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Dyslexia as a Multifactorial Disorder

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This review of the scientific literature addresses studies of dyslexia. Different views of the roles of genetic and external factors in the etiology and pathogenesis of this disorder are discussed. Results from neuropsychological and neurophysiological studies evidencing impairments to particular parts of higher mental functions in dyslexia are presnted. The main types of cognitive deficit seen in dyslexia are discussed: impairments to a number of measures of attention and working memory, decreases in information processing speed, and insufficiency of new skill automation processes. These data indicate that dyslexia is a multifactorial disorder with multiple deficits.

Keywords: dyslexia, learning difficulty, executive functions, Cortexin.

It is generally accepted that significant difficulties in children's assimilation of school study programs are not only pedagogical problems, but also medical. In the ICD-10, disorders manifest as isolated disorders of the formation of basic skills required for learning are separated into a separate nosological unit – Specific developmental disorders of scholastic skills (F.81), including Specific reading disorder (F81.0; dyslexia). Developmental dyslexia is a persistent, selective inability to acquire the skill of reading despite adequate intellectual (and verbal) development, the absence of any impairments to the auditory and visual analyzers, and the presence of optimum learning conditions.

The detection and active study of the problem of inability to learn successfully with normal cognitive activity and general level of development of intellectual capacities in children began in Europe at the end of the 19th century with the introduction of mass school education. The term "dyslexia" and the definition of its specific pathology as "the inability to read words while able to see them" was proposed by the German ophthalmologist Rudolf Berlin in 1887. The first focused study addressing disorders of the formation of the reading skill in children with normal vision and intellect was reported by Pringle Morgan in "A case of congenital word blindness" in the *British Medical Journal* in 1896. The case described in this report, of a 14-year-old adolescent, provided a very precise characterization of this disorder: "He has been at school or under tutors since he was seven years old, and the greatest efforts have been made to tach him to read, but, in spite of this laborious and persistent training, he can only with difficulty spell out words of one syllable... I may add that the boy is bright and of average intelligence in conversation. His eyes are normal... and his eyesight is good. The schoolmaster who has taught him for some years says that he would be the smartest lad in the school if the instruction were entirely oral." This report can be regarded as the first documented case of childhood dyslexia to include a multiplicity of the characteristics present in current definitions of this disorder: serious difficulty in learning to read with normal vision, average intelligence, and adequate training (cited in [1]).

Descriptions of several cases of impaired reading and writing in children with normal intelligence were published by Hinchelwood et al., in 1900 and 1907. In these reports, the author made a compelling case against explaining difficulty learning to read in terms of any disorder of visual function. He proposed a hypothesis for the etiology of dyslexia in which the primary disorder to forming the reading skill was not a consequence of any defect in the visual analyzer, but anatomical or functional changes in the parietal cortex, which integrates auditory and visual information (cited in [2]). Thus, at the beginning of the 20th century, the belief that difficulty reading and writing might be a specific isolated functional disorder of mental processes came to be

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formed. Evaluation of these symptoms merely as one of the components of mental retardation was rejected [3].

At the early stages of research into dyslexia as an independent disorder, it was suggested to be congenital in nature. The first reports addressing dyslexia (Hinshelwood, 1907; Stephenson, 1907; Thomas, 1905) noted that reading difficulty was inherited (cited in [2]). Repeated cases of dyslexia in two generations of the family of a child with impaired formation of reading skills was described in 1917 by Hinshelwood (cited in [2]). The role of inherited factors was later confirmed by results from studies establishing that the prevalence of dyslexia among the relatives of dyslexic people is significantly greater than that in the general population. The risk of dyslexia is significantly increased in parent-child and sibling pairs [4, 5]. Strong evidence was obtained for the inherited nature of dyslexia from twin studies: the concordance of this disorder ranged from 68% to 100% in monozygotic twins and from 38% to 52% in dizygotic twins, which is evidence for a significant role of the genome in the development of dyslexia [6].

Molecular genetic studies of extended families of probands with dyslexia seeking specific genes whose anomalies may be the cause of this pathology have appeared over the last 30+ years. Six candidate genes for dyslexia *DYX1C1*, *KIAA0319*, *DCDC2*, *ROBO1*, *MRPL2*, and *C2orf3*) have now been identified [7]. Current theories hold that the influences of candidate genes lead to impairments in the regulation of neuron migration processes, resulting in alterations to normal morphogenesis of the cortex and impairments to neuron connections at the cellular and network levels. This may be one of the causes of learning difficulties, which requires accurate, rapid, and prompt integration of different neuron systems [8, 9].

