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Rhythm and timing as vulnerabilities in neurodevelopmental disorders

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Abstract

Millions of children are impacted by neurodevelopmental disorders, which unfold early in life, have varying genetic etiologies, and can involve a variety of specific or generalized impairments in social, cognitive, and motor functioning requiring potentially life-long specialized supports. While specific disorders vary in their domain of primary deficit (e.g., autism spectrum disorder (social), attention-deficit/hyperactivity disorder (attention), developmental coordination disorder (motor), developmental language disorder (language)), comorbidities between neurodevelopmental disorders are common. Intriguingly, many neurodevelopmental disorders are associated with difficulties in skills related to rhythm, timing, and synchrony though specific profiles of rhythm and timing impairments vary across disorders. Impairments in rhythm and timing may instantiate vulnerabilities for a variety of neurodevelopmental disorders and may contribute to both the primary symptoms of each disorder as well as the high levels of comorbidities across disorders. Drawing upon genetic, neural, behavioural, and interpersonal constructs across disorders, we consider how disrupted rhythm and timing skills early in life may contribute to atypical developmental cascades that involve overlapping symptoms within the context of a disorder's primary deficits. Consideration of the developmental context, as well as common and unique aspects of the phenotypes of different neurodevelopmental disorders, will inform experimental designs to test this hypothesis including via potential mechanistic intervention approaches.

Keywords: neurodevelopmental disorders, rhythm, synchrony, language disorders, autism spectrum disorder, developmental coordination disorder

Introduction

Rhythm and timing are essential to successful development. Beginning in the neonatal period, infants are sensitive to rhythmic regularities present in music and speech, with EEG studies indicating detection of auditory changes occurring at rhythmically salient moments[1,2]. According to some theories, humans' sensitivity to rhythm to coordinate behavior is essential to the forming of social bonds critical for survival[3]. The importance of rhythm is exemplified by its prominence in infant-directed communication, which provides a predictable, temporal structure to facilitate coordinated interaction between infant and caregiver (e.g., modulation of attention, turn-taking vocal exchanges)[4]. Rhythm is also salient to infants in part because it crosses modalities[5]: for example, a mother singing a nursery rhyme to her child provides integrated rhythmic information across auditory (vocal acoustics), visual (facial and body movements), vestibular (rocking/bouncing motion) and haptic (patting child) modalities. By supporting temporal predictions regarding when and what will occur across modalities, rhythm provides a foundation for individuals to attend to the world around them and plan and execute behaviors. Indeed, success in early temporal coordination such as measured, e.g., by the relative durations of interpersonal pauses during an adult-infant vocal interaction, predicts an array of socio-cognitive outcomes in language, cognition, and attachment (e.g., 4).

Given the fundamental role of rhythm in typical development, it is perhaps not surprising that impairments in rhythm, timing, and synchrony/coordination occur across a variety of neurodevelopmental disorders (NDDs)[6–8]. NDDs, which impact millions of children and include both relatively common (e.g., attention-deficit/hyperactivity disorder (ADHD); autism spectrum disorder (ASD); developmental coordination disorder (DCD); language disorders) and rare (e.g., specific genetic syndromes) disorders, begin early in life and may require life-long, specialized supports. NDDs are characterized by specific constellations of strengths and weaknesses that involve cognitive, sensory, motor, and social functioning (Table 1). While the etiology and primary diagnostic deficit(s) of specific disorders vary, overlapping behavioral symptoms occur across NDDs and comorbidities between disorders are common[9]. Here we explore an emerging framework that suggests that impairments in rhythm and time processing may be associated with comorbidities and common areas of divergence from typical development across different NDDs; moreover, individual differences in rhythm processing could explain heterogeneity of skill development within disorders. In the current paper, we integrate knowledge from genetic, neuroscientific, behavioral and clinical perspectives to examine the development of rhythm in its phenotypic correlations and biological underpinnings across NDDs. We review cross-domain rhythm skills in a variety of NDDs and propose future directions that include rhythm in models of typical and atypical human development.

Genetic and Neural Perspectives in Rhythm/Timing Impairments: It's Time for a Transdiagnostic Approach

Human rhythm and timing sensitivities emerge very early in development and contribute to adaptive behaviors including language and social communication. If (impaired) rhythm processing plays a role in the manifestation of NDDs, we must consider what genetic factors might play a role in the development of rhythm processing. Similar to most cognitive traits that vary across the population, there is a continuous, normal distribution of rhythm sensitivity/skill in the population, and these individual differences can provide a lens into the underlying biology. Rhythm-related skills such as rhythm discrimination and sensorimotor tapping show moderate *heritability* (i.e., a proportion of the variance in rhythm skills are due to genetic factors), as demonstrated by twin studies (e.g. [10]). The molecular genetics underlying rhythm ability have also been recently investigated in a large-scale genome-wide association study (GWAS)[11]. Genetic associations with self-reported beat synchronization were examined in N=606,825 (the phenotype was responses to the item "*Can you clap in time with a musical beat?*", validated in relation to task-based synchronization to a musical beat in a separate sample). Findings indicated a highly polygenic genetic architecture, i.e., beat synchronization is associated with genetic variation at a large number of genomic loci occurring widely across the genome. These genetic associations showed enrichment for regions of the genome that regulate gene expression in the central

nervous system, both in fetal and adult brain tissue, highlighting potential early neurodevelopmental processes. The study also uncovered genetic *pleiotropy* (shared genetic architecture among distinct traits[12]) between beat synchronization and two types of biological rhythms: respiration and circadian chronotypes.

