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Epigenetic mechanisms in cognitive development

Abstract: This brief review focuses on the current knowledge of the epigenetic molecular mechanisms of cognitive development and factors causing the alteration of the epigenetic marks. Comprehensive understanding of this issue will help to start modeling favorable conditions to promote the cognitive development from the early childhood as well as to resolve the challenges resulting from the aberrant changes in expression of genes controlling the processes in the brain. We believe that of all factors, modifying the epigenetic marks at different stages of an individual's life, the non-pharmaceutical ones are of particular interest because of their potential to cause positive changes without harmful side-effects and the relative ease of implementation.
Keywords: inheritance, cognitive development, epigenetics, histone modification, DNA methylation

Introduction

The main goal of this paper is to analyze the factors determining the development of cognitive skills and to assess the relative contribution of inheritance in a person's perception and comprehension. An intensive research, conducted during the last three decades has revealed numerous gene loci, controlling cognitive development [1]. At the same time, the application of the typical genetic methods, including the use of modeled mutant lines for studying of the functioning of the normal cognitive development genes, does not provide straightforward information due to the complicated nature of the behavioral, on the whole, and cognitive, in particular, phenotypes [2]. On the other hand, variability of regulatory epigenetic marks during the individual's life and their dependence on a diverse spectrum of factors increase their significance as of potential markers of the developmental processes in the brain, causing the differentiation of cognitive abilities. It is reasonable to suggest then that, though the presence or absence of epigenetic marks are determined by genes and are even gender-specific, the changes of those marks, caused by the environment, can further affect the cognitive development. So, decoding of the molecular mechanisms of the cognition regulation can shed light on many aspects of the developmental processes in the brain, both normal and pathological. It is worthy to point out that it has believed that understanding of the genetics of cognitive development rather than cognition itself is more important, because, as noted above, it can make possible developing of methods, which will enhance an individual's learning as well as alleviate the conditions caused by the aberrant and atypical cognitive development.

Analysis of factors determining the development of cognitive abilities

Cognitive abilities determine the way one learns, remembers, thinks, priorities and solves problems, hence, they significantly influence all aspects of an individual's life in all age groups. Though the nature vs nurture debate has a long history, the results of many family, twin and adoption, as well as molecular studies, provide a lot of evidences of heritability of cognitive skills. The data collected

manifests the genetic component involvement in variation of cognition which is less than 25% in infancy rises to 70% in adolescence, which supposedly happens due to the activation of certain genes, which remain ″silent″ till the biological puberty and expression of which affects cognitive development [3]. As many agree, the question now is not whether cognition is heritable or not, rather than to what extend it is heritable. Yet the results, obtained in different studies testify that genes stably affect cognitive abilities in adolescence and adulthood, while the environmental factors, affecting these abilities, do not correlate with parent's cognition level [4].

Transactional models attempt to explain this seemingly controversial point by suggesting that genetically controlled behaviors in early childhood determine the occurrence of a child in a particular type of the environment, which, in turn, affects the cognitive development – 'higher IQ leads one into better environments causing still higher IQ, and so on' [5].

One of the implications of transactional models might be the promotion of the child's natural cognitive abilities through creation of the advantageous social learning environment for him. We suggest that learning the molecular bases of the cognitive development can help to elucidate further what environment factors, how and at what stage of the development should and can be modified for an individual's better development. That is why we think that, along with the abovementioned approaches to the study of the role of genetic factors in cognitive development, learning about the epigenetic mechanisms can provide a better understanding of the problem.

Epigenetics deals with the factors that influence the gene expression without interfering into the primary structure of the gene, i.e. the DNA sequence. There are three categories of the epigenetic marks - histone modification, DNA methylation and non-coding, or micro-, RNAs. What makes the epigenetic marks so promising from our point of view is their proneness to change in response to the environmental cues. Besides, in difference to the DNA sequence, which usually undergoes heritable changes due to some extreme environmental effects, epigenetic modifications can result from the less drastic and more common, natural, stimuli, such as maternal care, stress, malnutrition, traumatic experience, etc. At the same time, once acquired, the epigenetic marks can become fixed and affect the phenotype.

