Neurophysiological maturation in adolescence – vulnerability and counteracting addiction to alcohol

Roman Chwedorowicz1, Henryk Skarżyński2, Weronika Pucek1, Tadeusz Studziński1,3

1 Institute of Rural Health, Lublin, Poland
2 Institute of Physiology and Pathology of Hearing, Warsaw, Poland
3 Higher School of Humanities-Natural Sciences, Sandomierz, Poland


Abstract
The results of contemporary studies confirm the formation of two neural networks in the brain during the period of adolescence. The first is defined as emotional, located in the limbic system, develops earlier, quicker, and more intensively than the second one in the prefrontal cortex, called the judgement network, which fulfils the role of control and inhibition of emotional reactions. The domination of the emotional network in adolescence is manifested by hyperactivity of the limbic system, accompanied by intensified undertaking of courageous, reckless, risky, or even sometimes dangerous actions, so very characteristic in the maturation. The aim of the article is to present the state of the art in the field of latest achievements in experimental neurophysiology related to the maturation of the structural and functional processes in adolescents, and to alcohol vulnerability. Alcohol effect initiation starts in early adolescence, and therefore is connected with alcohol abuse and addiction in adulthood, which confirms the necessity for provision of an early prophylactic protection for juveniles, even before entering the phase of early adolescence. Some electrophysiological characteristics, such as low P3 amplitude of the Event-Related Potential (ERP) and Event-Related Oscillations (EROs), are manifested by their high risk offspring, and are considered to be biological markers (endophenotypes) of a predisposition to develop alcohol use disorders.

INTRODUCTION
Adolescence, as defined today by the World Health Organization (WHO), covers the period in human growth and development between childhood and adulthood (10–19), when the degree of physical, psychological and social development reaches the level of maturity. Despite the universal neurohormonal conditionings determining the process of development in adolescence, including sexual, emotional and social maturation, the onset of adolescence, its phases and termination vary among different communities and culturally different populations [1, 2, 3].

The period of adolescence, contemporarily prolonged by an entire decade, is the previous version of the definition increased by three years. Considering these changes, it is noteworthy that in Poland adolescence begins together with the start of education in the fourth form of primary school, and has features of universality in many regions of Europe. However, for both parents and teachers, as well as for fourth-year schoolchildren, it is difficult to acknowledge that according to this classification and interpretation they are no longer children in the sense of developmental neuropsychology, because they exceed the threshold of adolescence. Some researchers investigating the processes of neural maturation in adolescence push the upper limit as far as the age of 25, considering the added years as late adolescence, and not early maturity. The above-presented interpretation includes into adolescence the years of higher education, justifying this by the continuation of maturation and development of the neural network of the prefrontal cortex, which conditions more mature performance of the cognitive functions with respect to the control of impulse responses, capability for concentration and mindfulness, as well as an effective functioning of the working memory [4, 5, 6, 7, 8].

Together with entering into the period of adolescence, there occur changes in the psychology of young people who grow also dynamically; however, while still being children, radically differ with respect to many behaviours. In adolescence, there is a change in the scope and form of...
The high plasticity of the brain, most noticeable during the first years of adolescence, creates also an elevated danger considering the presence of increased sensitivity and vulnerability to the effect of environmental factors and hazardous stimuli. A special threat is caused by alcohol and psychoactive substances, as well as unacceptable risky behaviours which, meeting the plasticity of the features of even uncontrolled fluidity, most rapidly induce addictions, as well as behavioural and psychological disorders. It is noteworthy that in adolescence the highest intensity of alcohol consumption and experimenting with psychoactive substances are observed, which is translated into their abuse and tolerance leading to juvenile alcoholism. The period of adolescence is the time of developmental and plastic formation of new traits of mature personality. Alcohol and psychoactive substances simply displace these traits, change and adjust the structures and functions of the systems, consequently and inevitably subordinating them to exclusive control, manifested by the development and acquisition of conditioned responses in the form of habits and full-blown addictions, which are difficult or simply impossible to eliminate after entering adulthood [10, 19, 20, 21, 22].

Neuropsychiological maturation and proneness to alcohol in adolescence. The most distinctive characteristics of the brain of an adolescent is the capability for formation and change of the structure and functions of neural networks connecting various centres, and even the whole spheres of the cerebral cortex and subcortical centres. This characteristic of the brain, defined as plasticity, is understood as the capability for the formation, modelling and remoulding of neural networks with relation to the groups of neurons and their connections, together with their activity, and fixation of this activity within synaptic connections, as a result of adaptation to the environment and entire spectrum of environmental stimuli. Plasticity of the brain conditions cognition, adaptation, and acquisition of the skills of responding to the environment and its changes. This allows assumption of an active attitude, creative thinking and acting, and consequently, the adaptation and adjustment with the traits of individual connectedness and, at the same time, socialization. Environmental requirements enforce the individualization of actions in adolescence, associated with courage, great effort and formation of identity, maintaining peer, partnership, group and social connectedness. Individual activity in adolescence becomes a challenge, and simultaneously, the necessity which determines the most beneficial and optimum development of personality and individual talents in cohesion with the effect of the environment [18].

