eMERGE

Variable	Category	Cases	Controls
Assigned genetic ancestry			
	European	2,043 (68%)	5,551 (68%)
	African	836 (28%)	2,325 (29%)
	Asian	139 (7%)	255 (3%)
Sex			
	Male	2,042 (68%)	5,106 (72%)
	Female	976 (32%)	3,025 (28%)
Total N		3,018	8,131

Note. The table shows the number of EHRs from eMERGE per genetic ancestry/sex group in the cases and controls. Percentages are denoted in parentheses.

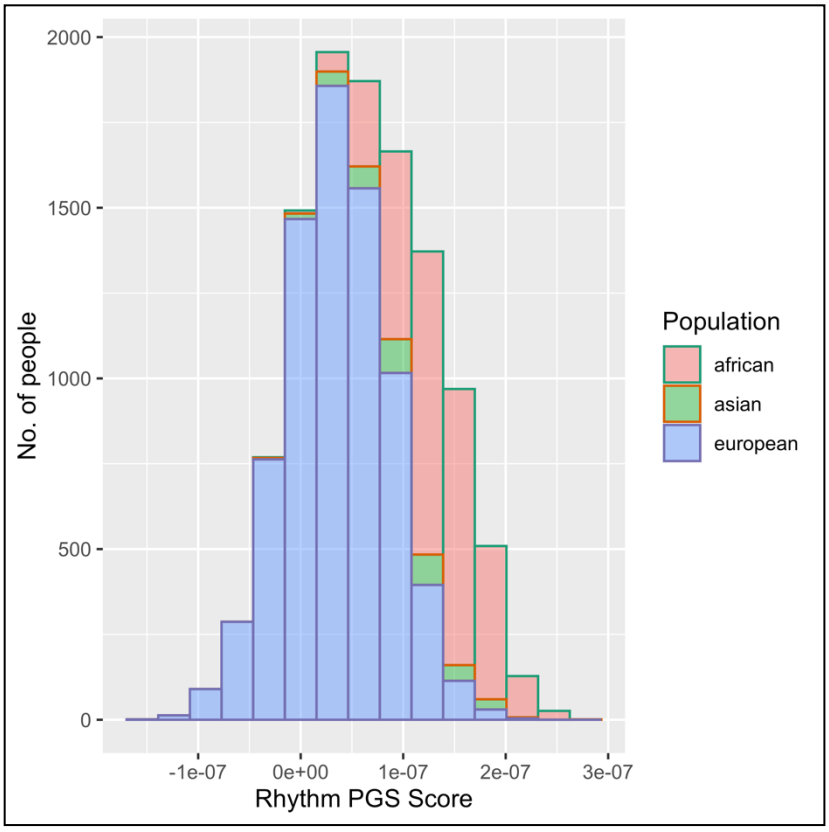
Quality Control of Genetic Data

The Genetic Co-ordination Centre of the eMERGE consortium was responsible for the QC, batch control, and imputation of the genetic data from the various biorepository sites. I conducted post imputation QC on the per chromosome VCF files with imputed genotyped variants, that we received from eMERGE. I filtered the chromosome VCF files on R^2 and MAF, to only include variants with MAF > 0.05 and R^2 > 0.7 and merged the individual chromosome VCF files. Using plink I converted the merged vcf imputed file to binary files. I then remapped SNP names in the binary files from vcfIDs to rsIDs and pruned duplicate variants. This was followed by extraction of the relevant cases and matched controls and pruning of third-degree relatives based on pihat estimates (pihat >= 0.125) from the IBD files provided. The final dataset consisted of 3018 cases and 8720 matched controls, with 76 cases that could not be matched to controls. The demographics of the cases and matched controls used in the polygenic analysis are shown in Table 4.6

Polygenic Score Generation

Using the beat synchronization GWAS summary statistics as the primary trait GWAS, I used the PRS-CS software (Ge et al., 2019) to generate a polygenic model of rhythm. I then applied this polygenic model to the eMERGE cases with symptoms of speech and language disorders and their controls, to generate a PGS-R for each record (in a European ancestry subset, and in the entire cohort of with mixed ancestries). For details of the PGS generation please refer to Chapter 3. I used the assigned genetic ancestries of participants from the eMERGE documentation and plotted the distribution of the PGS-R of the sample separated by the ancestries. The distributions of the scores were similar and, though the PGSs of people of African-American ancestry seem to be higher than those of European ancestry, there are no outlier groups by ancestry. The PGS-R distributions are plotted in Figure 4.4.

Figure 4.4: Distribution of Rhythm Polygenic Scores of EHRs with Speech and Language Symptoms and Matched Controls Identified from the eMERGE Database



Note. Figure 4.4 depicts the distribution of rhythm polygenic scores of all cases with symptoms of speech and language disorder, and their matched controls, in our cohort identified from eMERGE, grouped by assigned genetic ancestry.

Analysis

I performed a logistic regression analysis using the PGS-R as the independent variable and the speech-language symptom status (case vs control) as the dependent variable to test the associations between genetic risk of rhythm impairment and presence of symptoms of speech-language disorders. Sex, site, and the first 10 PCs were used as covariates. For this analysis, I z-scored (standardised) the following variables: the PGS-R scores (z-scored within each ancestry group), the PC values, and the site number, prior to building the regression model. Based on the observation that rhythm impairments often co-occur with developmental speech-language disorders,

we hypothesized that genetic risk of rhythm impairments would be associated with the developmental speech-language symptomology. That is, cases identified with presence of speech-language symptoms would have lower PGS-R as compared to the controls.