Neuroimaging studies using MRI scans have identified the most frequent changes in brain structure in children and adults with dyslexia. Thus, *local* changes to the white matter were seen in the left temporal-parietal area and the left inferior frontal gyrus. Typical features of dyslexia are increases in the area and volume of gray matter in the temporal pole, the postcentral gyrus, and the left insula. In addition, expansion of the area of the superior parietal gyrus of the right hemisphere and thickening of the cortex in the inferior frontal gyrus (pars orbitalis) were found [10, 11]. This type of change to brain structure is currently regarded as a quite significant brain phenotype in dyslexia. Studies reported by Darki et al. [12] showed a significant link between this phenotype and the presence of established risk genes for dyslexia, *DYX1C1*, *DCDC2*, and *KIAA0319* in a cohort of healthy adults. However, finding this link in people without diagnosed dyslexia is evidence that the presence of the *DYX1C1*, *DCDC2*, and *KIAA0319* genes determines the development of a defined brain phenotype but are not sufficient for clinical manifestation of reading disorder.

It has been suggested that the etiology of dyslexia, like all behavioral disorders, is multifactorial and is linked with a multitude of genes and environmental risk factors [1]. Both dyslexia and normal variations in the development of reading skill are familial and moderately inherited [13, 14]. On the other hand, as demonstrated by study data, the etiology of both dyslexia and other learning disorders may involve a significant role for unfavorable factors affecting the intrauterine development of the fetus and the early neonatal development of the child. Data reported by Kornev [15] indicate that harm in the ante-, peri-, and early postnatal periods is encountered in 85% of children with dyslexia. It has also been noted that the histories of 27% of cases of children with dyslexia indicate premature birth or twinning. Analysis of data from an American epidemiological study identified a correlation between learning disorders and low birth weight, i.e., intrauterine hypotrophy [16]. Xue et al. [17] published results from studies which suggested that the actions of heavy metals (selenium and silver) may be linked with dyslexia in China. It is possible that the actions of unfavorable environmental factors produce the defects in brain development during this period similar to those arising via the inherited route. Thus, these disorders can be regarded as less differentiated phenocopies of purely genetic impairments. This theory is supported by evidence from clinical data showing that purely inherited dyslexia is often an isolated learning disorder (lesser tendency to the presence of linked disorders) and produces less severe impairments than residual organic forms[15].

In 2005, Plomin and Kovas [18] proposed the "generalized genes" hypothesis, whereby most genes affecting learning ability in one area are probably also important for forming other learning skills. On these grounds, the effects of the corresponding genes are mainly general rather than specific. This hypothesis was confirmed by clinical data on the specific features and incidences of comorbid pathologies in dyslexia. Children with dyslexia have also been found to be at elevated risk of impaired learning ability in other areas, including decreased mathematical ability, poor speech development, and writing disorders [19]. Moll et al. [20] conducted a study of the linkage of specific learning disorders of different types. This study showed that comorbid learning disorders occurred just as frequently as isolated disorders. Analysis of the data obtained in this study showed that about half of children with specific learning disorders demonstrated deficits in only one area, while the other half also had concomitant learning problems. This is evidence for a quite high level of linkage between these disorders which in turn may be a sign of their common pathogenesis.

Dyslexia and specific speech development disorder (SSDD) occur together so often that the question of whether they are separate disorders or manifestations of a single pathology has long been discussed [21]. The combination of these disorders (at the ongoing time or in the history) is seen in 40–80% of cases [22, 23]. McArthur et al. [22] found that 55% of children with dyslexia had concomitant symptoms typical of SSDD and 51% of children with SSDD had

difficulty learning to read, meeting the diagnostic criteria of dyslexia.

It should also be noted that 45% of cases showed the combination of specific learning difficulty with attention deficit hyperactivity disorder (ADHD) [23]. Up to 70% of all children with ADHD completely met the criteria for at least one of the scholastic skills acquisition disorders – dyslexia, dysgraphia, or dyscalculia [24]. Neurophysiological studies of ADHD and dyslexia have shown that both groups had dysfunction of the regulation of stem structures with impaired cortical rhythmogenesis or functional immaturity of the frontothalamic regulatory system. These systems are known to play a not unimportant role in forming several of the components of attention and its stability and to determine motivation and involvement in actions on performance of cognitive tasks [25, 26].