Contemporary methods and techniques of examinations of the brain have shown such an orientation and formation of anatomical structures and functions of the brain in adolescence, which enables adaptation and undisturbed development, conditions and provides fullness of mature adulthood. It was a surprising observation that adolescent development and maturation of the brain do not consist in an increase in the number of neurons and thickness of the grey matter, but in their removal, with the reduction of synaptic connections (pruning). The discovery of synaptic pruning was a great and surprising finding in the studies of the processes of development and maturation of the brain, and its most measurable determinant was the reduction of the thickness of the grey matter in the cerebral cortex. Moreover,
the physiological sense and essence of pruning consist in specialization covering the preservation of only those networks and inter-neuronal connections which are most intensely used, and therefore, tested as useful. Preservation of these neural networks with the perspective of their fixation and further development, as well as achievement of high efficiency, has been considered as an indispensable adaptation and specialization adjusted to the conditions of the environment in which they were formed [5, 19, 23].

The process of pruning is accompanied by an intensive myelination of nerve fibres, which results in an increase in the thickness of the white matter, and the networks assume more numerous and efficient pathways in interneuronal conductivity of the nerve impulses. Intensive myelination of nerve fibres is associated with the process of strengthening synapses and synaptic conductivity. The functional neuronal effect of myelination and maturational synaptic strengthening is an increase in the abilities of information processing and neuronal transmission, which increases by as many as three thousand times, compared to the values in children. Pruning, myelination of the nerve fibres and strengthening of interneuronal synaptic connections, which are intensified stepwise in adolescence, increase and condition the effectiveness of coordination in the functions of various groups of neurons and nerve centres. An increase in the coordination of various groups of neurons is accompanied by an increase in cognitive effectiveness, analyzed in conditions of experimental use of task and memory tests. A dynamic increase in connections and activity in the structures of the prefrontal cerebral cortex is especially noteworthy, responsible for the evaluation of behaviours, cooperation with others, and the development and formation of emotional intelligence [22, 24, 25].

As early as from the first years of adolescence an increased sensitivity and vulnerability to the effect of the peer social environment is observed, when there arises the need for acceptance and group affiliation, associated with simultaneous achievement of autonomy and distancing from parents and adults. During this time, imitating is observed and uncritical assuming of peer behaviour patterns, including engagement in experimenting with alcohol and psychoactive substances which, while taking place at the time of formation of neural networks and brain plasticity, permanently code negative patterns. Similarly, the Internet forums (Facebook, You Tube, Twitter) presenting alcohol in advertisements exert a negative effect, which is easily translated into the actual acceptance of alcohol consumption, with a decreased perception of the hazardous effect of alcohol [26]. Also, executive functions, including planning, decision making, and control of emotions, depend on the formation, organization, fixation and specialization of neural networks in the prefrontal cerebral cortex. The skills, identity and organization, fixation and specialization of neural networks, depend on the formation, organization, fixation and specialization of neural networks in the prefrontal cerebral cortex, and is also called the judgement network [18, 21, 33].

The judgement network is located in the prefrontal cerebral cortex, and is also called the concentration and thoughtful acting network. This network regulates, controls, and counterbalances emotional and affective reactions. Therefore, the transmission and effect of strong affective states in adolescence, determined by the affective network, clears the way and precedes the achievement of regulatory efficiency and functional maturity of the cortical judgement network, the main function of which are thoughtful actions. The lack of developmental and functional balance between these two networks is sometimes defined as their desynchronization and mismatch, resulting in the occurrence of characteristic, typical changes in reactions, behaviours, and attitudes in underage individuals during adolescence. These changes, however, do not result from motives and background of pathological changes in the brain, but are features of the naturally and normally ongoing processes of neurophysiological formation of structures and functions in the central nervous system [21, 33, 34].