These initial GWAS results for rhythm align with conceptual frameworks of ongoing work in the psychiatric genetics field showing that widespread pleiotropy among cognitive/neurological traits is the rule rather than exception[13]. Not only is there emerging evidence of pleiotropy between neurological and psychiatric traits[14,15], but recent work analyzing the relationship between over 500 GWAS's shows that 90% of genomic loci were linked to multiple traits[16]. Indeed, pleiotropic genetic effects span clinical/developmental boundaries[13] and are reported for a growing number of clinically distinct disorders (see for example shared genetic liability of reading disability with several other NDD traits[17,18]). The Atypical Rhythm Risk Hypothesis (ARRH) predicts that genetic liability for atypical rhythm increases the risk of diverse developmental speech and language problems in part through genetic pleiotropy[6]. As evidence for this, ARRH points to atypical rhythm as a frequent feature among developmental speech and language disorders, with converging evidence of atypical rhythm in motor and attentional disorders that are often co-morbid with speech and language disorders[6]. Many different aspects of atypical rhythm task performance (e.g., rhythm discrimination, beat perception and synchronization) have been linked to these disorders (see below and Supplemental Table 1); there is not a clear, consistent pattern of a specific type of atypical rhythm being systemically linked only to a specific disorder. Indeed, performance on different rhythm tasks tends to be correlated[19], which may reflect some degree of underlying pleiotropy[12]. Per ARRH, some shared variance among genetics of atypical rhythm skills is expected to also overlap with developmental speech and language problems. Furthermore, frameworks such as ARRH are consistent with the development of transdiagnostic criteria [20], which focus on identifying behavioral and biological features co-occurring across diagnostically distinct conditions as an alternative to identifying single "core deficits" of each diagnosis, (see [21] for discussion of the limitations of core-deficit hypotheses in NDDs, and Table 1 for examples of cross-disorder comorbidities).

Genetic liabilities may link to impairments across disorders through neural endophenotypes for rhythm and time processing[6]. Rhythm and time perception and production involve interactions between the auditory and motor systems. Auditory rhythm processing involves a network of cortical and subcortical motor areas including basal ganglia, cerebellum, premotor cortex, and supplementary motor area (see [22] for a review). Neurologically, listening to auditory rhythms without movement activates motor regions of the brain (e.g.,[22,23]) and both transient brain stimulation and neurological disorders affecting motor regions impair time perception (e.g.,[24,25]). People's rhythm perception is impacted by how they move to the music[26] – or, in the case of infants, how the infants are moved to the music[27] -- as by vestibular stimulation[28]. Rhythm processing is subserved by neural oscillatory activity that synchronizes to external stimuli. Under frameworks such as Dynamic Attending Theory [29], neural entrainment to rhythmic stimuli involves extracting regularities from incoming sensory input to develop expectancies (predictions) regarding timing and content of upcoming events. Neural entrainment to rhythmic signals such as music and speech is also modulated by attention and experience[30,31]. Structural abnormalities and atypical functional activity for rhythm and time processing are observed across a variety of NDDs including speech/language disorders, developmental coordination disorder, ASD, and rare genetic syndromes (see below).

Rhythm and Timing Profiles in NDDs

We next review profiles of NDDs with a focus on the common theme of atypical rhythm skills and their association with a variety of functional impairments on tasks targeting attention, language, communication, and social functioning. We included disorders for which extant research has considered multiple aspects of rhythm and timing skills and because of their patterns of comorbidity with each other in these different domains of functioning.

Speech/Language Disorders

Speech/language disorders are common in childhood (3-16%) though many children are not formally diagnosed or treated[32]. As summarized in the Atypical Rhythm Risk Hypothesis (ARRH)[6], accumulating evidence demonstrates impaired timing skills across a variety of speech/language disorders, which exhibit frequent comorbidities among each other and with other disorders such as ADHD and DCD. The majority of rhythm research in speech/language disorders thus far has focused on dyslexia, a developmental disorder affecting ~3-10% of children with characteristic difficulties in word decoding, which impacts individuals' spelling performance and the development of reading fluency[33]. A few studies have investigated timing skills in children with developmental language disorder (previously known as specific language impairment), a similarly common developmental disorder with a ~3-7% prevalence rate, that is characterized by weak language abilities in one or multiple domains that cannot be explained by a known biomedical condition[34] (such as a brain injury, hearing loss or intellectual disability or autism spectrum disorder). Timing skills have also been examined in individuals with stuttering, which is a speech disorder appearing in ~0.3-5.6% of children[35]. The speech of children who stutter shows frequent occurrences of repetitions or prolongations of sounds, syllables, or words that disrupt the rhythmic flow of speech[9].

