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Early pathogenesis, risks, and interventions of dyslexia

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Abstract. Reading proficiency is a foundational skill crucial for academic and social development in children. Developmental Dyslexia (DD), characterized by reading and writing difficulties despite adequate intelligence, poses a significant challenge, with a prevalence of 4–17%. This literature review explores the pathogenesis, risk factors, and interventions associated with DD. Children with DD face challenges in decoding and phonological processing, accompanied by deficits in the magnocellular pathway, complicating precise detection. Genetic, neural, and environmental factors contribute to DD, necessitating an integrative approach. Early interventions, focusing on phoneme awareness, rhythm, and visual skills, show promise. Neurobiological investigations reveal abnormalities in brain regions and connectivity, emphasizing the multifaceted nature of DD. Environmental factors, including maternal behaviors and socioeconomic status, contribute to DD risk. Interventions, such as music-based approaches, educational games, and mobile applications, demonstrate transformative impacts. To conclude, this review calls for continued research, global collaboration, and inclusive practices to advance our understanding and intervention strategies for DD on a global scale.

Keywords: Developmental Dyslexia, Genetics, Developmental risk, Intervention

1. Introduction

Reading proficiency is a foundational skill that lays the foundation for a child's academic and social progression. However, the trajectory of literacy acquisition is notably disrupted by the advent of Developmental Dyslexia (DD), which is characterized by difficulties in reading and writing acquisition despite adequate intelligence and educational access. The epidemiological landscape of dyslexia reveals its ubiquity, with a prevalence rate of 4–17% [1]. This statistical prevalence accentuates the exigency of a nuanced comprehension of the challenges posed by DD. Its influence extends beyond cognitive deficits, affecting academic performance, self-concept, and social interactions [2]. These findings underline the necessity for early detection and individualized remedial strategies. Comprehensive insight into the far-reaching effects of DD is crucial for devising interventions that address not only academic difficulties but also support the psychosocial health of those with dyslexia.

Children with DD persistently face challenges in single-word decoding and phonological processing [3][4]. Compounding these difficulties are the observed deficits in the magnocellular pathway of the dorsal visual stream, which introduces additional complexity to the disorder [5]. The causal relationship between these visual processing deficits and dyslexia remains equivocal, posing challenges to precise detection and the development of targeted interventions. Explorations into the genetic, neural, and cellular substrates of DD have provided valuable insights, yet the progress is circumscribed. Thorough examination of genetic markers, neural circuitry anomalies, and cellular irregularities is required for an

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in-depth understanding of their intricate interactions. Studies indicate a substantial hereditary component, with familial lineages showing a continuity of reading challenges. Neuroimaging studies have also revealed deficits in visual and auditory processing, coinciding with anomalies in magno-cellular cells and white matter across various cortical regions [6]. Environmental determinants, encompassing familial socioeconomic status, parental educational levels, and genetic propensities, are increasingly recognized as significant contributors to the risk profile of DD [7]. Therefore, an integrative approach that combines genetic and environmental factors is imperative to fully comprehend the multifaceted nature of this developmental disorder.

Efforts to ameliorate the effects of DD have catalyzed significant advancements in intervention strategies, particularly those targeting visual and auditory processing. Training in phoneme awareness and early interventions, particularly those centered on pre-verbal rhythm and vocal music materials resembling parental singing, have shown promise in mitigating potential dyslexic challenges. These interventions are designed to bolster rapid temporal auditory processing and speech-sound discrimination abilities, as evidenced by research [8]. Additionally, educational games and activities that promote visual reading skills and word-spelling, such as fostering awareness of orthography and expanding vocabulary, are being integrated during the critical period of cognitive development around the school-age years [9]. The utilization of mobile technology offers new modalities for intervention, with bespoke applications aiming to reinforce morphological skills and literacy in children with DD [10]. These interventions, grounded in the conceptualization of DD as a specific learning disability with a neurologically basis, highlight the importance of precise, research-driven intervention models. Their efficacy accentuates the primacy of targeted, evidence-centric approaches in comprehensively addressing the multifaceted dimensions of DD and underscores the ongoing commitment to advancing therapeutic methodologies in this domain.

This exhaustive review is structured to navigate the pathogenesis, risk factors, and effective interventions associated with DD. By integrating insights from behavioral and neuroscientific research, the objective is to underscore the critical necessity for ongoing research initiatives and the development of innovative therapeutic strategies and addressing the complexities of dyslexia.