Neurons of the affective emotional network present structural and functional prevalence over neurons of the judgement network as early as from the first year of adolescence. This domination lasts until the age of eighteen, on average, when the neuronal and functional development of the judgement network catches up with the activity of the emotional network. It is noteworthy that neurons of the judgement network continue the process of development and specialization until the age of twenty-five, and according to some researchers, although in a slowed down pace, for several years longer. The domination of the emotional network in adolescence is manifested by hyperactivity of the limbic system, accompanied by intensified undertaking of courageous, reckless, risky, or even sometimes dangerous actions, so very characteristic and in contrast to the abandoned, but still close, childhood [11, 31].
Passing the threshold of adolescence and radicalization of behaviours related with profound changes of the structures and neuropsychological functions, as well as the lack of balance between the emotional network and judgement network, led to the presumption and statement concerning adolescent maladjustment, and even abnormality, or developmental incongruity. The occurring puberty, additionally propelling impulsive reactions and behaviour with a low capability for their inhibition and satisfactory counterbalancing, seems to confirm these interpretations and suggestions. Passing the threshold dividing childhood and adolescence is associated with a radical opening and intensification of the deep modelling of neurohormonal structures and functions. Difficult, or even painful and misunderstood individual experiences of each child entering adolescence, who is no longer a child in neuropsychological terms, should encounter the imparting of knowledge concerning this process, not omitting parents, educators and teachers, as well as society.

**Alcohol initiation in adolescence and alcohol addiction in adulthood.** The effect of early initiation of alcohol, defined as the consumption of the first drink or the first tasting in adolescence, indicated the occurrence of frequent alcohol intake in these individuals, as well as more frequent addiction in adulthood [12]. It was found that addiction to alcohol in adulthood was four times higher if the alcohol initiation took place at the age of under fourteen, compared to the results obtained in the control group, where alcohol initiation took place not earlier than at the age of twenty and over [12].

Similar results were obtained in studies targeted on the time of the first effect of alcohol in adolescence, which covered approximately six thousand juveniles, investigating also its later effect on alcohol abuse and addiction as evaluated during the subsequent twenty years [35]. Alcohol initiation at the age of eleven to fourteen significantly increased the risk of occurrence of abuse and addiction, evaluated according to the DSM-III-R criteria. It is noteworthy that these results, similar to those previously quoted, indicated the presence in adolescence of a narrow developmental age interval [11–14] and threshold age barrier of the age of fourteen, when alcohol initiation left a permanent trace, and increased preference and threshold age barrier of the age of fourteen, when alcohol intake in these individuals, as well as more frequent addiction and threshold age barrier of the age of fourteen, when alcohol intake took place not earlier than at the age of twenty and over [12].

The results of subsequent studies on a wide international scale, which covered approx. twenty-six thousand adolescents, provided additional justification for adopting the statements concerning the presence in adolescence of an elevated vulnerability to alcohol related with high vulnerability to addiction [29]. Also in these studies, the age of eleven proved to be a critical determinant, from which the frequency of addiction to alcohol increased [29]. Peak values were then observed at the age of eighteen, with subsequent decrease noted as late as from the age of nineteen.

Alcohol effect initiation started in early adolescence, therefore, is connected with alcohol abuse and addiction in adulthood, which confirms the necessity for provision of an early prophylactic protection for juveniles, even before entering the phase of early adolescence. The most effective and simplest method recommended for the prevention of alcohol addiction is therefore avoidance and abstaining from drinking (absenteeism) at the beginning of adolescence, and postponing in time of both alcohol tasting and initiation, best not before reaching the age of nineteen.

**Induced potentials and electrophysiological oscillations in evaluation of vulnerability to alcohol addiction in adolescence.** The potentials induced, also called the Event-Related Potentials (ERP), are released by the effect of somatosensory, auditory and visual stimuli, and are defined as an ‘event’ [36, 37]. The induced potentials are characterized by high stability of features and a high repetitiveness of their registration. Basic parameters of induced potentials are their positive or negative polarity, marked by the letter P (positive), or N (negative). The subsequent characteristics of potentials induced are the amplitude of particular waves expressed in microvolts (µV), time of latency, and time of duration of the potential and its individual phases, counted in milliseconds, as well as cranial localization and its reference to the cortical and subcortical spheres and structures of the brain [36, 37, 38].

The event-induced potentials (ERP), apart from stability, also show vulnerability to the effect of alcohol and change in conditions of acute and chronic effect of alcohol in the body, in tolerance, toxic inebriation, withdrawal and abstinence [39]. In the acute effect of alcohol, a decrease in P300 amplitude is observed, which is the main positive wave, registered after three hundred milliseconds from the effect of the stimulus inducing potential, expressed by the symbol P3, as the third subsequent change of potential [38]. The return to the baseline values takes place together with the development of tolerance and abstinence. After withdrawal, previously increased P300 amplitude returns to baseline values as late as in abstinence [39].