Rhythm skills are often assessed with tapping tasks and rhythm discrimination tasks. Tapping tasks measure the ability to temporally coordinate with a predictable event by asking participants to tap to the beat of music or together with an isochronous metronome[36]. Performance is typically described by the consistency/variability of the taps, the difference between the expected and the actual tapping rate, or the difference between the expected and the actual times of the taps. In rhythm discrimination tasks, participants are typically presented with two rhythms that are either the same or different as a result of changing the duration of one or more tones or the interval between two tones. Compared to age-matched typically developing peers, tapping rates of children with DLD and with dyslexia have been reported to deviate more from the expected tapping rate, and taps of children who stutter to occur significantly earlier than the expected time according to the stimulus [37–39]. There is some inconsistency across studies in regard to behavioral performance, however, and between behavioral and neural measures (e.g., some studies report reduced tapping consistency in dyslexia[37,40] while others observe intact consistency of synchronized tapping [41,42] but atypical neural responses[41]). Rhythm discrimination has been found to be impaired in dyslexia, DLD and stuttering [38,43,44]. Processing of low-level cues related to rhythm processing, such as amplitude rise time or duration, has also frequently been found to be weaker in individuals with DLD [45] and dyslexia [37,40,46,47] compared to their typically developing peers, though one study did not observe differences in duration discrimination in dyslexia [46].

Impairments appear in processing of timing-related aspects of spoken language as well. Children with dyslexia and DLD demonstrate impaired performance on tasks measuring word stress or sentence-level prosody processing [48,49]. In [48], word stress sensitivity was measured with two tasks in children with dyslexia and TD peers. At 9 years of age, children were presented with stimuli that had the same segmental information (the syllable *dee* presented repeatedly) but differed in their stress pattern, and had to choose the stimulus that matched a picture (e.g., the matching stimulus for a picture of Harry Potter was DEE-dee DEE-dee). Children with dyslexia demonstrated reduced sensitivity to word stress compared to age-matched and younger, reading-matched peers. At 13 years, stress sensitivity was measured with a stress discrimination task in which the same word was presented twice either with the same stress pattern or with different stress patterns (e.g., DIfficulty (SWWW) and diFFIculty (WSWW), and children had to decide if they are the same or different; children with dyslexia performed worse than age-matched peers [48]. Sentence-level prosody processing was found to be impaired in children with DLD in an artificial language learning task with and without prosodic cues (i.e., frequency, intensity and duration) to the underlying language structure. In contrast to children with TD, children with DLD could not take advantage of the prosodic cues in acquiring the rules of the artificial language [49].

Some of the structural and functional brain characteristics of children with speech/language disorders have been proposed to underlie atypical timing skills in these populations. Functional

connectivity measured with resting state fMRI in brain areas associated with rhythm processing (basal ganglia-thalamocortical network) as well as structural connectivity in areas supporting internal timing (putamen, SMA) appear to be weaker in individuals who stutter [50]. Interestingly, stuttering is significantly reduced if individuals are exposed to a regular external rhythm like a metronome and otherwise atypical brain activation patterns become similar to those in individuals who do not stutter in parallel with improved speech fluency [51]. Oscillatory activity in beta frequency band, which has been proposed to reflect functional coordination between auditory and motor systems and involved in timing, has also been found to be atypical in adults who stutter [50]. In dyslexia, the degree of neural entrainment to the speech envelope [52] as well as to non-speech stimuli [53] is less when compared to TD children. Neural entrainment to the regularities of auditory stimuli has been proposed to be impaired in DLD as well, but to our knowledge, this hypothesis has not been tested yet, nor have other neural correlates of impaired timing skills in DLD.

Performance on various measures of rhythm as described above (speech rhythm, rhythm discrimination, tapping to the beat) has been associated with language skills in children with language impairments in multiple studies (e.g., [54]) indicating that a common mechanism underlies the development of both rhythm and language processing. This idea is supported by a recent meta-analysis of neuroimaging studies showing that shared neural structures underlying temporal hierarchical processing and predictive coding are involved in both rhythm and spoken language processing [55].

Motivated by findings on 1) weak timing skills in children with speech/language disorders and 2) their associations with speech/language skills, it has been proposed that improving rhythm processing with music training could also benefit speech/language skills. In a randomized controlled trial, children with dyslexia performed better on rhythm reproduction, phonological awareness, and reading tasks following 30 weeks of music training focusing on rhythm skills, compared to a control group that completed a painting training[56]. Improvements in rhythm skills and phonological awareness were associated suggesting that mechanisms involved in rhythm-based processing support language acquisition and phonological development.

The short-term effect of rhythm on subsequent speech/language processing of children with DLD and/or dyslexia has also been investigated with rhythmic priming paradigms: for instance, Przybylski et al. [57] found that children with dyslexia and DLD (as well as children with TD) perform better on a grammaticality judgment task following an exposure to a rhythm with a regular vs. an irregular beat, indicating shared mechanisms underlying rhythm and speech/language processing.

Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is a common neurodevelopmental disorder (~4-7% of children) characterized by inattention and/or hyperactivity-impulsivity, which interferes with everyday functioning[9]. Children may exhibit ADHD symptoms independent of other disorders though ADHD also occurs comorbidly with other NDDs (e.g., language disorders, DCD, ASD)[58–61]. Children with ADHD have difficulties with perceiving, reproducing or comparing durations [62] as well as with beat perception in music that cannot be accounted for by duration coding problems [63]. Beat perception is, however, comparable to TD children's performance when stimuli consist of simple sound patterns instead of music with a complex structure[63].