2. Comprehensive Understanding of Dyslexia Pathogenesis: Unveiling Early Signatures

The pathogenesis of DD involves a cascade of events, encompassing genetics factors, early neural markers, dysfunctions in visual and auditory processing, distinct roles of specific brain regions, and changes in structural and functional brain connectivity. Understanding these intricate processes provides deep insights into the origin of DD and paves the way for early detection and intervention, promising a more focused and efficacious approach in assisting young children at risk of DD.

2.1. Genetic Factors

The heritability of DD is a well-recognized aspect, underscoring its propensity for genetic transmission and markedly elevating the risk for infants born into families with a history of dyslexia. A considerable portion of the variance in reading difficulties, estimated to be between 50% and as high as 70-80%, is attributable to genetic factors [11]. This genetic predisposition provides a crucial basis for in-depth investigations involving infants within dyslexia-affected families, thereby enabling the early detection of those at increased risk and the facilitating exploration of nascent markers associated with the disorder.

Within the realm of genetic research, specific genes, including DYX1C1, KIAA0319, DCDC2, and ROBO1, have been identified as significant contributors to dyslexia [6,12]. Recent evidence, particularly those related to Quantitative Trait Loci (QTLs) on chromosomes 7, 10, 12, 15, and 21, enrich the understanding of genetic factors associated with dyslexia. These QTLs, along with previously identified QTLs on chromosomes 1, 2, 3, 6, 15, and 18, expand genetic framework within which dyslexia is understood. Notably, up to 15 novel genes have been identified as potential candidates, necessitating further scrutiny to unravel their roles in the complex genetic architecture of dyslexia [13].

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2.2. Neurobiological Foundations: Early Markers and Sensory Dysfunction

In addition to genetic factors that contribute to dyslexia, early neural markers have been also identified as impactful causes of DD, particularly affecting auditory and visual processing. These factors extend beyond general predispositions, impacting aspects such as phonological representation, the perception of temporal cues in speech, visual attention, visuospatial span, and the magnocellular-dominated dorsal visual pathway.

Speech perception deficits, a hallmark of dyslexia, originate from impediments in developing phonological representations from auditory speech inputs [12]. Impairments in rapid auditory processing and amplitude modulation are known to contribute to challenges in discriminating auditory information, thereby impacting the ability to detect speech rhythm and prosody [14]. The widely accepted 'phonological core deficit hypothesis/model' posits that individuals with dyslexia face challenges in mentally representing sound patterns, leading to difficulties in phonological tasks [15]. The interaction between genetic factors and speech processing further extends to impairments in processing speech signals, including aspects related to durational features and structural intricacies. This common neural mechanism leads to deficits in the processing of finely tuned speech information, especially under conditions of perceptual demand [16]. Research highlights developmental variations in neural networks related to auditory and speech perception among children who have a familial predisposition for dyslexia [17]. Children at risk for dyslexia exhibit inefficiencies in representing the temporal envelope of speech signals, leading to less accurate of speech sounds. Magnetoencephalography (MEG) studies reveal deficits in auditory sampling at theta frequencies in infants at risk for dyslexia, suggesting the presence of potential early markers of dyslexia susceptibility [18]. Additionally, impairments in rapid auditory processing and amplitude modulation contribute to challenges in discriminating auditory information, adversely affecting the ability to perceive speech rhythm and prosody [14]. These findings underscore an early vulnerability to deficits in auditory and speech processing, indicative of a heritable neurodevelopmental reading disorder, emphasizing the neural underpinnings of learning difficulties experienced by dyslexic children.

