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REVIEW ARTICLE

Perception – Vulnerability – Development – Intellectual Health. Developmental aspects of perception

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Abstract

Maturation process of the CNS, including the sensory systems, requires not only energy resources, substrates, information molecules, etc., but is primarily dependent on the interaction of the input signals. Developmental plasticity represents a potential for both the positive and negative epigenetic factors to modulate the capacity of brain integratory functions at all its levels. Positive environmental factors as well as various forms of sensory deprivation or stressful situations, including prematurity and immaturity of newborns, are associated with the enhancement or detraction of the complexity of neuronal circuits and their integratory function. Various forms of sensory deprivation (hearing loss, some visual disturbances, social deprivation and nutritional disorders) are often associated with elementary dysfunction of neuronal circuits, like the elevated variability of cortical EEG responses or the failure to respond to a rapid sequence of stimuli. That could result in the impairment of principal cognitive function of humans – the communication skill (context understanding or the speech fluency, grammatical structure and sentence meaning).
Newborns are able to discriminate the intensity and quality of wide variety of odorants. Olfactory abilities are constantly developing between the age of 3 and 12 years, being enhanced during adolescence by increasing verbal abilities to name the gaining new experiences. The relationship between odor identification and verbal abilities is primarily genetically mediated. This suggests that odor identification and verbal ability in general concern the same cognitive domain.

Introduction

Almost all medical disciplines – to a greater or lesser degree – study and consider – the impact of a given pathology on so-called cognitive processes. These are usually presented as more or less homologous issues (learning, memory, recall, retention, differentiation processes, etc.). However, they represent a multi-layered process that has its beginning in the process of perception. Long before J. LOCK (1632–1704) ("*Nihil est in intellect quod non prius fuerit in sensu*"), Zenon of Kittia (about 340-265 B.C.) or Aristotle (384-322 B.C.) said the same in other words (and they were not alone)!

If today's person receives up to 90% of all information by sight and hearing, it is appropriate to wonder whether sensory perceptions captures the external reality faithfully, so that its subsequent processing, analysis and confrontation with memory in associative neuronal circuits cannot lead to misinterpretations or even serious distortions. These errors would then increase the risk of defective "output", i.e. in an improper behaviour. Ophthalmologists and otorhinolaryngologists have enough experience not only to admit such risks but also to be able to treat them therapeutically.

The influence of sensory experience on the development of neuronal circuits of the cerebral cortex

In this paper, we are talking about the potential vulnerability of the visual, auditory and olfactory systems due to various - negatively - acting factors at the early developmental stages of the organism. There have shown that the maturation process of the CNS – and hence the sensory systems – requires not only energy resources, substrates, information molecules, etc., but is primarily dependent on the interaction of the intrinsic developmental processes. Marty (1962) was one of the first authors dealing with this issue in a methodically modern way. He showed significant changes in maturation of the functions of visual system in newborn cats. They had a perfect maternal care (food + nest + temperature, etc.), but they were raised for a long time in absolute darkness. Changes in the evoked potentials were characterized mainly by a significant prolongation of latencies and as the main finding the author states that these cats, even in adulthood, were not able to register rapidly repeating visual stimuli. Thus, sensory deprivation (absence of light) during a certain period of time – precisely at the early developmental stages of postnatal development – resulted in impaired visual perception.

In our arrangement (Mourek *et al.* 1967) we exposed newborn Wistar rats either to short-term (one-day) fasting and thirsting (between the 5th and 6th postnatal day) or to repeated ("chronic") fasting between days 5 to 10 for 7 hours per day (always under euthermic conditions). Then the rats were always returned to the mother in the nest (standard number of animals in the nest was eight). It was shown that these nutritional stresses significantly influenced the development of evoked potentials, both in the auditory and visual cortex (Fig. 1). Latencies had always been prolonged; the first positive wave appeared as the most sensitive component of the evoked potentials, the first negative wave was the most resistant. At the end – by analogy with Marty (1962) – these rats, nutritionally traumatized in the early developmental stages, were also unable to "register" stimuli of a rapid frequency (10 Hz) in both the visual and auditory cortex. Thus, a different negative intervention during maturation showed analogous consequences.