A recent study [63] found lower synchronization consistency in children with ADHD than in TD children in a finger tapping task, both when children were asked to synchronize their taps with tones and with the beat of music. Children with ADHD had more difficulty tapping to real music than simple tonal stimuli. Children with comorbid ADHD and DCD demonstrated even lower performance than children with only ADHD. The authors suggest that the greater difficulty with synchronizing to music may indicate difficulties with internal generation and maintenance of the beat in ADHD because the beat in music must be inferred based on the rhythmic patterns (versus it being provided by a periodic, acoustic cue as with a metronomic tone series) [63]. Interestingly, children with ADHD showing better beat tracking abilities also performed better on tasks measuring flexibility and inhibition, which are characteristic impairments in ADHD [63]

Structural brain abnormalities described in ADHD appear to be associated with these timing deficits. Duration discrimination impairments were related to atypical function of corticocerebellar and cortico-striatal pathways [64]. The basal ganglia and their connectivity with cortical areas (e.g., supplementary motor area, premotor cortex, auditory cortex) have been suggested to be associated with internal beat generation and maintenance (i.e., perceiving and maintaining the beat from the hierarchical rhythmic structure even without the onset of a physical acoustic cue at each beat time) [65]; abnormalities in these areas and pathways may underlie rhythmic difficulties with this process in individuals with ADHD, who often show structural basal ganglia abnormalities. In addition, research has revealed atypical resting state oscillatory activity in children with ADHD, which is proposed to play a crucial role in temporal processing according to several theories (see [66] for a review).

While several studies have found impaired timing skills as well as structural/functional abnormalities in timing-related brain areas/functions in children with ADHD on the group level, these characteristics are not general across all children with ADHD. These results highlight individual differences within an NDD and suggest that timing impairments may be a feature of a subgroup of children with ADHD (see [66][63]).

Developmental Coordination Disorder

Developmental coordination disorder (DCD) is a neurodevelopmental disorder with a prevalence of around 5-6% that involves deficits in fine and/or gross motor skills, postural control, balance, and motor learning that are significant enough to affect self-care and activities of daily living. While different criteria for diagnosis have been used (see [67]), the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition[9], definition of DCD includes early-developing very poor coordinated motor skills for age (e.g., scores < 16th percentile on the Motor Assessment Battery for Children, MACB-2) that affect activities of leisure and play, impact academic and vocation performance, and that cannot be explained by intellectual impairment or other neurological conditions affecting motor function. DCD is heterogenous, involving fine and/or gross motor skills. Children with DCD may have trouble with tasks from running to throwing and catching a ball to tying their shoes to using pencils and scissors. For more than half of children diagnosed with DCD, the impairments continue into adolescence, suggesting that it is not simply a question of delayed motor development[68].

DCD has high co-morbidity with other developmental disorders involving difficulties with timing and rhythm[8]. It has been estimated that 50% of children with DCD also have a diagnosis of ADHD, and vice versa[58,59]. DCD has also been linked to language disorders, including DLD and dyslexia[69,70]. While children with ASD frequently exhibit DCD symptoms (up to 79%; [71]), less than 10% of children with DCD have ASD [72]. There are few genetic studies to date, but heritability estimates for DCD have been as high as 70%[73].

There is relatively little research in general on DCD compared to other developmental disorders, and the majority of studies have focused on motor or visuo-motor impairments. However, several studies using questionnaires indicate that children with DCD also have general sensory processing difficulties, including in the domains of audition, balance (vestibular) and body awareness[74].

Motor deficits in DCD critically involve deficits in motor and sensorimotor timing[75], and poor timing (often conceptualized as poor predictive internal modeling) can explain their less accurate, slower, and more variable performance on a number of motor tasks[8,76], including rhythmic multi-joint coordination, motor sequencing, motor learning, use of feedback, automatization and anticipation[75,76], as well as visual tracking of objects[77], visual-motor coincident timing[78] and tapping along to rhythmic sequences of visual[79] or auditory[80] events. Neuroimaging studies show general abnormalities including reduced cortical thickness, reduced white matter in sensorimotor tracts, and compromised connectome distributed networks (for a review, see [75]). The timing and rhythm deficits in DCD are particularly consistent with reported abnormalities in cerebellar function [75,81].

While the auditory and motor systems are intimately connected, little research has investigated auditory time and rhythm perception in DCD in the absence of a motor task. Chang et al. [82] hypothesized that children with DCD would show deficits in both auditory duration perception and

auditory rhythm perception given evidence that the auditory system connects with the motor system to accomplish time perception. Using psychophysical methods, they found that, compared to typically developing children, those with DCD had poorer discrimination thresholds for detecting changes in the duration of single time intervals, and detecting the presence of non-isochrony in an otherwise isochronous tone sequence, while their pitch discrimination thresholds were relatively unaffected. Furthermore, electroencephalography (EEG) showed delayed event-related potential responses in the DCD children in response to change detection for duration and rhythm, but not pitch.

Autism Spectrum Disorder (ASD)

Individuals with Autism spectrum disorder (ASD), a heterogeneous but highly heritable NDD[73], constitute approximately 1.5% of the general population, and exhibit impairments in social engagement, communication, and restricted/repetitive behaviors, which includes sensory atypicalities[9]. Individuals with ASD often exhibit comorbidities with various other psychiatric disorders and conditions, including epilepsy, ADHD, motor coordination deficits, anxiety, and cognitive impairment[60]. Speech and language problems may also occur with some individuals not developing spoken language and others exhibiting fluent speech[83]. As for motor development and function, children and adults with ASD often show poor lower-limb coordination during tasks requiring balance, agility, and speed, and poor upper-limb coordination during visuomotor and manual dexterity tasks[84]. Sensory and motor difficulties may contribute to and/or reflect social communication impairments in ASD[85] including in regard to rhythm and timing[86].