Moving beyond auditory processes, DD extends its challenges to visual sensory functions as well. Children with dyslexia often exhibit impairments in visual attention span and visuospatial attention, emphasizing the critical role of visual attention in processing task-relevant information [14]. The neurobiological significance of visual attention is demonstrated by the enhanced functional connections between the dorsal attention system and the presumed visual word form area (VWFA), which evolves in parallel with reading proficiency [19]. Studies have also indicated that an increased reliance on brain regions associated with visual attention can be beneficial or reading achievement [20]. Besides attentional issues, visual deficits in dyslexia also involve the magnocellular theory, which links abnormal function of magno-cells in the lateral geniculate nucleus to dyslexic symptoms [14]. This theory implicates the magnocellular-dominated dorsal visual pathway, crucial for rapid visual stimuli processing [21]. Dyslexic readers exhibit deficits in this pathway, impacting attention, ocular motor control, and letter position encoding. Notably, these deficits are not a consequence of reading failure, as children at familial risk for dyslexia exhibit dorsal stream deficits prior to formal reading instruction, indicating an inherent visual impairment preceding formal reading [21]. Investigations into the magnocellular-dorsal pathway deficit emphasize a temporal oscillatory dysfunction related to this visual pathway, potentially disrupting sub-lexical processes essential for reading development. This establishes a connection between magnocellular abnormalities and the reading difficulties observed in dyslexia [22].

Collectively, visual and auditory deficits hinder foundational processes essential for reading acquisition. Compromised phonological recoding interferes with the fluid transition between written and spoken language, leading to difficulties in accurate word recognition. Deficiencies in rapid auditory processing and amplitude modulation impair the precise perception of speech sounds and prosody, thereby influencing overall language comprehension. Simultaneously, challenges in visual attention and disruptions in the magnocellular pathway impede the efficient encoding and processing of written text, culminating in sluggish and imprecise reading abilities. As children with dyslexia approach school age,

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these interrelated deficits increasingly predispose them to significant academic and psychosocial challenges.

2.3. Neurobiological Insights: From Brain Regions to Connectivity Alterations

From a neurobiological standpoint, specific brain regions assume pivotal roles in reading development and are closely linked to DD (Figure 1). The Left Fusiform Gyrus (LFFG), particularly the Visual Word Form Area (VWFA), exhibits atypical early functional connectivity in infants with a familial dyslexia background, underscoring its significance in early word form recognition during the initial stages of reading acquisition [23]. The hypoactivation of VWFA in these infants provides deeper insights into the neural deficits leading to DD. Furthermore, the left intraparietal sulcus (IPS), a component of the reading network, is significantly involved in processing the positions of relative letters during visual word recognition, as revealed by functional magnetic resonance imaging (fMRI) and event-related potentials (ERP) studies [24]. The neural activity within the IPS contributes to a more nuanced understanding of the neural mechanisms in DD, emphasizing the intricacies of visual word processing and the critical role of specific brain regions in neurobiological intricacies of dyslexia.

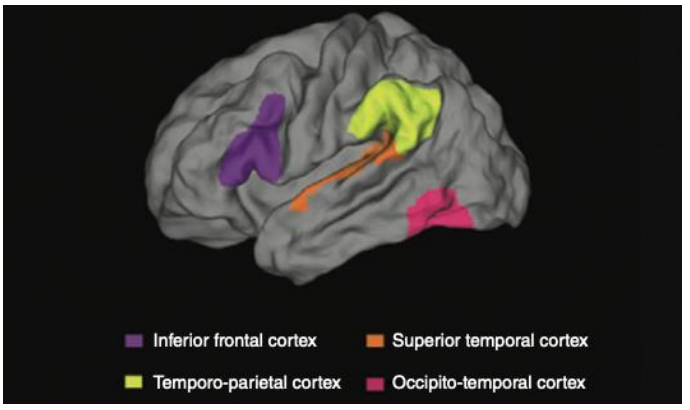

Figure 1. Regions of the brain crucial for reading [6]. The regions related to reading including the inferior frontal cortex, superior temporal cortex, temporo-parietal cortex, and occipito-temporal cortex, are frequently observed to exhibit abnormal function or structure in individuals with dyslexia.

FMRI and diffusion model studies have revealed noteworthy white matter changes in individuals with DD, particularly in the left anterior arcuate fasciculus. These alterations provide valuable insights into structural and functional connectivity changes across the left hemisphere (Figure 2). Notably, these white matter alterations are detectable in infants at familial risk for dyslexia, positioning them as potential early predictors of later literacy challenges. This brain region, instrumental in connecting language areas, shows a correlation with pre-reading abilities as early as kindergarten, indicating that these structural connectivity anomalies may contribute to the onset of reading difficulties [25,26]. Crucially, the evidence suggests that such connectivity alterations are inherent and may play a causal role in the atypical language and reading development in dyslexia, rather than being merely a consequence of reading challenges. In infants at familial risk of dyslexia, early-onset atypical functional connectivity patterns reveal a breakdown in communication between key regions crucial for word form recognition during reading acquisition [23]. Concurrently, dyslexic children exhibit structural changes that indicate increased local specialization but reduced global efficiency, unveiling a potential "disconnection syndrome" [27]. This disconnection syndrome implies a fragmentation in the integration of information across the brain, which is essential for the complex processes in reading. Collectively, the alterations in white matter, functional connectivity, and brain network organization altogether underscore the extensive neural implications of DD, illustrating the interaction between brain regions crucial for reading acquisition and reinforcing the notion that disruptions in connectivity are integral to the broader neurobiological landscape of dyslexia.