A very interesting and almost essential information was published in 1964 by Hrbek. He studied visual perception in premature newborns and then in a group of oligophrenic children. The results can be summarized as follows: first of all, there is a prolongation of latencies of the evoked potentials, that was more pronounced (greater) in the more immature newborns. He also noted some variability of evoked potentials, but again, the dominating feature was the failure of the ability to respond to a rapid sequence of stimuli. A similar finding is described Hrbek in oligophrenic children (13 to 14 year-old). For control measurements the optimal frequency was 12 Hz, for oligophrenics 8 Hz. Also more recent findings confirmed that children with developmental disorders do not only suffer from a visuospatial attention deficit but also have auditory attention deficits, as revealed by changes in cognitive evoked potentials (Holeckova *et al.* 2014)

Interpretation of these findings both in experiments (Marty 1962; Mourek *et al.* 1967) and neonatology (Hrbek 1964) was related to contemporary knowledge. Disorders of the process of myelination (delayed), possibly defective synaptogenesis. These findings are still valid today. The inability to repeat a rapid sequence of stimuli in the visual and auditory cortical areas can be explained only today. During the visual perception, the retinal photopigment rhodopsin must be recycled and recovered. After exposure to light, it decays (is split to opsin + all-trans retinal). Retinal is transported via the Müller cell to the base of the rod, where it is again fused with opsin and thus restores its capacity to respond to the light. Transport is co-provided by docosahexaenoic acid (DHA-22: 6n-3).

The finding of high concentration of PUFA-OMEGA-3 in the retina of the eye was described by Neuringer (Neuringer *et al.* 1988). A precise explanation of the biological significance of this acid in the eye has only followed (Gordon & Bazan 1990). We do not know details of auditory perception yet, but sufficient supply of PUFA-omega 3 always has beneficial effects (threshold of sensitivity, latency, effectivity of transduction). This positive effect on auditory perception has been shown in compromising conditions – such as reduced blood perfusion of the inner ear, insulin resistance-diabetes, oxidative stress, high levels of proinflammatory cytokines, early onset of arteriosclerotic changes, etc. (Martinez-Vega *et al.* 2015).

But what are the relations of the beneficial effects of PUFA-Omega-3 and the above findings in the vulnerability of visual or auditory perception at the early stages of postnatal development?

The supply of PUFA-Omega 3 during the maturation of the organism is one of the very important conditions not only for the maturation process itself, but also for the quality of postnatal life. The presence of DHA in the cortex of mammals (including humans!) reaches up

to 20% of all fatty acids present. We have shown that all risk conditions for a newborn (prematurity, hypotrophy, gestational diabetes) are accompanied by a significant deficiency of PUFA-Omega 3.

There is a direct correlation between the weight of a newborn and the content of PUFA-omega-3 in its organism (serum) (review Mourek *et al.* 2007, Mourek & Dohnalová 1996). In addition, any stress in young organisms leads to a significant decrease of PUFA-omega 3. Therefore, we believe that stressful situations (in the experiment), including prematurity and immaturity of newborns, are associated with a lack of these fatty acids. This deficiency then has its negative consequences. The lay public is unaware that hearing is our most sensitive system of perception. It is causally connected with the development of *homo sapiens sapiens*, especially with the development of communication skills, i.e. with the development of speech. Few people at the same time realize that even the development of writing is secondarily dependent on the ability to perceive and shape the sound. Scripture emerging from the pictograms - and thus visually dependent - was transferred to the ALFA-BETA system, which is dominated in the first place by both the formation of relevant sounds and their parallel perception.