In alcohol addicts who are in abstinence the processes of sensory perception, neuronal transmission, its processing and control, show dysfunctional changes, which are revealed in electro-encelographic recordings at rest, performance of test tasks, as well as in stimulation releasing induced potentials. It should be emphasized that the resting state of EEG activity and recordings of waves and functional discharge have the features of individualization, defined as recording patterns which present differently, both in the conditions of alcohol effect, and in the state of sobriety and abstinence in individuals addicted to alcohol [40, 41].

For a long time it was considered that changes in potentials induced in individuals addicted to alcohol result from the neurotoxic effect of alcohol. Therefore, the detection of these characteristics called endophenotypes, in induced potentials was surprising, in both adult alcohol addicts in the state of abstinence, and in children who have never been under the effect of alcohol [40].

It should be explained that the concept of ‘endophenotype’ means the presence of a biological or psychological trait, also defined as a marker, genetically transmitted to the offspring, and present also in close relatives. The requirements necessary to consider a trait as endophenotype concern its physical or chemical existence, heritability, and presence in relatives, as well as measurability and the reality of performing measurement, related with the authentic and manifested presence of such a trait [42, 43].

The P300 response, which is a positive potential released by a luminous or acoustic signal of the frequency of 600 Hz or 1600 Hz, and registered in the electroencephalographic recording within the range of delta and theta waves after three hundred milliseconds from the effect of the luminous or acoustic signal, has been considered as the endophenotype of vulnerability to alcohol and alcohol disease, if its value...
is changed. It should be added that the P300 response is often defined by the symbol P3, the genesis of which comes from the third subsequent change of potential released by a stimulus or event. The genesis of the name of the P300 response comes from the time of latency which is three hundred milliseconds. The P3 response is further varied into the subsequent components, i.e. Pa, Pb and SW (SW – slow wave [36, 37, 38]).

A decreased value of the amplitude of the induced potential P300, which is a characteristic feature and called the electrophysiological endophenotype, remains under indirect genetic control and precedes in reality the process of addiction, which may also be viewed as a secondary or consequent phenomenon. This has justified ascribing genetic predispositions for an increased vulnerability for alcohol abuse and facilitated alcohol addiction to individuals possessing this electrophysiological endophenotype [39, 44, 45]. Alcohol addiction started to be related causatively with genetically and family inherited vulnerability and inclination represented by the P300 endophenotype and its decreased amplitude. It has even become justified by some researchers to consider this feature of the induced potential as an electrophysiological signature, identifying via P300, the presence and expression of specified genes [46, 47].

The results of studies of genes encoding the synthesis of receptor proteins of neurons in the central nervous system showed the presence of feedback between high vulnerability to alcohol and gammaaminobutyric acid receptors (GABA), functioning as the main inhibitory neurotransmitter in the central nervous system. The variant of the gene encoding the alpha2 subunit of the GABA-A receptor, located on chromosome 4, is responsible for the reduction or even advanced deficiencies in tonic inhibition of GABAergic cortical interneurons. The then observed prevalence of activity of the pyramidal neurons in cortical networks dominates over the activity of GABAergic inhibition, generating the growth of power and amplitude, the highest within the range of Beta 1 wave (12.5 – 16 Hz), and slightly lower Beta 2 (16.2 – 20 Hz) and Beta 3 (20.5 – 28 Hz). It was confirmed that an increase in amplitude and power of Beta waves presents the features of electrophysiological endophenotype in the form of an increased predisposition for addiction to alcohol. It must also be said that this endophenotype is accompanied by disorders of behaviour, already in childhood, and more frequent use of psychoactive substances in adolescence, and more frequent anti-social behaviours and attitudes [48, 49, 50, 51].

The presence of an altered GABRA2 gene and its expression, conditioning the synthesis of receptor protein of decreased inhibitory effectiveness, manifested by distorted behaviours as early as in childhood, adolescence and adulthood, is manifested by an increased amplitude and power of Beta waves, which was ascribed the properties and characteristics of endophenotype. It was also found that an increased vulnerability for alcohol addiction is also related to hyperactivity of cortical functions, resulting exactly from impaired functions of GABAergic receptors inhibition [52].