Attention problems are commonly observed in individuals with ASD[73]. Challenges in modulating attention to others (e.g., joint attention) may contribute to language impairments in individuals with ASD[87]. Reduced attention to social audio-visual speech synchrony is observed in children with ASD compared to children without ASD[88] and sensitivity to audiovisual synchrony is associated with language skills in children with ASD[89]. In regard to speech skills, some individuals exhibit repetitive, stereotyped language and/or atypical speech prosody[9,90]. Impairments in vocal turn-taking occur beginning in infancy[91] while difficulties maintaining appropriate conversational turn-taking are observed in some older children and adults[92].

In regard to nonverbal social coordination, children with ASD exhibit different and less stable forms of social synchronization, or the ability to synchronize one's body together with a partner[93]. For example, individuals with ASD show reduced synchronization to others during rhythm interaction activities such as swinging a pendulum[94], rocking in a rocking chair[95], and rhythmic clapping or drumming games[93,96,97]. Difficulties with behavioral imitation are also common[98]. Some studies relate social synchronization difficulties to performance on other social tasks though findings are somewhat mixed at this time perhaps due to task and population heterogeneity[93,96,97]. A growing body of research seeks to enhance social-emotional capacities such as joint attention, eye contact, emotion inference and empathy via supporting interpersonal coordination and synchrony in both children and adults with ASD[99–101].

A few studies have investigated musical rhythm skills in ASD. Studies indicate age-appropriate musical rhythm perception (same/difference judgments of musical rhythm patterns)[102] and rhythm production (tapping rhythmic patterns with an example)[103], with performance increasing with age and degree of metric structure (i.e., better performance for strongly metrical vs. weakly metric rhythms). In contrast, impairments are observed for rhythmic sensorimotor synchronization on tasks requiring speaking or tapping to a beat, particularly in regard to lower consistency of synchronization in individuals with ASD[42,86,104]. Impairments are also observed in discriminating auditory durations, especially for shorter (subsecond) intervals[105]. Neuroimaging studies in individuals with ASD reveal reduced connectivity of fronto-temporal and cortical-subcortical networks[106,107], as well as structural abnormalities in the cerebellum and basal ganglia[107,108]. Children with ASD who participated in a music therapy intervention demonstrated increased resting state functional connectivity between auditory, striatal, and motor regions post-intervention compared to children in a non-music control intervention, which was related to children's communication skills on a parent questionnaire[109].

Williams syndrome

In comparison to the previously reviewed disorders, Williams syndrome (WS) is a rare (~1/10,000) neurodevelopmental disorder with a known genetic etiology, the deletion of ~26-28 genes on chromosome 7 [110]. Nevertheless, WS is included here because of its unique cognitive-behavioral phenotype, which presents both overlaps with, and differences from, several of the disorders discussed above, as well as the existence of a robust literature into musical and rhythm processing in WS.

The WS phenotype includes mild to moderate cognitive impairment with deficits in visuospatial construction skills[111]. Common comorbidities include ADHD (~65%; particularly in childhood), as well as anxiety and phobias (~50%)[112]. While initial profiles of WS focused on their strengths in verbal and social skills, more recent research from the last decade highlights a more nuanced profile of strengths and difficulties within these domains[111].

Language development is delayed in WS, though areas such as concrete vocabulary, verbal short-term memory, and grammatical skills become relative strengths later in development (at mental-age expected levels)[111]. Of relevance to rhythm and timing skills, reduced sensitivity to word stress patterns are observed, as well as atypical speech prosody (such as observed in ASD)[113–115]. While WS is associated with hypersociability, difficulties with social pragmatics are common and ASD-related symptomatology is elevated in WS even compared to other non-ASD developmental disabilities[116]. Social coordination difficulties are observed in WS across the lifespan such as impairments in joint attention and integrating social gaze during the early years (before verbal skills develop), and impairments in initiating and maintaining conversations in older (verbal) individuals[111,114,115].

Rhythm and timing skills have also been assessed in WS through music perception and production tasks. Many individuals with WS experience auditory sensitivities and heightened emotional responsiveness to music, but there are substantial individual differences in musical skills. In general, rhythm skills in WS are reduced compared to chronological-age matched peers but commensurate with mental-age abilities. For example, individuals with WS perform worse than age-matched peers on tasks involving same/difference judgments of rhythmic patterns, detecting beat alignment to real music, and reproducing rhythmic patterns by clapping or singing[117–120]. Motor difficulties are often common including coordination of rhythmic motor movements and disrupted perception-action coupling[121,122].

Only one study has assessed neural correlates of rhythm skills in WS using EEG [123]. During passive listening to rhythmic patterns, adults with WS exhibited the canonical oscillatory activity in beta and gamma bands in response to beat onsets. However, individuals with WS also exhibited greater alpha activity, as well as increased amplitude of auditory evoked potentials. This suggests that rhythm and beat processing may connect with their atypical auditory attention profile (e.g., increased responsiveness, poor inhibition and attention disengagement). Neuroimaging studies in WS also reveal differences in brain structure and connectivity in areas important for beat and rhythm processing (e.g., reduced basal ganglia volume)[124].