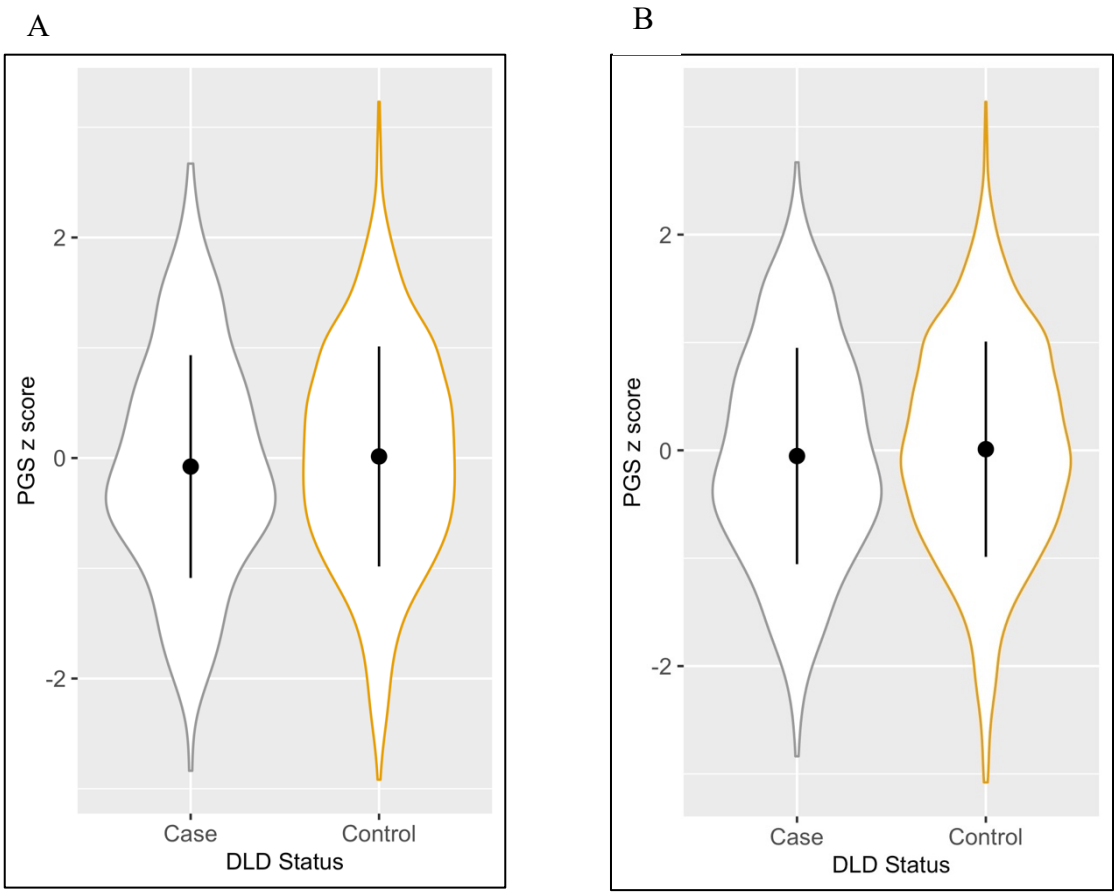
Results

Aim 3a. Testing the Atypical Rhythm Risk Hypothesis in a DLD cohort.

We tested the Atypical Rhythm Risk Hypothesis in our sample of genotyped DLD cases using PGS-R as the predictor for presence of DLD. The results of the log regression show that PGS-R is negatively associated with DLD case-status, in both the sample of mixed ancestry ($r = -0.09$, $p = 0.12$), and in the sub-sample of European ancestry alone ($r = -0.1$, $p = 0.2$), though the association is weak and non-significant. A negative estimate indicates that people with higher PGS-R are less likely to be classified as DLD cases. The direction of this interaction is in the expected direction. The violin plot in Fig 4.5 shows the comparison between DLD cases and controls in both the sample of mixed ancestries and the European-only sub-sample. The small sample size of our DLD cohort might contribute to the lack of statistical significance of the analysis; larger studies may be needed to evaluate this relationship.

SNP-based heritability estimates using GCTA-GREML analysis on the European-ancestry specific DLD cohort showed that 5% of the phenotypic variance in DLD could be explained by the genetic variants in our sample ($V_G/V_P = 0.05$, $SE = 0.22$, $p = 0.39$). Using a web-based tool that calculates power for GCTA-GREML analyses (Visscher et al., 2014), and based on these observations, to achieve ~80% power, we would require a sample of around 5000 DLD cases and 20,000 controls to conduct heritability-based analyses with DLD.

Figure 4.5: Violin Plots Depicting the Distribution of PGS-R in DLD Cases and Controls



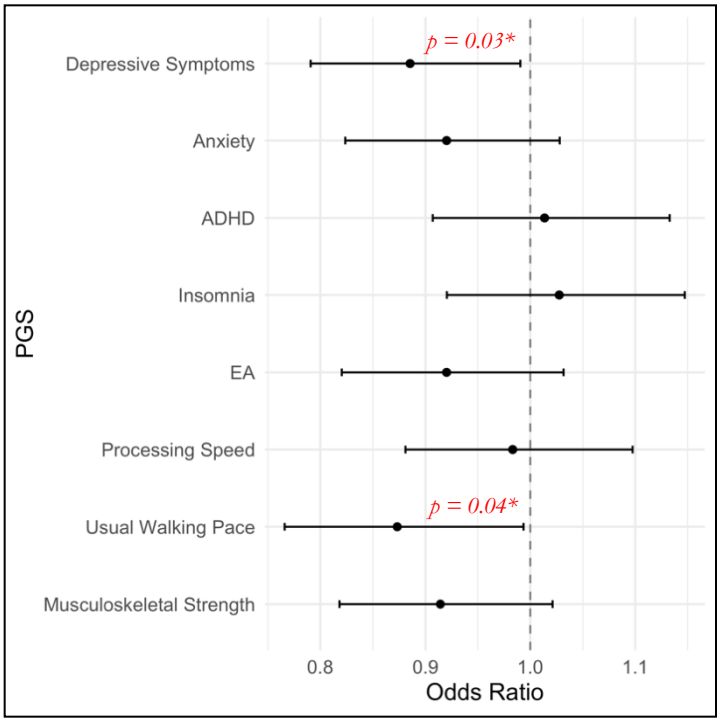
Note. This figure demonstrates the distribution of PGS-R in DLD cases and controls in a European ancestry only sample (A), and in a sample of mixed ancestries (B). Mean and 1 standard deviation of the distribution is also shown with a point-range within the violin plots.