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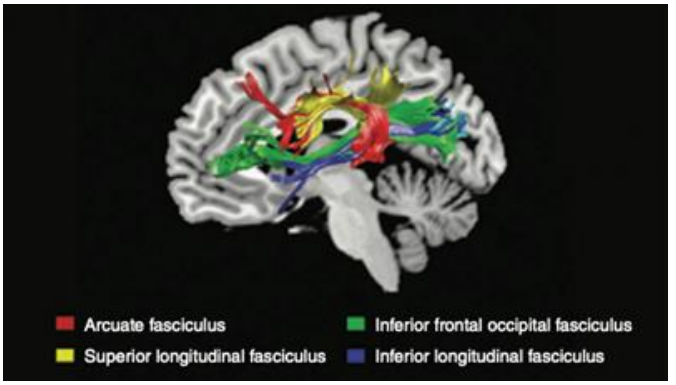

Figure 2. Substantial white matter pathways for reading [6]. Substantial white matter pathways for reading include the arcuate fasciculus (depicted in red), superior longitudinal fasciculus (depicted in yellow), inferior frontal occipital fasciculus (depicted in green), and inferior longitudinal fasciculus (depicted in blue); the corpus callosum is not shown in the figure.

3. Exploring the Nexus of Environmental Influences: Key Contributors and Implications

While neurobiological factors are crucial in the development of DD, the importance of environmental risks during early childhood cannot be overstated. This section delves into the environmental factors that might induce DD in the early stages of life. Drawing on recent research and empirical evidence, we delve into the intricate landscape of maternal behaviors, prenatal influences, familial dynamics, and socioeconomic conditions that impact the emergence of dyslexia (Table 1).

Maternal interactive sensitivity is a crucial component, positively linked to language and literacy development, acting as a powerful protective factor. These factors are integral in shaping early social interactional skills and representational skills, which, in turn, lay the foundation for future language abilities. A clear continuity in developmental trajectories is observed. Notably, there are robust correlations between infants' early social interaction skills at 14 months and their expressive language abilities at 18 and 30 months. Furthermore, there is a significant relationship between symbolic play skills and subsequent language comprehension [16]. Maternal interactive sensitivity, which encompasses strategies for directing attention and linguistic expansion, is a significant predictor of children's later language comprehension abilities.

Maternal negative behaviors and medical conditions before, during, and immediately after pregnancy are identified as substantial environmental risk factors. These include smoking, a history of psychiatric disease, infectious diseases, difficult vaginal delivery, and neonatal asphyxia [13]. The influence of prenatal nicotine exposure on reading-related outcomes, such as reading speed, accuracy, and comprehension, underscores the adverse effects of maternal smoking on literacy skills [30]. Furthermore, research shows a higher prevalence of maternal smoking during pregnancy among dyslexic children, particularly in Chinese demographics [31]. The period of influence extends beyond infancy, with specific prenatal conditions, such as low birth weight, having enduring effects on cognitive and reading skills throughout childhood and adolescence [13,32]. Moving beyond the prenatal period, additional pre- and perinatal hazards linked to dyslexia are identified, such as familial history of psychiatric diseases, maternal infectious diseases, difficult vaginal delivery, and neonatal asphyxia [30]. These factors remain significantly associated with dyslexia, even after adjusting for confounding variables.