Summary and Future Directions

Rhythm is an early-emerging and essential component of human development and interactions; yet, as reviewed here, impairments in rhythm are associated with a variety of NDDs including relatively common disorders with complex and varying genetic etiologies (e.g., ADHD, language disorders, DCD, ASD) as well as rare genetic syndromes of known etiology (e.g., WS). Indeed, as reviewed above, the available research finds that many types of rhythm impairments are evident across multiple NDDs (see Supplemental Table 1). Rhythm impairments may be associated with particular facets of individual NDDs, the common comorbidities across NDDs, and broader social-emotional/behavioral difficulties frequently observed (Figure 1). Indeed, regardless of the "primary" domain of a given disorder, profiles of impairments that include increased timing and rhythm deficits in children with various NDDs increase the risk of mental health problems, social problems, and poor academic performance [60,112,125,126].

In this summary section, we consider how transdiagnostic investigations into rhythm and timing skills across domains may be fruitful for elucidating underlying biology, characterizing psychological/behavioral sequelae, and designing effective interventions for individuals with various NDDs. Frameworks that consider heterogeneity within and across NDDs dovetail with ongoing efforts to identify the etiology of features and function that are common across multiple mental traits and disorders[127], leveraging phenotypic heterogeneity and comorbidities as an important source of biological covariation (e.g., as in the National Institutes of Mental Health Research Domain Criteria (RDoC) Project). Although rhythm is not currently formally included as an RDoC domain, motor processes and sensory domains (important components of rhythm processing) have recently been incorporated into RDoC [128,129]. Increasing evidence suggests that transdiagnostic investigations across NDDs may be more powerful for revealing links between underlying mechanisms and functional outcomes than comparisons of specific NDDs and typical controls[21,130].

Critical to NDDs is the focus on *development*; these are disorders that unfold over time and reflect interactions among genetic vulnerabilities, neural development, and a variety of environmental factors (Figure 1). Overlapping difficulties as well as the degree to which different domains are impacted across different NDDs may reflect similarities and differences in the timing, amount, and how widespread (e.g., across neural systems) are the instantiation of atypical developmental processes[131]. Additionally, development is a dynamic process and any vulnerabilities in rhythm processing will both impact and be shaped by other (common and unique) vulnerabilities as well as experiences (e.g., as in neuroconstructivist approaches[131]). For example, rhythm is integrally connected with the motor system suggesting potential feedback loops between vulnerabilities in rhythm perception and motor skills; as summarized above, motor impairments of varying degrees commonly occur across NDDs [6,58,69,71]. Another example comes from rhythms in social contexts. Rhythm and timing deficits may impair attention shifting and modulation that contribute to successful social interactions; at the same time, atypical (decreased or increased) interest in social information may reduce opportunities to develop and refine rhythm and timing skills needed for social coordination[132].

Given the developmental context of NDDs, one important and growing direction for future research includes longitudinal designs of rhythm sensitivity early in life in children with or at risk for various NDDs (due to family risk status or other health risk factors) in order to investigate trajectories of rhythm sensitivity development, as well as relationships between early rhythm sensitivity and later functional language, social, emotional, and motor skills. While some studies with infants at risk for ADHD, ASD, and/or language disorders, as well as children with genetic syndromes such as WS, have investigated early motor, language, sensory, or attentional functioning, rhythm processing has generally not been a focus of these studies [61,131]. Yet the evidence presented in the current paper suggests theoretical support for such future work. One recent study reported associations between infants' temporal sensitivity (amplitude envelope rise time discrimination, important for synchronization of neural oscillatory activity to the temporal signal and reflective of the speech rhythm) and later vocabulary development[133]. Ladányi and colleagues suggest that rhythm may be a powerful means of early identification of children at risk for language disorders due to shared underlying biology[6]. Large-scale population-wide epidemiological studies are needed to test the prediction that atypical rhythm increases the risk of presence of developmental speech and language problems, as well as DCD and ADHD. Furthermore, specific familial influences (genetic and environment factors) accounting for the hypothesized shared risk will need to be disentangled and may point to specific convergent or divergent biological pathways.

From an assessment standpoint, in order to better conceptualize common and unique rhythm difficulties across different NDDs, transdiagnostic approaches should thoroughly assess participants for comorbid conditions in order to appropriately characterize their samples (e.g., DCD+DLD vs DCD alone). Additionally, studies should utilize task batteries that incorporate a variety of rhythm and temporal processing activities (e.g., beat perception and production, interval timing, simple vs. complex rhythms). Tasks must also consider different domains (e.g., visual, auditory, tactile, multisensory) and consider tasks with and without motor components, as well as tasks with and without social contexts. Parsing

specific rhythm and timing skills across domains may reveal rhythm profiles across different disorders and/or profiles of comorbidities. For example, some children may be particularly impaired in tasks that involve explicit motor components (i.e., rhythm production) while others may perform similarly across perception and production tasks; some children may be supported by rhythm tasks embedded in linguistic/speech or social stimuli while others may be particularly impaired in such contexts. More nuanced studies of the processes underlying tasks would also clarify profiles across disorders or comorbidities. For example, impairments in rhythmic synchronization to beat-based stimuli are observed across nearly all NDD disorders (see Supplemental Table 1). However, it is unknown if difficulties across disorders involve the same or overlapping components (e.g., beat finding, beat maintenance, beat adjustment, error correction). Comparisons across disorders with different types of beat synchronization tasks may be informative for parsing specific impairment profiles (e.g., tapping at different tempi, fixed vs. variable tempi, manipulating the metrical strength, specific acoustic characteristics of stimuli).