Epigenetic mechanisms of cognitive skills have been intensively explored during the last decade. One of the most promising ideas understood so far is that learning and memory storage are based on the same molecular signaling systems as cell division and differentiation, namely, mitogen-activated protein kinases (the MAPKs) for synaptic plasticity and memory, brain-derived neurotrophic factor (BDNF)-dependent phase in the hippocampus for the long-term memory storage persistence [6], or the DNA methylation and chromatin modification in memory formation [7].

MPAKs, the mitogen-activated protein kinases, are important for the intracellular transactional pathways, involved in the control of fundamental processes such as the cell growth, division, differentiation, apoptosis and responses to the extracellular stimuli. In the series of experiments, mitogen- and stress-activated protein kinases were demonstrated to act as key molecules in chromatin remodeling in hippocampal-dependent long-term memory-formation. According to [8], MAPKs, among the others, control acetylation of histone H3 in the hippocampus, thus strengthening the long-term memory. On the contrary, dysfunctioning of MPAKs has been shown to be one of the key factors in developing the Parkinson's disease [9]. Brain-derived neurotrophic factor, BDNF, is an important regulator of excitatory and inhibitory synaptic transmission and plasticity. The expression of the BDNF gene is regulated at the transcription, translation and post-translational periods, which some researchers consider as an evidence of the high complexity of the processes where the BDNF is involved. It is noteworthy that the BDNF and its pre-cursor molecule, pro-BDNF, have opposing effects on cellular function, with the former being associated with the cell survival but the latter inducing apoptosis, while both facilitate the long-term memory [10]. In the majority of studies conducted so far, the BDNF has been shown to decline with age and in neurodegenerative conditions such as Alzheimer's disease, Huntington's chorea and Parkinson's disease. It is interesting that people with these diseases manifest different profiles of cognitive impairment, which is due to the different regions of the brain experiencing the BDNF-deficit in each case - hippocampus, parietal, entorhinal and frontal cortex in Alzheimer's disease or striatum and motor cortex in Huntington's chorea.