Aim 3b. Testing Cross-Trait Genetic Correlations using Results from Phenotype Enrichment Analysis

The forest plot with the exploratory cross-trait PGS associations between DLD and the curated list of comorbidities is shown in Figure 4.6. The traits we used in our cross-trait analyses were depressive symptoms, anxiety, ADHD, insomnia, educational attainment (EA), processing speed, usual walking pace, and musculoskeletal strength. We found that Depressive Symptoms and Usual Walking Pace are significantly associated with a DLD status. For usual walking pace, the

polygenic score for walking was negatively associated with a DLD status, thus indicating that faster walking pace is more likely to occur in controls, with DLD cases have slower walking pace (r = -0.14, p = 0.041). We used usual walking pace as a possible measure of motor co-ordination and control, and our findings are in line with literature that shows that people with DLD often also show impairments in the realm of motor function (Finlay & McPhillips, 2013; Flapper & Schoemaker, 2013). For the depressive symptoms PGS analysis, higher report of depressive symptoms is associated with controls than with cases (r = -0.12, p = 0.034). This observation is contrary to our expectations and with clinical observations that show people with DLD are also likely to suffer from depression later in life (Botting et al., 2016)

Figure 4.6: Forest Plot of Cross-Trait Analysis



Note. This figure depicts the forest plot of the odds ratio and confidence intervals of the all the cross-trait associations we tested with DLD. p values of traits whose polygenic scores were associated significantly with DLD are indicated in red. ADHD = Attention Deficit Hyperactive Disorder; EA = Educational Attainment.

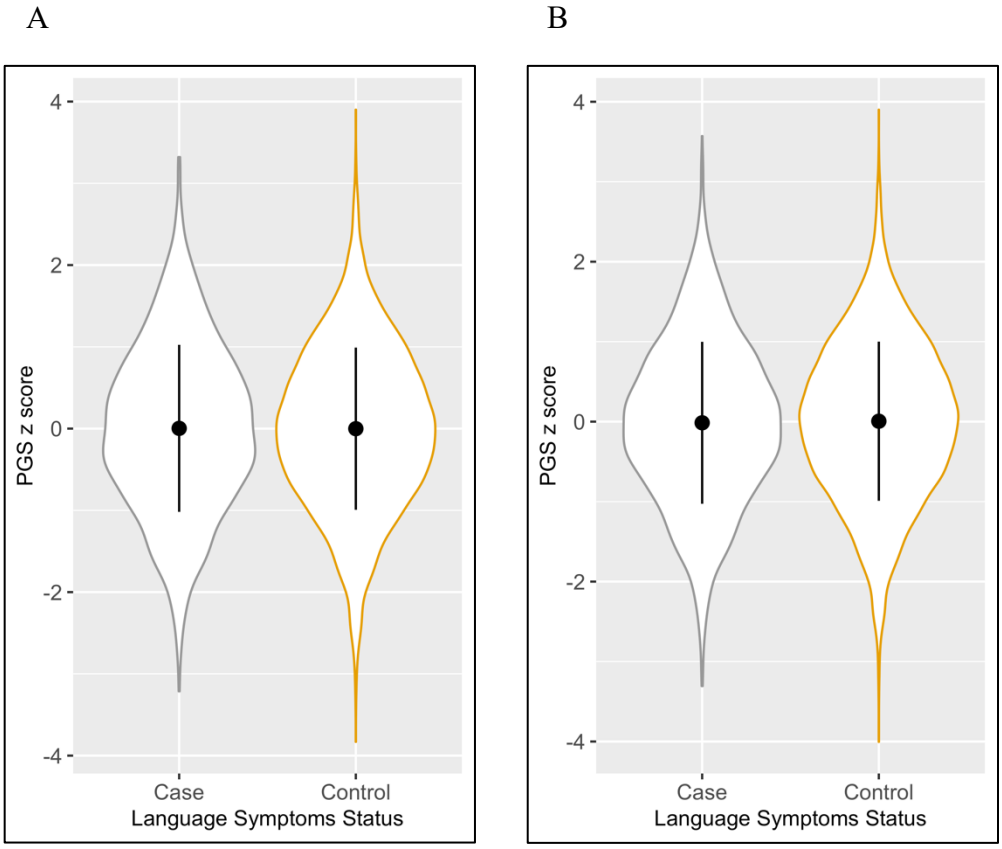
Associations between the other traits and DLD status were non-significant, and the conclusions drawn from these results are elucidated in the Discussion for this chapter.

Aim 3c. Using the Atypical Rhythm Risk Hypothesis to Predict Prevalence of Speech-Language Symptoms

For this aim, I tested the predictions of the Atypical Rhythm Risk Hypothesis, in a cohort that met a wider definition of developmental speech-language symptoms, rather than in a particular speech-language disorder. It is possible that atypical rhythm is an accompanying feature of some type of atypical development, that regardless of diagnosis, is more likely to be associated with atypical speech and language. In such cases it is also likely that that genetic variation linked to rhythm impairments would also predict presence of speech-language symptoms.