It is also critical to identify mechanisms by which rhythm processing contributes to individual differences in phenotypic expressions across NDDs and whether overlapping behavioral difficulties are subserved by the same neural mechanisms across different NDDs or if different (potentially compensatory) profiles are observed. Rhythmic processing involves temporal predictability (e.g., Dynamic Attending Theory[29]), impairments in which are associated with multiple downstream effects including attention to (or attentional disengagement from) sensory stimuli. For example, the Temporal Sampling Framework proposes that impairments in processing slow rhythms (caused by inefficient phase-locking of neural oscillatory activity at low frequencies) are predictive of reduced phonological development in language disorders[134]. Another potential mechanism may involve reward processing, which is impacted in multiple NDDs[135]. Reward processing shares neural pathways (e.g., caudate) with rhythmic sensorimotor synchronization and connects synchrony with subsequent prosocial behavior[136]. In addition to assessing neural activity (e.g., EEG, MEG), other methodological approaches that allow for assessing how behaviors unfold over time (e.g., movement tracking, eye-tracking) may elucidate mechanistic processes underlying rhythm skills across NDDs, as well as links to functional skills across domains.

As noted in the reviews of different NDDs, there is substantial interest and growing research in rhythm-based interventions for children with NDDs [56,100,101]. Rhythm-based intervention studies take a variety of forms and target a range of outcomes measures. The general principle of these interventions is that providing structured, predictable, rhythmic stimuli increases relevant neural activity to support behavioral task performance (e.g., increasing oscillatory power at the stimulus frequency). As proof-of-concept designs, several studies have used rhythmic priming activities, in which regular rhythmic stimuli precede or co-occur with target stimuli (e.g., hearing or reading sentences, completing a motor task), to investigate rhythm facilitation of task performance [57]. Other studies involve single or multi-session auditory-motor training activities, often using music/music and movement activities or interventions [100,109]. While there is promising evidence from several studies, larger studies with appropriate comparison conditions are needed, as well as a broadening of the types of symptoms and NDDs being targeted. As with all interventions, clearly elucidated theories of change are needed in order to optimize intervention design; indeed, intervention studies can be used to test connections between proposed mechanisms and outcomes behaviors. Mechanistic intervention research across and within NDDs will support intervention development and help determine for whom interventions are most appropriate and for what target outcomes.

Conclusion

Rhythm and timing underlie a variety of human behaviors including attentional, sensory, motor, linguistic, and social domains. There is considerable evidence that rhythm and timing deficits are common across a variety of NDDs with overlapping profiles of rhythm impairments. The presence of timing and rhythm processing deficits across NDDs suggests there may be overlapping genetic and neural vulnerabilities for developing NDDs and potentially explains one facet of the high comorbidity across disorders. Individual differences in rhythm skills in different domains may also help to explain

heterogeneity within disorders in regard to magnitude and scope of co-occurring challenges. Transdiagnostic approaches that include rhythm impairments in models of NDDs may point to novel mechanisms of action for characterizing NDDs and in the design of intervention strategies to support children with NDDs.

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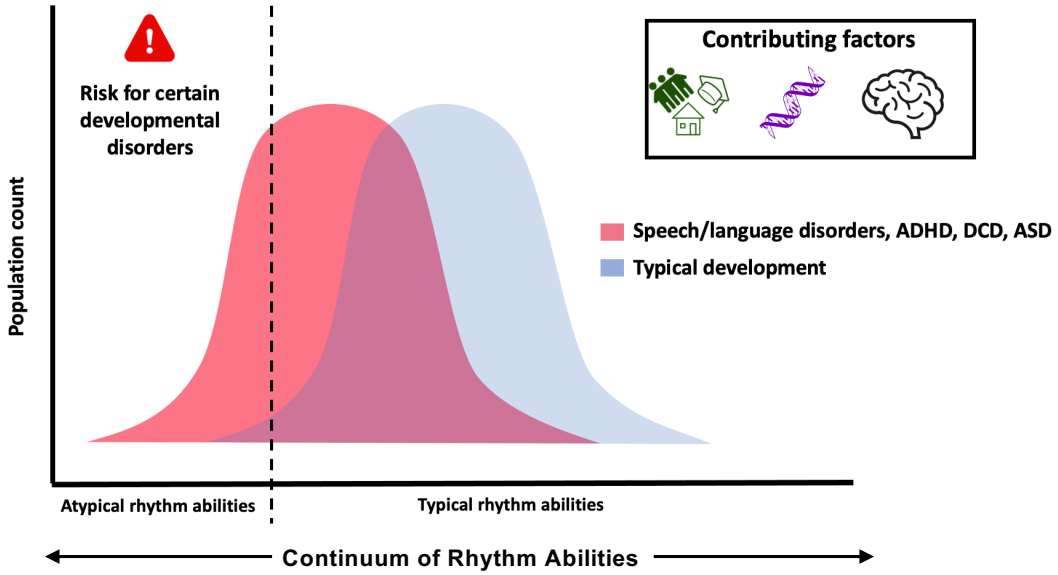
Table 1. NDDs associated with impairments in rhythm/timing skills. NDDs emerge early in development and involve impairments/delays in one or more functional domains.