Hearing and development of speech mechanisms

The importance of hearing for speech development has long been known. However, in the deaf-mute, speech loss was originally attributed to both hearing loss and impaired brain function. This also explained the accompanying "reasoning" disturbances of the deaf-mute (Hippocrates, Aristotle). Only the development in the state of knowledge during the Renaissance allowed the separation of cause and effect, and thus offered the opportunity to intervene into the process of speech development and to reduce the disability of these persons (in Apostolides 1997).

Even nowadays some works show lower IQ or slower development in deaf-mute children. However, it depends very much on the timely recognition of hearing impairment and on the quality of aftercare that the child receives (Chengyi *et al.* 2010). Already these observations show that beside the auditory information input, the development of speech is influenced by a number of other factors. The ability to communicate through speech has undoubtedly a genetic basis. Anatomical differences between the right and left hemispheres in the structures associated with speech (*planum temporale* – responsible for multimedial associations) arise prenatally. The left area is larger for most people (including left-handers). During the later development, side related structural differences arise both in the Broca center (motor speech center) and Wernicke center (sensory – primarily auditory speech center). Relatively smaller bilateral differences exist in the area of Heschl's gyrus (primary auditory cortex – distinction of sound elements of speech) and Gyrus angularis (visual entry into speech centers). Also in the Premotor area, that controls the motor component of speech and writing, side differences are described, but more often they are related to motor dominance (Devous *et al.* 2006). Studies on the hemispheric asymmetry confirmed the relationship between the asymmetry for verbal performance and for the general nonverbal intellectual abilities (Špajdel 2017).

It can be assumed, that certain types of auditory information (speech) are preferably processed at the speech centers of the dominant hemisphere and thus modulate their further development. Neuroplastic processes of the developing neuronal circuits (learning and memory) bring functional connection with other areas of the brain. That explains, for example, the different response of the infant to the mother's voice comparing other known voices. It results in the higher probability of repeating voice phenomena and thus it confirms the mother's primary role in the process of speech development. The activity of the neuroplastic mechanisms necessary for speech development decreases significantly at the age of 10–12 years. If the child from some reasons does not learn to communicate (by sign language, at least), the later ability of learning to speak is very low. Also, the development of other cognitive functions is usually impaired. An example can be the repeated observation of children growing up in isolation from humans or growing up in a society of animals who, after returning to human society, do not manage not only language communication, but also a large part of social interactions (Mowgli syndrome – "feral child") (Werker &Tees 2005).

Genes responsible for human speech also affect the communication sounds of other species (birds singing). The FOXP2 gene is popularly referred to as the Speech Gene, similarly to other genes CNTNAP2, CTBP1, SRPX2. However, these genes are not specifically "language genes", they are rather controlling general mechanisms of plasticity and are also related to memory development. However, it is interesting that the genetic disorder of the FOXP2 gene is manifested in humans as "apraxia of speech" (Ogar *et al.* 2005) and its exclusion in birds significantly worsens the imitation mechanism of singing learning. It seems that man has a certain genetic disposition to learn to speak, but it must be strengthened by auditory, social and other stimuli in early childhood. Noam Chomsky (Chomsky 1955) has already commented on this with his theory of Universal Grammar.

Auditory input is usually the first in speech development. Very soon other sensory inputs play a role, especially the visual one. Audiovisual speech association (lip-reading) is important not only in learning the mother tongue (while watching the mother), but also in learning other languages and also later on in cases of age-related hearing loss (presbycusis) (Jääskeläinen

2010). Similarly, the cortical motor control regions, not only the Brocca center, but also the adjacent orbitofrontal cortex are gradually involved. These regions of the cerebral cortex allow formation of structured (temporally and spatially) motor programs, i.e. organization of the sentence structure (grammar) of the expressed flow of ideas and associations. Such communication programs are then converted within the primary motor centers to the real motor output (spoken speech with its non-verbal components or written form). An important role can be played by "mirror neurons", i.e. the mechanisms of learning by imitation or by "common experience". These mechanisms, including the feedback of the children's own sounds (later also its own speech) as well as the feedback of other components of behaviour, allow to build an appropriate response to other people's speech, which is the basis of social interaction. Autism is thought to be a disorder (delayed development) of these mirror neurons (Dick *et al.* 2010).