Our expected results would show that a lower PGS-R would be associated with the presence of speech-language symptoms (i.e., cases as defined in this cohort). The log regression analysis found that though there is a negative correlation between speech-language symptoms and PGS-R in both the sub-sample with mixed ancestry ($r = -0.02$, $p = 0.25$), and the one with European ancestry (-0.02, $p = 0.54$), the correlations were small and non-significant. The figure below (Figure 4.7) illustrates the distribution of the PGS-R between the cases and the controls using a violin plot.

Figure 4.7: Violin Plots Depicting the Distribution of PGS-R in eMERGE Cases and Controls



Note. This figure demonstrates the distribution of PGS-R in eMERGE cases and controls in a European ancestry only sample (A), and in a sample of mixed ancestries (B). Mean and 1 standard deviation of the distribution is also shown with a point-range within the violin plots.

Discussion

The major focus of this chapter was in testing the predictions of the Atypical Rhythm Risk Hypothesis (Ladányi et al., 2020). This hypothesis was a result of the collation of evidence throughout literature that point to the presence of rhythm impairments in developmental speech and language disorders. Generally, studies employing a group design in children with DLD (or Specific Language Impairment) have shown that rhythm impairments measured via rhythm discrimination tasks (Bedoin et al., 2016), tapping to beat/speech/music tasks (Corriveau & Goswami, 2009;

Cumming et al., 2015), rhythm perception abilities (Sallat & Jentschke, 2015), and rhythm processing (in music and speech) tasks (Caccia & Lorusso, 2021), co-occur with DLD more than they do in typically developing children. Studies have also shown that much like children with typical language development, children with DLD show improvement in performance on grammaticality judgement tasks (Ladányi et al., 2021; Przybylski et al., 2013) after listening to regular rhythmic primes, though their performance is still below their peers with typical language development. Given the evidence that musical rhythm and language skills are correlated, and there is an inverse correlation between impairment in music rhythm perception and production, and language development, we utilised methods to explore this relationship at the genetic level.

Complementing phenotypic studies that showcase the associations between language and musical rhythm are useful because they capture the range of abilities across two traits, underlying questions about the biology of such correlated traits could be explained by the genetic influences behind these traits (Nayak et al., under review). One driving mechanism that could be responsible for the correlations seen between rhythm and language could lie in genetic architecture common to both traits. Genetic pleiotropy occurs when one gene or a set of overlapping genes influence two or more phenotypic traits. When considering the phenotypic links between musical rhythm and grammar, a common subset of genes could directly be influencing common biological pathways that are used in processing rhythm and grammar. It could also be that a common set of genes is responsible for the development of specialized neural processes and structures that in turn play a role in musical rhythm and language perception. The study of shared genetic architecture is problem that can be approached from many different angles. Because DLD is a disorder that is underdiagnosed, population-based genetic analyses that rely on large sample sizes are harder to implement. However, using cross-trait polygenic score analysis, is another path to look for

indications of shared genetic architecture between two phenotypically correlated traits, and is the method we employed in this Chapter.

In Aim 3a, we tested whether a PGS-R would be able to predict the presence of DLD in a cohort of EHRs from BioVU classified as DLD using APT-DLD. Our analysis found that there is no significant detectable relationship between polygenic score for (impaired) rhythm and DLD case status, in our sample. We believe that this could simply be because the identified cohort is small, and we need to increase sample size to gain power. SNP-based heritability as estimated by GCTA-GREML showed that around 5% of the phenotypic variation in our DLD cases can be explained by genetic variants, showing that there is some genetic contribution to DLD driven by common variants in the population. We have tested APT-DLD (Walters et al., 2020) in other biorepositories and EHR systems as well, as a first step in classifying DLD cases and accruing a larger sample size. APT-DLD has been successfully deployed in external EHR systems that only have phenotypic data in the form of ICD codes and demographics, and has classified larger DLD cohorts, showing that it is indeed a scalable algorithm. In biorepositories, our observation has indicated that there is a lack of genotyped paediatric records, and as a result, we have not been able to identity a larger population of DLD records with available genetic data that could be used for polygenic analysis.

Because we have a larger pool of DLD EHRs with phenotype information in the form of ICD codes, we decided to use a phenotype-enrichment approach to explore the comorbidities associated with DLD classified from within EHR systems. This phenotype-enrichment analysis (Shaw et al., in preparation) found several comorbidities to be associated with DLD. From the results of the enrichment analysis, a literature survey, and the list of publicly available GWAS', we selected a list of comorbidities we could use to expand the pleiotropy analyses to include other phenotypes associated with DLD. We used depressive symptoms, anxiety, ADHD, insomnia,

educational attainment, processing speed, usual walking pace and musculoskeletal strengths as the comorbidities of choice to explore polygenic associations with DLD.