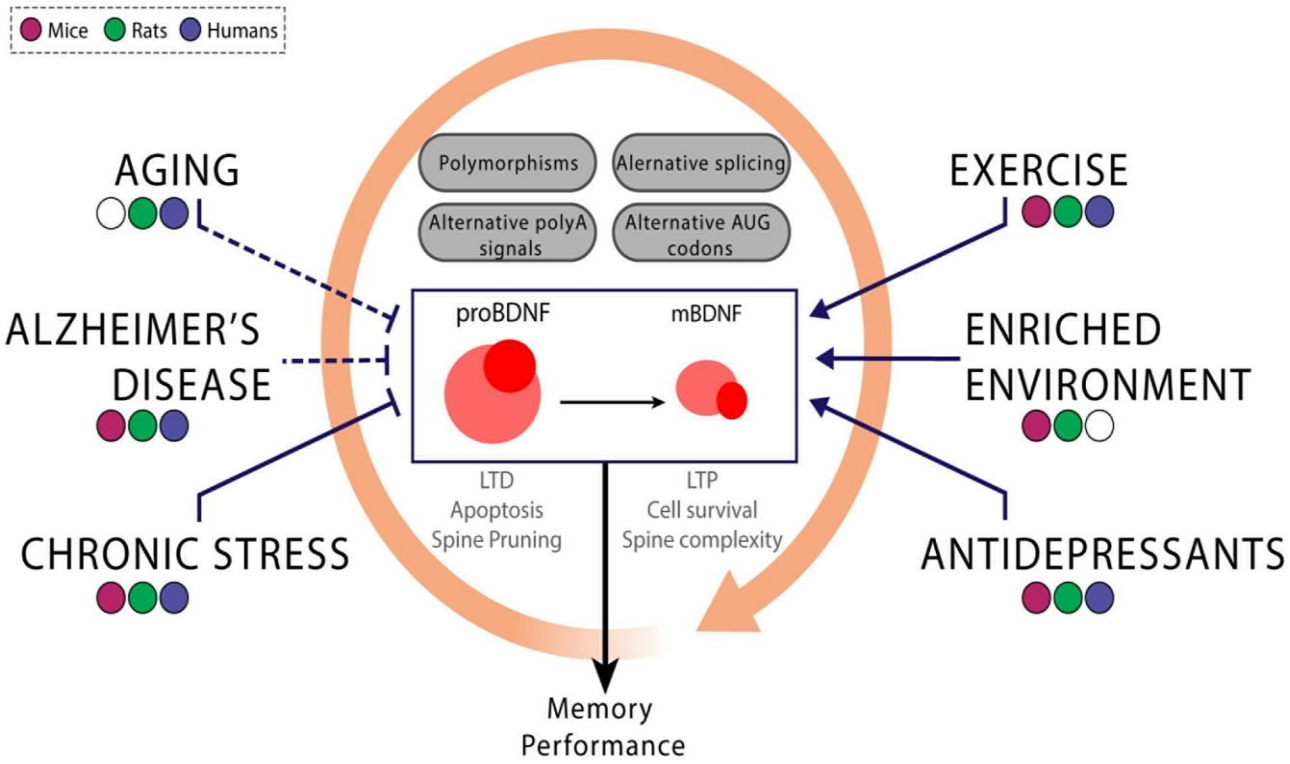

Figure 1. Modification of the BDNF gene expression as a result of the interactions between the genetic and environmental factors. https://www.frontiersin.org/articles/10.3389/fncel.2019.00363/full

There are different types of histone modifications. Histone acetyltransferases (HATs) transfer acetyl group to histone proteins, generally, causing activation of transcription, while histone deacetylases (HDACs) remove acetyl groups, leading to the opposite effect on gene expression. Histone methyltransferases (HMTs) and histone demethylases (HDMs), respectively, add or remove the methylation marks, switching genes off and on.

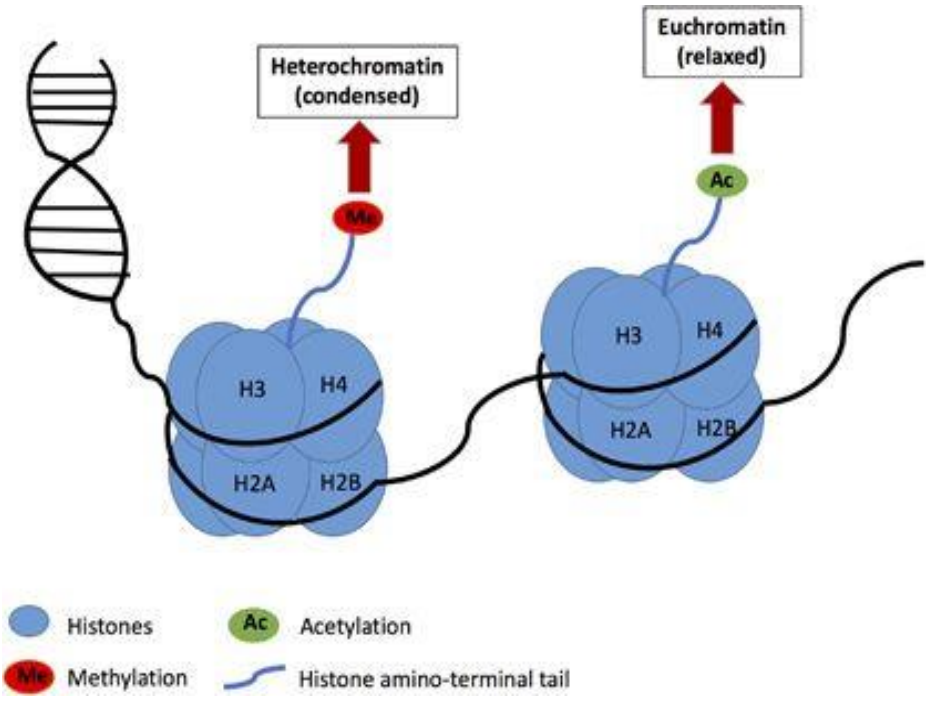

Figure 2. Schematic drawing of histone methylation and acetylation in relation to chromatin remodeling. https://www.nature.com/articles/emm2016140/figures/1