The aim of many scientific studies, both at the early stage of research into dyslexia and in the present time, has been to detect deficient mental functions underlying difficulties in developing reading skills. One of the first theories, which remains its relevance to the present day, is the phonological (or phonematic) deficit theory. This holds that the main impairment in dyslexia is a deficit associated with the cognitive processes of the acquisition, representation, storage, and activation of phonemes [2]. As long ago as 1937, the American neuropathologist Orton wrote in the book *Reading, Writing and Speech Problems in Children* [27] that many of these children have histories of problems with oral language and proposed that dyslexia should be considered part of wide spectrum of speech development disorders. The theory of atypical interhemisphere cerebral asymmetry or "mixed hemisphere dominance" was suggested as the basis of this state and may underlie disorders of visual and auditory perception and the inability to link letters with the sounds they represent. For many years, dyslexia was described as a "language" disorder. Such descriptions were applied mainly to the phonological deficit as the main feature of dyslexia [28]. However, some studies have reported that apart from the phonological deficit, children with dyslexia also have weak expression of other aspects of speech development, including vocabulary, morphology, and syntax [29]. On the other hand, reading difficulties themselves can lead to slowing of language development, as the greater part of language is acquired through experience of reading [30].

Data from neurophysiological studies show that the reactions of the brain to verbal stimuli in children with developing dyslexia differ from the reactions of children with normally forming reading skills [31]. A deficit of low-level sensory processing underlies the formation of phonological problems linked with impairments in the integration of visual symbols with their corresponding speech sounds [32, 33]. Thiede et al. [34] indicate that processing speech phonemes is more laborious in dyslexia. Boets et al., [35] published neuroimaging results showing that the reactions of the brain to phonetic contrasts in the primary and secondary auditory cortex were identical in adults with and without dyslexia, though structural and functional connections between the auditory cortex and the left inferior frontal gyrus were reduced in patients with dyslexia. The authors suggested that these results may be evidence of the "lower accessibility" of phonetic representations in dyslexia.

Data from neuropsychological studies indicate that specific changes in attention and memory may play a significant role in the mechanisms of dyslexia. At the early stages of research into this question, Tkachev (1933) [36] drew on data from clinical studies of children with difficulty learning to read and proposed that the main cause of the inability to acquire reading skills was memory deficit. The clinical severity of this manifestation is the inability to retain syllables in working memory during reading of a word, which leads to its distortion. Mnukhin, in his work "Congenital alexia and agraphia" (1934) [37], noted that children with impaired formation of reading and writing skills were characterized by insufficient formation of a variety of mental processes. Of all the impaired mental processes observed in dyslexia, disorders of "integral structural formation" were present at the highest frequency, implying that the capacity of working memory was limited. Many results have now been published from studies confirming that poor working memory, which produces difficulty in retaining and manipulating verbal and auditory information, is a typical symptom of dyslexia [38, 39]. Children with dyslexia often demonstrate degradation of the main measures of auditory-verbal and visual memory, which leads to difficulties in assimilating the visual images of letters and recognizing words during reading, along with impairment to memory for sequences of letters and letters in words. In addition, these patients experience difficulties in performing phonological manipulations, which require retention of phonological information during changes [38, 40, 41]. Thus, in tests for recognition of graphical images of words, young schoolchildren with dyslexia experience difficulties with word recognition. Increases in the number of letters in the word to be recognized increase the number of errors made by dyslexics, i.e., there is an inability to simultaneously remember a large number of symbols in a sequence and retain it in short-term memory [42, 43]. This difficulty in maintaining and manipulating information may be linked with impairment to the formation of reading skills, leading to specific reading errors.

A number of studies have also demonstrated insufficiency of various components of the attention system in dyslexia [44, 45]. Performance of correction tests shows degradation of both the quality (significant number of errors) and time taken for task performance, which is evidence of decrease functional capacity for maintenance of attention [42]. One current theory of dyslexia links reading impairment with slowed switching of attention, i.e., distraction of attention from the ongoing object for subsequent

transfer and involvement in the processing of other data [44]. Other authors [46] working in this field have clarified these reports, confirming that the attention system in dyslexia primarily degrades the elementary speed characteristics rather than more complex mechanisms.

Deficit in the rate of information processing and the associated reductions in the speed characteristics of activity are often regarded as among the key impairments in dyslexia [47, 48]. In this light it has been suggested that slow information processing speeds exacerbate deficits in various components, hindering compensation for these deficits by stronger aspects [48].

The main cause of slow speed and poor quality of reading in dyslexia may be impairments to the process of automation of this skill, leading to the need for conscious voluntary control of all the relevant processes. The problem of automation of acquired skills is a general characteristic of children with learning difficulties [49]. Clinical confirmation of this may be provided by typical symptoms such as the absence of a "task entry effect," i.e., the lack of adaptability. This is evidenced by the fact that the types of reading error in children with dyslexia are no different from the errors made by healthy children (so-called growth errors), though errors typical of the early stages of learning to read are persistent in dyslexia, which is also a sign that these acquired skills are insufficiently fixed and automated [15].