In Aim 3b, we used this curated list of co-morbidities, and their GWAS summary stats to generate polygenic scores of each of the comorbid phenotypes and test the associations between the polygenic scores and the presence of DLD. We observed significant correlations with DLD for usual walking pace and depressive symptoms. The polygenic risk for depressive symptoms was negatively and significantly associated with DLD cases. Previous evidence has indicated that the neuropsychiatric profiles of children and adults with DLD are fairly complex (Tomas & Vissers, 2019). Children with DLD often show poor social engagement (Tervo, 2007), are reserved in interactions(Rescorla et al., 2007), exhibit depressive symptoms (Carson et al., 1998; Hawa & Spanoudis, 2014), and might also develop schizotypal features as adults (Elbro et al., 2011). Further, ADHD and developmental dyslexia are common comorbidities observed in children with DLD (Snowling et al., 2020; Westerlund et al., 2002). Based on these observations we believed that depressive symptoms, anxiety, and ADHD might share genetic features with DLD. We expected there to be a positive correlation between genetic risk of depression and DLD, that is a higher polygenic score for depressive symptoms should be predictive of presence of DLD. Our results were contrary to our hypothesis, and it is a possibility that while clinically noted depressive features co-occur with DLD, there might not be shared genetic architecture between these two traits, and the hurdles in communication faced by people who have DLD are influencing the association between depression and DLD. For ADHD our results showed correlations in the predicted direction, though this associations were non-significant. The correlation between DLD status and anxiety, much like in the case for depressive symptoms was in the opposite direction, with higher anxiety being associated with controls rather than with the presence of DLD.

A study by Strom and Silverberg (2016) demonstrated that co-occurrence of eczema and ADHD or sleep disturbances have an accumulative risk for speech disorders in children. This observation is supported by Botting and Baraka (2018) who demonstrated poor sleep profiles both for going to sleep and waking in children who have DLD. Sleep EEG (electro encephalogram) studies by Dlouha et al.(2020), Picard et al.(1998), and Echenne et al.(1992) have further shown that there is a prevalence of nocturnal and sleep related epileptiform discharges in children with DLD, which can hamper neural development in childhood (Holmes, 2016). Bearing in mind the relationship between sleep abnormalities and DLD, we hypothesized that there would be a direct correlation between the polygenic risk score (PRS) for insomnia and DLD status. The analysis showed that there is indeed a positive correlation, though the small sample of DLD might be underpowered to enable detection of this association.

Global delays in general expressive language, with late-talking, is a hallmark of children who have DLD (Paul et al., 2008). Given that effective use of language is important in an educational environment (Conti-Ramsden et al., 2002; Conti-Ramsden et al., 2018; Laasonen et al., 2018), children with DLD are often also diagnosed with learning disorders like dyslexia and dyscalculia (Manor et al., 2001; Pennington & Bishop, 2009), which results in poor long-term educational outcomes, including increased instances of academic failure (Aguilar-Mediavilla et al., 2019). A large GWAS using education attainment as the trait, was used in the cross-trait analysis with DLD. This analysis showed that there is a negative association between increased education attainment polygenic score and DLD, which is a non-significant correlation, though in the expected direction.

Impairment in processing speed is a construct of cognitive ability that co-occurs with DLD. General processing speed measured by slower response time in a flanker task was shown to be predictive of verbal language abilities in children (Kautto et al., 2021). Similarly nonverbal processing speed measured using visual tasks was predictive of language outcomes, with DLD children

consistently being slower than their TD counterparts (Ebert, 2021; Park et al., 2020). The results of our processing speed PGS – DLD analysis found a negative association between faster processing speed (higher PGS for processing speed) and DLD status, though once again this correlation was not significant.

Usual walking pace was negatively associated with DLD cases (i.e., genetic risk of slower walking pace was associated with cases), and this finding is convergent with clinical observations. Another measure for motor function in our analyses was musculoskeletal strength (measured as grip strength of the right hand), which was also negatively, though non-significantly associated with DLD cases as expected. The prevalence of motor dysfunctions in the realm of developmental language disorder has also been explored in previous studies. Neural imaging has demonstrated that the cerebellum and basal ganglia structures are recruited during the processing of language (Booth et al., 2007; Kotz et al., 2003; Macoir et al., 2013; Silveri, 2021). Notably these regions of the brain are also part of the circuitry that controls motor learning and movement (Groenewegen, 2003; Turner & Desmurget, 2010). Children with DLD systematically show poorer performance on tests of gross and fine motor skills (Zelaznik & Goffman, 2010), are impaired at tasks that require them to synchronize to a musical beat (Corriveau & Goswami, 2009), and show delayed motor development (Diepeveen et al., 2018). Our results from the analyses between walking pace and musculoskeletal strength go hand-in-hand with the fact that developmental co-ordination disorder is often comorbid with DLD (Bishop et al., 2016; Dlouha et al., 2020; Flapper & Schoemaker, 2013; McGregor et al., 2020).

These cross-trait analyses should not lead to causal inferences since they are exploratory in nature. However, they are a starting point to start considering other genetic methods that look at genetic correlations between associated traits, to better understand pleiotropy between them. Several of the PGS analyses yielded non-significant results which might be a direct function of the small

sample size of our DLD cohort. It is also entirely possible that the nature of DLD in the cohort we identified using APT-DLD might be driven by rare genetic variants as compared to common genetic variants. It is common genetic variation which is captured by genotyping and used in population-based analysis like GWAS and polygenic score-based methods – with rare variants requiring a different experimental design. As a result, the methods used for analyses as part of this chapter are not adept enough to capture the effect of rare genetic variants in our cohort.

Finally, we broadened our definition of language disorder to include 'symptomology of speech and language disorders' in a paediatric population to be able to test the Atypical Rhythm Risk Hypothesis in a larger sample. Since ICD codes are often not a formal diagnosis but are indicative of the presence of the symptoms and comorbidities, it is possible that among children with a wide range of medical phenotypes, that are indicative of atypical speech and language features, but agnostic to a diagnosis of a disorder, that genetic variation linked to impaired rhythm would also predict presence of speech-language symptoms. We hypothesized that lower polygenic score for rhythm (i.e., genetic risk of rhythm impairments) would be correlated with presence of speech language symptoms (i.e., cases). Our analysis showed a negative association between PGS-R and cases status, as expected, though the correlation was not significant.