NDD	Primary Characterization	Estimated Prevalence	Common Comorbidities (examples)*
Attention-Deficit/ Hyperactivity Disorder (ADHD)	Persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development[9].	~4-7 %	Learning disorders including dyslexia (18-45%)[137], DLD (45%)[138], other externalizing disorders (e.g., oppositional defiant disorder; 50-60%)[139], DCD (50%) [139]
Autism spectrum disorder (ASD)	Early emerging and persistent deficits in social communication and interaction and restricted, repetitive patterns of behavior[9].	~1.5%	ADHD (20-59%)[140,141], anxiety (20-40%)[141], intellectual disability (33%)[142]
Developmental coordination disorder (DCD)	Impairments in motor skills and coordination (e.g., clumsiness, slowness and inaccuracy of motor skills) that significantly and persistently interfere with everyday activities[9].	~5-6%	ADHD (50%)[143,144], learning disorders including dyslexia, DLD [140,141], anxiety (16-48%)[145]
Developmental language disorder (DLD)	Difficulties in understanding and/or using language in one or multiple domains (e.g., expressive grammar) that cannot be explained by a known biomedical condition (such as a brain injury, hearing loss, intellectual disability, or autism spectrum disorder)[34].	~3-7%	ADHD (46%)[146], DCD (20-75%)[147], dyslexia (17-67%)[148]
Dyslexia	Learning disorder involving difficulties in word decoding and identifying speech sounds, which impact the development of reading and spelling skills [33].	~3-10%	ADHD (18-42%)[137], DLD (15-55%)[148], DCD (40-57%)[149]
Stuttering	Speech disorder characterized by frequent occurrences of repetitions or prolongations of sounds,	~0.3-5.6%	ADHD (6%), subclinical ADHD symptoms (~50%)[150],

	syllables, or words that disrupt the rhythmic flow of speech[9].		language disorder (35%)[151]
Williams syndrome (WS)	Neurodevelopmental disorder caused by the deletion of ~26 genes on chromosome 7; associated with mild to moderate intellectual deficits, attention problems, hypersociability, and auditory sensitivities[110].	~0.01%	ADHD (65%)[112], anxiety / phobias (50%)[112], intellectual disability (43%)[152], ASD (10-20%)[114,115]

* Prevalence rates of comorbidities may vary across studies in part due to study design (e.g., population sample vs. clinical cohort; screening surveys vs. clinical interviews; self- vs. parent-report) and changes in diagnostic criteria across time (including whether or not diagnosis of specific separate comorbid disorders was permitted)

Figure 1. Impaired rhythm processing skills may be a risk factor for developing a variety of neurodevelopmental disorders (NDDs) and may help explain high levels of comorbidities across disorders and broader patterns of behavioral/emotional problems. Genetic vulnerabilities, environmental factors (e.g., education, training, social interactions), and neural processing contribute to rhythm skills, development of NDDs and profiles within and across NDDs.



upplemental Table 1. Summary of performance on different types of rhythm and timing tasks across NDDs

	Interval (Duration) Timing	Rhythm Perception and Production	Beat Perception and Synchronization	Speech Rhythm/ Prosody	Interpersonal Movement Coordination
ADHD	↓ perceiving or copying event durations; ↓ duration discrimination [62,64]	--	↓ beat alignment perception in real music; ↓ sensorimotor synchrony to beat (tapping consistency) especially for real music; ↓ detection of non-isochrony in music but ~ in tones[63]	--	↓ intentional interpersonal movement synchrony[153]
ASD	↓ duration discrimination [105]	~ rhythm pattern perception[102]; ~ repeating precise rhythm patterns[103]	↓ sensorimotor synchrony to beat (tapping consistency) [42,86,104]; reduced error correction for tempo changes [42]	↓ word stress production; atypical prosody[9,90]	↓ spontaneous and intentional interpersonal movement synchrony [93–97]
DCD	↓ duration discrimination [82]	--	↓ sensorimotor synchrony to beat (tapping consistency, tap alignment, tapping rate at slow tempi) [80]; ↓ detection of non-isochrony [82]; delayed ERP response to non-isochrony[82]	--	--
DLD	↓ duration discrimination [45]	↓ rhythm pattern perception [38]	↓ sensorimotor synchrony to beat (tapping rate) [38,54]	↓ sentence-level prosody perception [49]	--
Dyslexia	↓ duration discrimination [37,40,47] or ~duration discrimination[46]	↓ rhythm pattern perception [43]	↓ or ~ sensorimotor synchrony (tapping consistency, rate) to beat across studies[37,40–42]	↓ word stress perception [48]; ↓ neural entrainment to speech envelope[52]	--
Stuttering	--	↓ rhythm pattern perception[44]	↓ sensorimotor synchrony to beat (tap alignment) [39]	Speech repetitions and sound prolongation [9]	--
WS	--	↓ rhythm pattern perception*[118–120]; ↓ repeating precise rhythm patterns* [118–120] *may compare to mental-age level	↓ beat alignment perception in real music[117]; ↓ meter recognition[117]; ~clapping in time to simple music [119]; ~beat and gamma activity, ↑ alpha activity and ERP amplitude during beat perception [123]	↓ word stress perception[113]; atypical prosody[114,115]	--

lote: Summaries reflect general trends across multiple studies when available; there is heterogeneity across individuals within all studies
= poorer performance compared to chronological age-matched peers
= similar performance to chronological age-matched peers
= increased response compared to chronological age-matched peers
= not enough data available in category