It is interesting that histone modifications are gene- and site-specific; the results of multiple experiments demonstrate a positive correlation between the histone modification and memory as well as associative learning [11]. The site-specificity of histone modifications attracts a special attention, as such site-specific modifications act as a «code» to activate or repress the gene transcription while the fact that these «codes» occur at the same genes, suggest the gene-specific regulation of histone modification. So far, different histone modifications were demonstrated being associated with such cognitive skills as learning and memory. For example, increase in H3K4 dimethylation, H3K4 trimethylation, H3S10 phosphorylation and H3S10/H3K14 phosphoacetylation in the CA1 region of the hippocampus was associated with a hippocampus-dependent form of the memory, so-called, contextual fear conditioning, while none of the epigenetic changes were found in the control group, which was not exposed to the fear conditioning, thus providing an evidence for these modifications being specific to the associative learning. Memory formation is correlated with the different combination of histone modifications in different age groups. According to a reference [12] , histone acetylation is associated with age-dependent memory impairment in mice. Combination of acetylations at H3K9, H3K14, H4K5, H4K8, H4K12 in the hippocampus in young mice interrelated with elevated gene expression of hundreds of genes, while in elderly mice, with the H4K12—deacetylated site, followed fear-conditioning, no transcriptional change was observed in those genes.

Methylation of DNA occurs when DNA methyltransferases transfer a methyl group to the 5th carbon of cytosines, mainly the ones preceding a guanine nucleotide, so-called CpG sites, and cause silencing of genes. Methyltransferases form a cluster of enzymes, including the *de novo* DNMTs, which add the methyl groups to the certain non-methylated regions on the DNA molecule and maintenance DNMTs, binding methyl groups to hemimethylated DNA and repairing DNA methylation. One of the most important maintenance DNMTs is the DNMT 1, which is highly expressed in mammalian tissues, including the brain tissue [13].

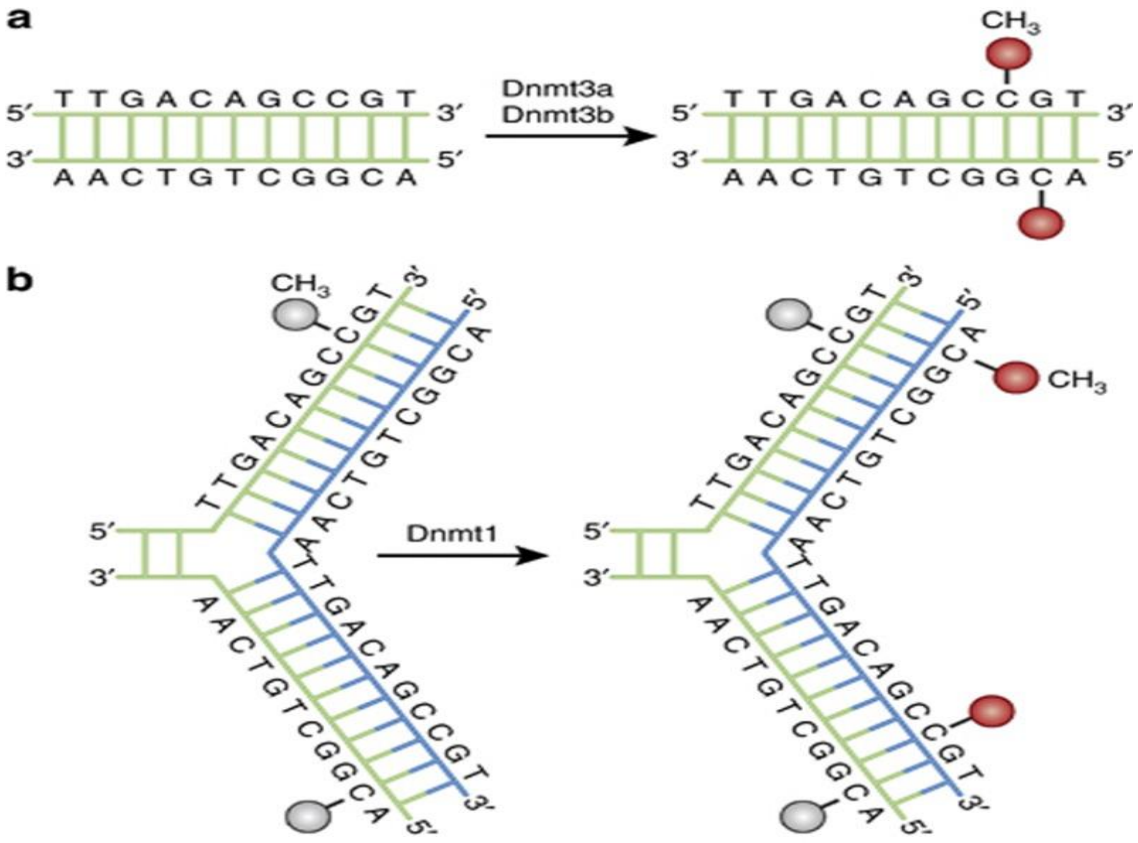

Figure 3. DNA methylation pathways. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3521964/