The involved aetiology, profile, and outcome trajectory of DLD provides insight into how DLD is complex genetic trait. The study of complex genetic traits using GWAS approaches, requires very large sample sizes to clearly unravel the underlying architecture. Large sample sizes for DLD at the population level are challenging to find since the diagnosis of DLD is a labour-intensive process, leading to DLD being commonly underdiagnosed (Tomblin et al., 1997) and understudied (McGregor et al., 2020). Lack of consensus on the definition exact clinical manifestation of DLD, further makes it harder for clinicians to effectively identify DLD, and for families of children with DLD to seek necessary intervention. Developing phenotyping algorithms that leverage existing

information in data-rich medical health record repositories to identify cases is one possible way of expanding the focus of DLD identification from the community to the population level. Meta-analysis of genetic data across cohorts identified from several EHR and biobanks can be a valuable way to use GWAS to study DLD.

By conducting genetic analyses with DLD and other associated traits, as we have during the Chapter, we are attempting to understand the genetic architecture of a complex trait like DLD. Cross-trait or multi-trait analyses are useful in increasing the sample size and therefore the power to detect variants and provide much needed insight into the biological overlap between two traits. While GWASs are useful in identifying variants which are associated with a trait, they are focused on a singular trait, and miss out on the opportunity to integrate available phenotypic data on other traits to spearhead novel genetic discoveries. Cross trait analyses have proved useful in identifying genetic pleiotropy between several types of cancers and *MYC* (Ghoussaini et al., 2008; Grisanzio & Freedman, 2010), type 1 diabetes and auto-immune diseases (Smyth et al., 2004), and recently with asthma and mental health disorders (Zhu et al., 2019, 2021). The 2018 BrainStorm Consortium study showed interesting genetic pleiotropy between several psychiatric disorders demonstrating that there are common genetic factors that might influence the observed clinical co-occurrence seen in these psychiatric disorders (Anttila et al., 2018). Such findings regarding shared biological mechanisms and causal effects may eventually affect identification and personalized treatment of DLD, further laying emphasis on a precision medicine approach (Solovieff et al., 2013).

A cross-trait approach to unravelling the possible pleiotropy underlying DLD and musical rhythm was the primary focus of this chapter. Given the well documented phenotypic correlations between musical rhythm impairments and presence of speech-language disorders, we considered both a disorder specific and broader symptom-based case definition to test the pleiotropic predictions laid out in the Atypical Rhythm Risk Hypothesis. Several of our results showed non-

significant associations, and we believe that even though we used well-powered GWASs to conduct our polygenic analysis, the sample size of our DLD cohort was too small to be well powered for this kind of analysis. Apart from a small sample size, there is a possibility that DLD might be driven by rare genetic variants as opposed to common variants. To account for these hurdles, we need a multi-pronged approach, one that focuses on increasing efforts to identify and genotype individuals with DLD, but also on alternative methods to test pleiotropy. The use of methods that test structural variations, copy number variants, fine mapping, and gene mapping approaches that are more sensitive to capturing the effect of rare variants in a disorder would be one avenue to explore.

In addition to the small sample size and the contribution of rare genetic variants to the DLD phenotype identified in our cohorts by APT-DLD, there might be alternative reasons why we could not detect a significant relationship between the PGS-R and language impairment. For one, there is a possibility that even though there exists an association between language abilities and rhythm perception, there is no underlying shared genetic architecture that influences these two traits. In such a situation, the phenotypic correlation seen might be due to overlap in neural endophenotypes, but these neural pathways would be influenced by independent genetic loci. According to this hypothesis, we would not see a cross-trait correlation between the genetic architecture of music and grammar phenotypes. It is also entirely possible that the DLD cohort we identified from BioVU, has language impairments that are not driven by genetic factors, and the language concerns in these records stem from undetected primary neurological disorders that are heterogeneous in nature with language phenotype manifesting as a comorbidity. Given these possibilities, it would be interesting to explore the rhythm-language link using other disorders that also demonstrate comorbid rhythm perception and production impairments like dyslexia, stuttering, and ADHD. Leveraging well characterised disorders like dyslexia, would also grants us access to larger sample sizes, for testing our hypothesis, and if we can reliably demonstrate shared genetic architecture between other

language disorders and atypical rhythm, efforts to retest in DLD in future larger samples would also be warranted.

Chapter 5

Global Discussion, Conclusions, and Future Directions

Global Discussion and Preliminary Conclusions

Studying individual differences provides us with a constellation of abilities, thus painting a more elaborately detailed picture of the variability of an observed trait. Using this broader spectrum of abilities also lends insight into how complex the processing and development of these trait might be (Lubinski, 2000). Rhythm and language skills are the two traits we are most interested in exploring, given the intriguing associations between them. This dissertation leveraged both phenotype-based modelling methods and genetic analyses to study individual differences in rhythm and grammar across populations with typically developing and atypical language skills. Understanding these individual differences and how they are reflected in the context of rhythm and grammar associations will be valuable at the both the translational and basic science levels.