Additionally, Socioeconomic status (SES) and a rich home literacy environment (HLE) emerge as influential predictors of reading skills. Familial SES, which includes factors such as parental education, literacy skills, and family income, significantly associates with children's reading abilities across various demographics [33,34]. Mascheretti and colleagues' study in 2015 corroborates the emerging consensus that SES is a critical variable in the study of neurodevelopmental disorders like DD. SES not only influences the severity of dyslexic symptoms but also potentially affects the efficacy of interventions. Furthermore, HLE, characterized by elements such as exposure to books, frequency of reading activities,

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and parental attitudes towards reading, is consistently associated with a reduced risk of reading difficulties [32,35]. According to research, an enriched HLE can create an environment more favorable for language acquisition in children, thereby mitigating the impact of maternal education on children's reading readiness [32].

Table 1. The summary of evidence of environmental factors.

Reference Language of the Sample Sample Size Study Design	Environmental Risk Variables	SES Variable	Objectives	Findings
Mascheretti et al., 2013a [28] Italian Cross-sectional Family-based Dyslexic sample n=244 Control sample n=111 Family sample n=165	Maternal smoking Likelihood of miscarriage Infant birth weight Breastfeeding Parental age Parental education Parental employment (SES)	Middle SES	To explore gene-environment interactions (GxE) involving DYX1C1, KIAA0319, DCDC2, and ROBO1, along with a collection of frequently mentioned environmental factors.	DYX1C1 demonstrates a modulating impact on reading performance in conjunction with birth weight and SES, as well as on memory performance in conjunction with maternal smoking during pregnancy. Both alleles of DYX1C1 1259C/G have a negative influence on reading in the presence of environmental disadvantages. The effects of DYX1C1 in developmental dyslexia are influenced by maternal smoking during pregnancy, birth weight, and SES.
He et al., 2014 [29] Chinese Cross-sectional Case-control	Literacy activity Book types available at home Duration of device use	N/S	To examine the correlation between the Home Literacy Environment	Key components of the HLE include the duration of electronic device usage, engagement in literacy-related activities, and limitations on electronic device usage. An analysis
Dyslexic sample n=195 Control sample n=4868	Literacy activity Book types available at home Duration of device use Limit on device use at home Areas of internet use Reasons for internet use Parent-child TV Finish-homework pressure Time spent on homework Frequency of encouraging children to engage in activities	N/S	(HLE) and Chinese Developmental Dyslexia (DD) in an extensive sample of school-aged children.	using a generalized linear model indicates that the risk of DD is positively linked to the total time spent on electronic devices and negatively associated with engagement in literacy-related activities.
Mascheretti et al., 2015 Italian Cross-sectional Family-based Family sample n=466 Individual n=1623	Maternal smoking Likelihood of miscarriage Infant birth weight Breastfeeding Parental age at child's birth Parental education and SES	N/S	To explore elements of the phenotypic characteristics of DD that can be attributed to the influence of GRIN2B.	Noteworthy correlations exist between GRIN2B and DD, intelligence quotient (IQ), auditory short-term memory, and phonemic elision, with no significant gene-environment interaction (GxE) effects.

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Regarding broader implications, these environmental risks carry significant weight for educational interventions and support systems. The presence of socioeconomic disparities and the impact of parental behaviors necessitate tailored approaches in educational contexts. It is essential for educators, parents, and policymakers to work collaboratively to establish environments that support children who are at risk for, or have been diagnosed with, dyslexia. The findings highlight the importance of considering the complex interplay of dyslexia's etiological factors and devising interventions that are responsive to the variety of environmental risks involved.

4. Navigating Multifaceted Interventions: Transformative Impacts

Given the significant impact of DD on the academic performance, self-esteem, and socio-emotional development of young children, the necessity for creating accessible and effective interventions becomes increasingly vital. Recent research has shed light on a variety of interventions, encompassing musical approaches, educational games, and targeted mobile applications.

Musical interventions, particularly those involving active and social engagement with music, have emerged as promising avenues. Musical activities, whether formal or informal, have been associated with enhanced auditory neural development, improved neurocognitive skills, and positive socioemotional outcomes [36]. Early music interventions, especially when caregivers participate, have shown potential benefits for at-risk infants, including those with DD, aligning with the findings on the maternal interactive sensitivity and HLE findings mentioned previously [37]. Music, being nearly all-encompassing in early development, plays a crucial role in parent-infant interactions; these interactions involve playing songs, singing lullabies, and engaging in rhythmic movements, all of which contribute to language development and auditory processing [37]. The DyslexiaBaby and Singing Kangaroo studies further underscore the role of music in promoting early development, highlighting its impact on language skills, auditory cortical processing, and pre-communicative development in at-risk groups [36]. Additionally, engaging caregivers in music activities at home, guided by professionals, has also shown evidence for reducing parental anxiety and having a positive impact on the future of children with DD [37].