The effect of the second epigenetic mechanism, DNA methylation, in cognitive skills development has been explored less than the one of the histone modification. It is known that the changes in gene expression happen as a results of functioning of methyl-binding domain proteins, MBDs, which have an affinity to methylated cytosine. In the neurodevelopment disorder Rett-Syndrome, characterized with the

affected synaptic plasticity in memory formation in the hippocampus, MeCP2 (a type of MBD) is mutated [14]. The evidence was collected that if the DNA methylation in the brain changes due to the inhibition of the DNMT activity, hippocampal LTP, as well as histone acetylation get blocked, which in turn, affect memory consolidation [15]. However, pharmacological increase of histone acetylation prevented the memory decline. There is some controversy regarding the role of the third type of epigenetic markers – non-coding RNA- in cognitive skills development, but this controversy is mainly attributed to the precise changes the nc RNAs cause, while their contribution to the brain complexity development as well as to the neurological disorders and cognitive deficits is now undeniable.

As can be seen from the above mentioned data, if new technologies and novel methods, employed in experimental research, serve as one source of the information to increase our understanding of the role of epigenetic mechanisms in the development of cognition, the neurodevelopmental diseases of cognition serve as another source. These disorders of the CNS are characterized by the deficit of memory and learning, and include Rett Syndrome, Angelman Syndrome, Rubinstein-Taybi Syndrome, Fragile X-syndrome and Alzheimer's disease. Clarifying the etiology and pathogenesis of these disorders will help not only to find the therapeutic methods of treatment, but will also promote the theoretical knowledge of the genetic and epigenetic factors in cognitive functioning.

However, along with considering neurodevelopmental and neurodegenerative conditions associated with impaired cognition and memory, it is worthy to look at epigenetic modifications, correlated with aging-related cognitive dysfunction. Though the memory problems in AAMI are minor compared to those in dementia, considering the increase of the average life span at the present time, knowledge of the mechanisms, underlying these processes will improve the life quality of aged people and, possibly will prevent the further deterioration of brain functioning. Burke and Barnes distinguish two modes associated with age-related memory – declarative or episodic, anatomically based predominantly in hippocampus, and working memory, based in the prefrontal cortex [16]. Approximately at the same time when Burke and Barnes wrote their paper, different groups of researchers identified a few genes, controlling the "memory well-being", called immediate-early genes (IEGs) such as Arc (activity-regulated cytoskeletal gene), zif 268 (nerve growth factor inducible A) BDNF (brain derived neutotrophic factor), the increased expression of which was shown to be related to the memory disconnection and memory disorders. The Arc-gene transcription is confined to the principal cells of the hippocampus and other brain regions and is associated with the spatial learning and memory; while zif 268 regulates the transcription of twenty delayed-response genes. Damage to the hippocampus deteriorates spatial learning and memory. At the same time, it was demonstrated that worsening of the hippocampus-dependent memory with age does not happen because of the massive cell death or changes of the electrical properties of neurons such as resting membrane potential, membrane time constant, input resistance and the threshold to achieve an action potential. However, the synaptic plasticity mechanisms, including long-term potentiation, becomes altered. All these discoveries provide an evidence that the neurobiological evidence of the age-related memory decline also depends on the altered transcription of genes, controlling the brain 'plasticity' [17].

Another issue we would like to stress in this paper is that factors, which can potentially influence the gene expression through the changes of the epigenetic marks, are not only the pharmaceutical ones. Physical exercises cause histone acetylation [18]. There is a lot of evidence that exercises stimulate acetylation of histone H3 in hippocampus and cerebellum. According to a reference [19] such a stimulating effect of exercise on histone acetylation happens in the promoter of the BDNF IV sequence and promotes the BDNF transcription. As stated in a reference [20], acetylation of H4K12 caused by physical activity, led to the improvement of the cognitive skills in experiments on animal models. According to the same source, de novo DNA methyltransferases (DNMTs) play role in the consolidation of long-term memory. Maltreatment and tramautic experiences were found to correlate with increased methylation of certain genes such as serotonin transporter gene, the glucocorticoid receptor gene and dopaminergic genes, which, in turn, was found to be associated with "differential physical and mental health risks" for maltreated children compared to the non-maltreated ones [21].