In Chapter 2 we used a phenotype-based modelling approach to study the relationship between musical rhythm sensitivity and grammar task performance in a typically developing population. This analysis was conducted in a considerably sized group of 132 school-aged children and was focussed on exploring the possible mediators between musical rhythm and grammatical skill. The two mediators in question were sensitivity to prosody, which is a key element in parsing speech and is leveraged by babies and toddlers in language learning, and working memory, a process that helps us store, manipulate and process information during cognitive tasks, and which is also associated with rhythm synchronisation ability as well as with the process of identifying grammatical violations (Ireland et al., 2019; Miyake et al., 2000; Zhou et al., 2017). By employing a path model to test for mediation, we hoped to better understand the cognitive processes that might be bridging the associations between musical rhythm and grammar. In line with prior evidence, we showed a

positive, significant correlation between musical rhythm sensitivity and expressive grammar task performance, between musical rhythm sensitivity and prosodic perception, between prosodic perception and expressive grammar task performance, and finally between musical rhythm and ability to parse complex syntax in grammar (Fig 2.5 A-D). Interestingly, our path model did not show evidence of a mediatory role for either prosodic sensitivity or working memory (Fig 2.6). Even when controlling for IQ in the path model the correlation between musical rhythm and expressive grammar was positive, significant, and not influenced by our chosen mediators (Fig 2.7). The path models testing complex syntax ability as the outcome mirrored our results with expressive grammar (Fig. 2.8 A-B). Although we did not see a mediatory effect of prosodic sensitivity or working memory abilities on the rhythm-grammar association, because we used highly reliable language characterization and behavioural tests, these results might hint at underlying processes that were not explicitly tested in our study. These findings suggest that the direct effect of musical rhythm on grammatical ability might lie in their shared organisation and structure, and hierarchical processing is the hidden mediating factor behind the rhythm-grammar correlation. The clinical implications of demonstrating this stable relationship between musical rhythm perception and grammatical abilities are far reaching. If musical rhythm abilities are predictive of language skills, early identification of children at risk of developing language disorders could help such individual seek timely diagnosis and intervention. Given that developmental language disorders are common, yet underdiagnosed in the paediatric population, leveraging a non-language based, early-identification method would be valuable to the clinical field.

Chapter 3 extended the phenotypic observations from the previous chapter to the realm of genetics. Studies in plants, animals, and recently in humans have shown that the phenotypic correlations between two seemingly unrelated traits, usually foreshadow underlying genetic correlations and hint at pleiotropic genetic interactions that are influencing these traits (Cheverud,

1988; Sodini et al., 2018). We used a polygenic score approach to test the possible causal overlap between the genetic architectures of musical rhythm and grammar (Solovieff et al., 2013). We applied polygenic scores derived from the beat synchronisation GWAS to our genotyped sample of school-aged children. These children were part of several studies in the lab that looked at a broad range of language development and included children with deeply phenotyped grammatical and musical rhythm traits with a wide range task performance. Using the polygenic scores as the predictor and the grammar and musical rhythm phenotypes as the outcome measures, we sought to test whether there would be a positive correlation between polygenic score for typical beat synchronisation and performance on expressive grammar and musical rhythm sensitivity tasks. Given our small sample size of participants in this study, we believe we may have been underpowered to detect significant correlations between our variables (Tables 3.2, 3.3).

Finally in Chapter 4, we tested the Atypical Rhythm Risk Hypothesis using DLD, and with presence versus absence of a broad array of speech/language symptoms as the outcome measures. To combat the smaller sample sizes that are often seen in language-trait genomic studies, we developed an automated tool (APT-DLD), to spearhead classification of DLD in large EHR databases (Walters et al., 2020). APT-DLD is capable of using EHR-associated ICD-codes and dates of these ICD codes to rapidly classify EHRs with symptoms of language disorders into those consistent with DLD (where the language disorder symptoms are idiopathic), and those whose language disorder symptoms can be explained by another factor (e.g., traumatic brain injury). Using this tool, we identified a set of DLD EHRs with genetic data to use as our cohort in this study. We generated rhythm polygenic scores for these DLD EHRs and their matched controls and tested if DLD status was associated with increased genetic risk for rhythm impairments. Further, we employed a similar approach to test for cross-trait associations between these DLD cases and a curated list of DLD-relevant comorbidities. While we did not see significant results for predicting

DLD status with rhythm polygenic scores, we did see interactions between DLD status and motor co-ordination and depressive symptoms (Fig 4.5, 4.6). These results, though not causal, indicate a promising avenue for employing cross-trait polygenic approaches as another way to resolve the genetic architecture of complex traits like language and rhythm processing. Further, we implemented a broader definition of speech and language symptoms in the eMERGE biobank (rather than a specific disorder) to identify EHRs with ICD codes indicative of symptoms that capture an umbrella of speech and language symptoms. Since atypical rhythm perception is noted in other language disorders like stuttering and dyslexia as well, it is likely that regardless of diagnosis, speech-language concerns share some genetic architecture with atypical rhythm. By applying the rhythm polygenic score model to a case-control set identified from eMERGE, we tested if genetic risk of atypical rhythm was associated with speech-language symptomology (Fig 4.7). As with the DLD cohort, we did not observe significant results in our analysis.

While sample size seems to be likely culprit in Chapter 3 and 4, it is also possible that musicality traits like rhythm perception, and language do not in fact have shared genetic architecture. Independent sets of genes could be responsible for influencing common mechanisms and cognitive processes involved in decoding music and language. It is also possible that in our sample of DLD records in Chapter 4, the language impairments are not driven by genes that particularly affect language. Future work should focus on several other avenues – including testing the relationship between the genetics of other language disorders and rhythm impairments, exploring the possibility of mediated pleiotropy and of independent genetic architectures, and leveraging other language and musicality-based GWAS' to test possible cross-trait pleiotropy.

Future Directions

The studies described in this dissertation barely begin to chip at the surface of what are intriguing and complex biological processes. Elucidating the genetic and biological mechanisms that are central to the ubiquitous human traits of musicality and language will require a combination of approaches, some which tackle the developmental underpinnings, some which look at the neural correlates and adopt a neuro-cognition based path, others which take a population-based approach, and even some that are based in behavioural psychology. In this dissertation, we have used the broadest possible definition of language abilities – which includes but is not restricted to the components of language, as well as speech and reading abilities, thus covering the understanding and communication of language. Teasing apart the rhythm-grammar links is an interdisciplinary undertaking – one that will involve neuroscience, psychology, genetics, molecular biology, and developmental sciences. While this may seem like a monumental task, approaching the question using varied methods will most likely help paint the clearest picture possible of such an interesting phenomenon.