The ratio of automatic and controlled processes on performance of specific tasks and the speed of information processing are directly linked with the level of cognitive loading. It has been suggested that the more processes require voluntary control, the greater the level of cognitive loading. On the other hand, the faster information constantly arriving in consciousness is processed, the lower the chance of extreme loading of working memory and loss of the productivity of the activity [50]. Thus, slow rates of information processing decrease reading fluency, while slow voluntarily controlled and energy-dissipating reading leads to excessive cognitive loading. In these conditions, working memory lacks resources for analysis of content, which is reflected in the understanding of the meaning of the material read [51]. A side effect of increased cognitive loading is increased fatigue and exhaustion of mental processes [52]. This is supported by EEG studies, which show that the early stages of recognition in visual tasks show a left-hemisphere profile of asymmetry in the components of the θ rhythm not only in the posterior associative areas of the cerebral cortex (posterior temporal and parietal), but also in the anterotemporal area, which is linked with speech functions. This may indicate insufficient formation of regulatory mechanisms due to excessive and uneconomical involvement of the anterotemporal area at the beginning of the recognition process [42]. During execution of tasks associated with reading, children with dyslexia show hyperactivation in the frontal cortex and striatum. Hyperactivation in these areas is generally interpreted as a form of neuronal compensation associated with processing of articulation, though hyperactivation may also arise as a result of fundamental impairments associated with the processes of reading such as phonological processing [33].

At the systems level, it is noted that many children with verbal learning difficulties also show weakness in various components of executive functions [53]. Analysis of the results of neuropsychological studies of children with difficulties acquiring scholastic skills show a high incidence of deficits in programming and control processes, along with signs of deficit to processes regulating activity [54]. This is consistent with data from neuropsychological studies providing evidence that of all the regulatory structures of the brain, the formation of learning difficulties is primarily influenced by immaturity of the frontothalamic regulatory systems supporting the processes of local selective modulatory activation of individual areas of the cortex [55].

It is now recognized that neuroplasticity provides the neurophysiological basis of learning processes, i.e., the ability of neural systems to respond to exogenous and endogenous stimuli by adapting by means of optimum structural-functional rearrangements [56]. One of the fundamental principles of neuroplasticity is the phenomenon of synaptic pruning: a constant process of the destruction and creation of connections between neurons. This process supports the acquisition and fixation of new skills and is the basis of learning [57]. Current theories of the pathogenesis of dyslexia propose insufficiency of neuroplasticity. Support for this was obtained by Perrachione et al. [58] during studies of fMRI responses to repeated stimuli of different modalities in people with dyslexia. The results showed that rapid neuronal adaptation in stimulus-specific areas of the cortex is significantly decreased in children and adults with dyslexia. The decrease in neuronal adaptation may be a sign of impaired formation of connections in neural networks, i.e., a decrease in neuroplasticity in the brain.

Thus, the use of medications affecting neuroplasticity in the treatment of dyslexia is pathogenetically based. Cortexin is a nootropic agent which has long and effectively been used in the practice of psychoneurology. Its influence on improvements in neuroplasticity have repeatedly been demonstrated in clinical-biochemical studies. The potential molecular mechanisms of the neuroprotective effects of Cortexin are numerous and affect the key processes underlying neuroplasticity: signal transduction, energy metabolism, proteolytic modification of proteins, brain cell structure, and neuroinflammatory processes. The wide spectrum of mechanisms of action of Cortexin is based on its content of multiple different neuropeptides [59].

Platonova et al. [60] showed that Cortexin has high efficacy in the treatment of different types of cognitive impairments in children. The use of Cortexin in children with SSDD produced significant improvements in all the main indicators of speech development apart from pronunciation after courses of treatment [60]. Studies of the efficacy of Cortexin in children with organic asthenic disorder showed

significant improvements in the volume of memory and the fixation of memory traces in both younger and older age groups [62]. In addition, a screening study demonstrated the high efficacy of Cortexin in the treatment of ADHD [63]. Results from a multicenter study of the use of Cortexin in children aged 3–7 years with a variety of psychoneurological pathologies demonstrated statistically significant improvements in the major cognitive functions (thought, attention, and memory) in ADHD, SSDD, and asthenic disorders [64]. Thus, data from clinical trials indicate that the use of Cortexin correlates with improvements in many of the mental function seen to have deficits in dyslexia, and its use may promote improvements in reading skills.

The authors have no conflicts of interests.

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