In addition to music-based methods, educational games have also proven effective in ameliorating DD symptoms and enhancing reading performance. Examples include Lindamood-Bell's 'Seeing Stars' reading intervention and the GraphoGame (GG), both of which target the visualization of letters, syllables, and words. The 'Seeing Stars' reading intervention game promotes visual imagery of orthographic presentations, improving phonological awareness, and enhancing word recognition through interactive features. The game address specific aspects of dyslexia, including motor/tactile and articulatory elements of word presentation [5]. Despite comparable pretest scores between children who underwent the intervention during the summer and those who did not, the majority of word reading, pseudoword reading, and text reading outcomes showed relative improvements in children who received the intervention. In contrast, those in the control group experienced relative stagnation or declines in scores [38]. In terms of the GraphoGame (GG) interventions, which involve a gradual progression from introducing larger units in whole word form to manipulating smaller, consistent units based on orthography. This approach aims to stimulate orthographic awareness, accumulate vocabulary, and foster the precursors of reading acquisition during the pivotal postnatal period [39]. By focusing on cognitive maturity and the timing of intervention, GG aims to provide a comprehensive approach to managing dyslexia. Integrating such visual- oriented games into educational settings holds the potential to positively impact dyslexic students' reading and spelling abilities, providing a holistic intervention approach.

Additionally, in recent years, mobile smart applications have emerged as essential tools in dyslexia screening and intervention. These applications are tailored to address various dyslexia symptoms, offering specialized support for reading, writing, mathematical skills, and memory exercises [10]. The convenience and accessibility of mobile apps make them a valuable tool for dyslexic students, enabling personalized and adaptable interventions [10]. Research has also indicated that mobile apps not only aid in screening for dyslexia but also assist in the development of essential skills. However, a larger

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proportion of the apps are focused specifically on reading, with only a few designed to address other cognitive functions [10].

Collectively, addressing interventions for DD necessitates a comprehensive, multi-dimensional strategy. Each intervention method contributes uniquely to the management of dyslexia, emphasizing the importance of early intervention, caregiver involvement, and personalized, accessible tools for skill development. These interventions offer promising prospects for positively influencing the trajectory of children with DD, fostering better literacy outcomes and enhanced overall well-being.

5. Conclusion

Over the years, research on early developmental dyslexia has made significant strides, shedding light on various challenges posed by the complexities of writing systems across different languages and scripts. The comprehensive exploration of genetic, neural, and brain region factors, coupled with the design of interventions tailored to diverse needs, emerges as a promising avenue for addressing DD on a global scale.

In terms of pathogenesis research, longitudinal studies are instrumental in comprehending the genetic architecture and specific biological mechanisms underlying dyslexia. The exploration of neurogenetic biomarkers continues to hold potential for predicting dyslexia risk in a child's early development, while neural studies, particularly those delving into auditory event-related potentials (ERPs) and measures of brain activation, also highlight the significance of early identification of children at high risk for reading-related challenges. Further investigations into cortical areas and brain connectivity, including the lateralization of phoneme discrimination and the functional organization of the visual word form area (VWFA), are likely to provide deeper insights into the evolving neural dynamics associated with dyslexia.

In the realm of future intervention research and design, the prospect of tailoring interventions for children with predefined deficits in auditory and visual processing skills holds great promise. Incorporating reading and word learning training can enhance language skills alongside cognitive growth. Early auditory ERP studies can serve as reliable predictors of language and reading problems, facilitating targeted support. Also, the role of visual processes, including aspects such as vergence control and visual attention, in dyslexia remains an area that warrants further investigation.

DD, with its labyrinthine causative and consequential matrix, demands a concerted perspective to achieve a profound comprehension and facilitate the development of affected individuals. Global collaboration, open databases, crowdsourcing, cross-cultural field studies, and equitable collaborations that eliminate biases and foster inclusive practices, will be crucial for advancing the field. The overarching aspiration is not only to unveil the mechanisms and development of dyslexia on a global scale but also to pave the way for interventions that empower children and adults to navigate realms of learning and literacy with sagacity and competence.

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