According to references [22, 23], the impact an embryo receives during the prenatal (in utero) and early postnatal development, is a «major determinant» of an individual health. A lot of evidence collected led the authors to suggest that any type of malnutrition (nutritional deficits, deficiency diseases as well as nutritional excess) causes lower cognitive performance later in life. Beside the nutrition, systemic inflammation and hormonal background significantly affect the cognitive development. Some of the nutritional factors that have been shown so far in modeled experiments to influence the cognitive development via the epigenetic modification, are as follows:

- Iron-deficit - reduced expression of H3 demethylases in the hippocampus; decreased DNA methylation at exon IV of BDNF and, consequently, lower concentration of BDNF;
- Zinc-deficit - lowered histone modification;
- Choline and folate - are involved in ethyl-donors production, alteration of DNA methylation and histone modification;
- Methionine - one of the essential amino acids, is a substrate for the S-adenosylmethionine, hence, its deficit also lowers the DNA methylation.;

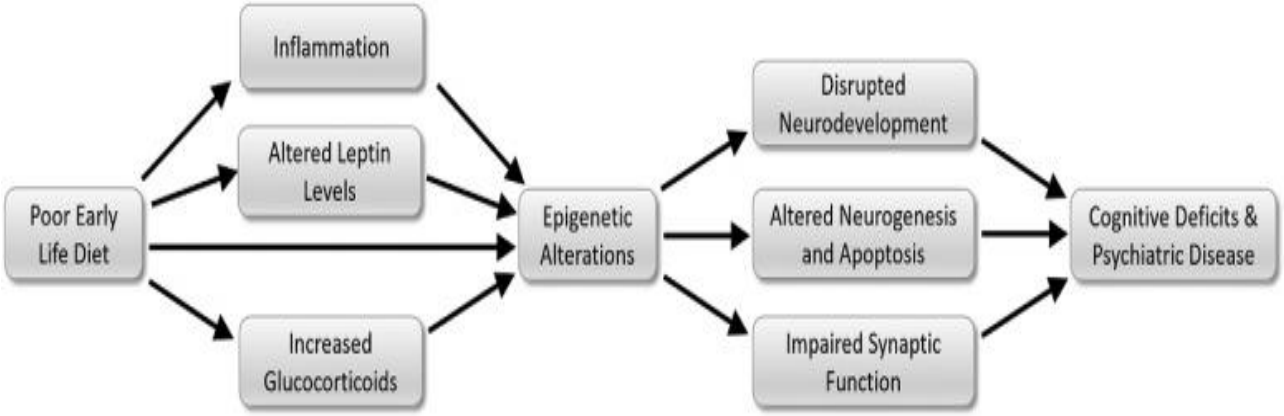

Figure 4. A modifying effect of a poor early-life diet on epigenetic markers and cognitive development. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5347110/figure/fig1/

Fatty substances such a butyrate and acetate, affect both HDACs and DNA methylation, while acelyl-coA, one of the key metabolites, affects the rate of histone acetylation. Besides, high fat diet intake was shawn to correlate with changes in hormonal and inflammatory states, leading to the DNA hypermethylation. This kind of epigenetic modifications, if happening in cerebral cortex, were demonstrated to cause memory problems.

Along with the abovementioned factors, the impact of daily life reactions and phenomena such as stress and different teaching/learning techniques on cognitive competence was discussed and the adverse effect of stress on learning skills was pointed out. [24,25,26,27] A special emphasis was made on the greater efficiency of early remediation programs for developing cognitive skills of younger generation.

Conclusions

The genetic component significantly influences the cognitive development. The results of numerous experimental researches provide evidences of different epigenetic mechanisms playing a key role in development and manifestation of differentiated cognitive skills in different age groups. These epigenetic mechanisms are, in their turn, influenced by the conditions an individual experiences at different stages of life. The further accumulation and analysis of the related data will make it possible to design and implement the special programs aimed at helping individuals to achieve all standards they are capable of and realize their full intellectual potential at all ages.

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