Our results from the path model indicated that the associations between musical rhythm sensitivity and grammatical abilities are not influenced by prosodic sensitivity or working memory, when controlling for age and IQ. This relationship is unique and not driven by the mediators in our study. We discuss our findings in the light of hierarchical processing, a general cognitive process that is employed when processing inputs that are organised in a hierarchy that unfolds over time. Further evidence for the possible role of hierarchical processing comes from neuro-imaging studies (Heard & Lee, 2020) that looked at regions of the brain employed during musical rhythm-based tasks and grammar tasks (especially those involving syntactical processing) and found that areas involved in deciphering hierarchies overlap somewhat with areas active during rhythm and language tasks. Perhaps using a cognitive task that taps into hierarchical processing like artificial grammar learning

can provide a measurable phenotypic trait to be used as a mediator (Westphal-Fitch et al., 2018). Artificial grammar learning tasks, which have visual demands, have been shown to share processing similarities with linguistic syntax, and might thus shed some light on the common cognitive mechanisms at play in the associations between musical rhythm sensitivity and grammatical skill.

In Chapter 3 and 4, while it is likely that lack of large samples played a role in our analyses being non-significant for the tested hypotheses in the DLD cohort, it could also be the case that in our sample of DLD EHRs classified from BioVU, the developmental speech and language hurdles have rare variants contributing to their variance, as compared to common variants. Even when considering complex traits, incorporating the effects of rare variants together with methods like polygenic scores that leverage distribution of common variants, has been shown to improve the predictive capabilities of these methods (Smail et al., 2020). We could adopt several approaches to refining our analytical methods – first, we should continue to search out external biobanks to apply APT-DLD in and identify larger cohorts of DLD cases that can be used in a meta-analysis. The second possibility is to opt for rare-variant association analyses using sequenced data (either whole-genome or even whole exome sequenced data), and test for functional gene related associations within our cohort to DLD (S. Lee et al., 2014). GWASs and strategies that leverage GWAS data are better suited for identifying the contribution of common genetic variants to complex traits, than they are at identifying rare variants. Association tests that can account for the burden of common and rare variants and their contribution to the trait, are even more powerful (Curtis, 2019). The third way is to consider a functional genomics approach using eQTL analysis with FINEMAP or transcriptome-wide methods such as gene-set and expression-based approaches like PrediXcan and FUMA (Gamazon et al., 2015; Watanabe et al., 2017; Zhu et al., 2021). A newer method that generates a polygenic-transcriptome scores (Liang et al., 2022) – similar to polygenic risk scores but

based on gene-expression levels has been shown to be even more accurate at modelling risk across ancestries.

One feature of rhythm-language links, that we have not considered are the associated motor traits. Evidence for the involvement of the motor system comes from neuroimaging studies that show a link between the motor and linguistic domains. Speech perception engaged the cortical motor and pre-motor areas of the brain (Berent et al., 2015; Sheng et al., 2018), especially when listening to action-related words (Pulvermüller et al., 2005). Increased motor-area activation was seen during second-language based tasks (Tian et al., 2020), and motor regions were also engaged during, though differentially, during tasks that involved processing of literal vs. abstract language constructs (Guan et al., 2013; Tian et al., 2020). In addition, there is evidence for auditory-motor coupling when listening to beat-based rhythms, showing that the motor cortex and associated regions of the motor system are activated during rhythm perception and processing as well (Cannon & Patel, 2021; Cheng et al., 2022; C. L. Gordon et al., 2018; Penhune & Zatorre, 2019). In all, the motor system has an interesting functional overlap with language and rhythm processing indicating another avenue which could be used to better understand the correlations between musical rhythm perception and grammatical abilities.

Further insights into the recruitment of the motor regions of the brain in rhythm and language comes from observations made in neuro-developmental disorders that affect language and neurodegenerative disorders that affect movement. A general delay in achieving motor milestones and impairments of fine and gross motor skills in children with developmental language disorders has been demonstrated through several studies (Diepeveen et al., 2018; Finlay & McPhillips, 2013; Zelaznik & Goffman, 2010). Children with such developmental language disorders also show rhythm perception and production impairments (see Ladányi et al., 2020 for a review) and children with developmental coordination disorder also often show rhythm impairments (Trainor et al.,

2018). Similarly, studies in patients with Parkinson's Disease, a neurodegenerative disease that particularly affects the basal ganglia and is characterised by motor features, have demonstrated that apart from loss of motor coordination, patients have trouble both with discrimination of beat-based rhythms, and with language production (Grahn & Brett, 2009; Macoir et al., 2013). Rhythmic priming experiments that involve listening to metrically regular or irregular rhythms, have indicated a positive effect of regular rhythms on grammaticality judgements. In parallel, rhythmic auditory stimulation experiments, that involve training movements to a regular beat, have been shown to impact gait in patients with Parkinson's (Bella et al., 2017; Nombela et al., 2013). Both rhythmic priming and rhythmic auditory stimulation test the effect of entrainment and provide converging evidence for the role of the motor system and the basal ganglia in rhythm and language (Schön & Tillmann, 2015).

Understanding all three features – rhythm, language, and motor coordination, will help paint a clearer picture of the genetic and neurobiological architecture of rhythm and language. Considering the role of the motor system in the music rhythm and grammar associations could be key in unravelling the underlying biological and genetic influences of these traits, and thus deserves further investigation.

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