Another neurotransmitter of similar importance in relation to the effect of alcohol is acetylcholine, an allelic version of the CHRM2 gene encoding the synthesis of muscarinic type-2 receptor protein, which is associated with hypersensitivity to the effect of acetylcholine in the neurons of the central nervous system. Cholinergic muscarinic receptor, the protein of which is encoded by the variant of the CHRM2 gene, located on chromosome 7, is characterized by hypersensitivity to acetylcholine, and its presence is connected with alcoholism and depressive disorders. The scope of these disorders, connected with a decreased P300 amplitude, covers the syndromes of decreased inhibition, abuse of psychoactive substances, distorted and anti-social behaviours, and the Attention Deficit Hyperactivity Disorder (ADHD). In the EEG recordings of individuals addicted to alcohol who are carriers of this gene, the stimulation of cholinergic muscarinic receptors M2 changes the pattern of the recording of slow waves of the delta and theta frequencies, accompanied by the effect of decreased oscillation values induced, which were also considered as endophenotype [49, 53].

An importance similar to the P300 response was attached to the oscillations and power of the delta and theta waves, and were ascribed the features of endophenotype. It is noteworthy that an additional causative role in the formation of induced oscillation of theta and delta as an endophenotype, is fulfilled by glutamate and GRM8 gene, conditioning the synthesis of metabotropic glutamate receptor protein. The GRM8 gene located on chromosome 7, in close vicinity of the CHRM2 gene, which encodes the synthesis of protein in the cholinergic muscarinic receptors M2 and conditions inclination towards alcohol abuse and alcohol addiction. Electroencephalographic oscillations induced within the range of the theta and delta waves (Event-Related Oscillation- ERO), considered as endophenotypes and markers of increased vulnerability for addiction, present three groups of genes and three types of neurotransmitters, with gamma aminobutyric acid, acetylcholine and glutamate as neurotransmitters in the central nervous system. It should also be emphasized that in studies of alcoholics and adolescents from families at a high risk of addiction, the power of theta and delta oscillations induced occurred to be a more sensitive indicator of vulnerability than the induced P300 potentials [41, 54].

A new research approach consisting in the application of electroencephalographic methods and techniques in developmental and genetic studies of the conditioning of varied vulnerability, and especially increased preferences for alcohol tasting and abuse in adolescence, provide unique possibilities for comprehensive and deepened studies which may contribute to the prevention of alcohol addiction, the genesis of which, to a great extent, is related with the effect of causative environmental and genetic factors during adolescent development.

CONCLUSIONS

The presented results of studies of original, cognitive and applicatory values concerning an increased vulnerability for the effect of alcohol during adolescence resulting from the neurophysiological developmental conditioning, fully justifies the wider social communication of these findings. An interest in the results of the above-mentioned study results should be evoked in the environments directly engaged in the processes of widely- understood primary, secondary and university education, as well as in institutions dealing with specialist protection and prevention of the pathology of alcohol addiction, and other addictions among children and adolescents. Considering the increase in alcohol consumption by European adolescents which has been observed in the last
two decades, and previously not noted, which happens at the time of high activity of the mechanisms of neurophysiological formation of cerebral structures and functions, determining pathological consequences manifested as early as in adolescence and transferred into adulthood, simply enforce the necessity for undertaking effective prophylactic actions with the wide participation of competent environments, parents, as well as the children and adolescents.

The proposal seems justified to undertake experimental attempts to cover schoolchildren with education in the area of essentials of adolescent neurophysiological development of the brain and its vulnerability to functional disorders and structural damage caused by alcohol. The expansion of the subject 'Education in the Family' by plots or pathway concerning the hazardous effect on the brain at the time of passing the threshold of adolescence – between the ages of nine and eleven of life – although not radical, would be justified by experimental testing, which would present the effectiveness of the implementation of the method of 'life without alcohol' in adolescence, obviously in combination with a set of supplementary actions of an adequate programme.

The undertaking of studies with the use of releasing induced potentials and electrophysiological oscillations in children during neurophysiological adolescent development in order to identify endophenotypes as markers of increased vulnerability for alcohol addiction, might be a non-invasive and easy to apply method for diagnosing the genetic and thus inherited conditioning and predispositions for early alcohol initiation, alcohol abuse and addiction to alcohol. It is noteworthy that considering the genetics causativeness of alcohol addiction in European populations, which is 60%, endophenotypic electrophysiological identification of this vulnerability could provide an early diagnosis, which might precede alcohol initiation, without being a stigma, but the diagnosis of inherited genes determining increased preferences and inclinations towards more frequent and abundant alcohol intake.

Awareness of inherited possession of an increased risk of addiction would allow an early and more effective self-control as prophylaxis, as well as more effective counteracting, also targeted therapy considering the restoration of a distorted neural function of the brain against the induction of structural changes in the chronic effect of alcohol, which hinder or simply exclude the effectiveness of therapy.

Acknowledgement
This study was financed from resources for science in the years 2011–2015 as Research Project No. N N404 316940.

REFERENCES