The role of the dominant hemisphere for speech is, besides the genetic basis, largely due to individual development, the impact of the cultural environment and specific elements of learning and education (e.g. the kind of symbols used in written speech). An example may be interhemispheric cooperation in the processing of multisensory input information, allowing recognizing and forming elements of non-verbal communication (speech emotions, accompanying gestures). The historical evolution of human communication probably involves a phase where the information was more strongly modulated into the pitch of the voice. This way of information transmission is also used by some contemporary languages (Mandarin Chinese) (Cao *et al.* 2011). Similarly, in the development of speech in childhood, there is a phase where the child manages intonation communication (e.g. to express emotions), while verbal communication begins later. The ability to recognize the pitch, its color and rhythmic component is part of the semantic analysis of auditory communication. Intonation modulation is not only a syntactic component of speech, but also includes the emotional context of communication (Dehaene-Lambertz *et al.* 2010; Kraus & Chandrasekaran 2010).

Targeted development of this ability can be achieved by teaching music in childhood. Music education also develops the ability of selective attention, use of working memory and basic syntactic rules. It also helps develop the ability to differentiate the semantic component of speech from the noise. A parallel to the positive effect of multisensory stimulation on speech development is the sensory deprivation (Sakai 2005). Not only the aforementioned hearing loss, but also some visual disturbances and especially social deprivation, often associated with nutritional disorders, cause serious developmental problems (Mourek *et al.* 2010), including difficulties at the level of speech fluency, the grammatical structure and meaning of sentences (Prado & Dewey 2014). For example, prenatal drug exposure may have even more severe consequences (Cone-Wesson 2005).

On relations between olfactory and cognitive abilities

Most research in the field of cognitive psychology is focused on investigation the contribution of visual and auditory perception on the development of cognitive abilities. Smell is often considered to be a "neglected" sense, because in medical practice it is relatively rarely investigated and patients themselves are often unaware of their olfactory problems, and not at all the importance of impairment of this sense. Despite the fact that humans belong to the microsmatics, smell significantly affects the quality of their life. Smell can alert us to danger like gas leak or rotten food, protects us against inhalation of some toxic gases and influences digestive processes. Whereas the olfactory system is the main source of afferentation for the limbic system, it is also involved in regulation of emotion and sexual behavior.

Recently, smell has been arousing a great deal of interest in the field of neuroscience, mainly due to the findings that dysfunction of this sense may be a strong predictor of many serious diseases. Changes in olfactory perception have been observed in various neurodegenerative diseases (Doty 2012) and smell examination is considered to be particularly important in Parkinson's and Alzheimer's disease, where olfactory decline precedes other clinical symptoms for several years. In patients with neurodegenerative diseases, there is a spectrum of smell dysfunction, therefore olfactory testing may be useful in differential diagnosis as well. Olfactory dysfunction has also been shown in some neuropsychiatric disorders such as depression, schizophrenia or epilepsy. Specific changes in olfactory function were found especially in disorders involving the dopaminergic pathway (e.g., ADHD, autism, and schizophrenia) (Schecklmann *et al.* 2013).

The olfactory system, believed to be the phylogenetically oldest part of the neocortex, is unique among the central nervous system (CNS), what is mainly related to its complex neuroanatomical properties (Price 1987). It is the only sensory system of the CNS lacking projections to the thalamus, that is common to all other sensory pathways. Sensory receptors synapse directly into the olfactory bulb, which incorporates its own thalamic equivalent (Kay & Sherman 2006).

The olfactory activity is composed of two independent processes, where the first is based on the capability to perceive odor (can you smell it?), while the second is involved in the ability to identify odor (what is it?). Odor detection principally represents sensory processes, whereas odor identification reflects both sensory and cognitive processes (Wijk & Cain 1994). Odor identification indicates the point at which the process of sensory functioning and the process of

cognitive abilities intersect. For olfactory identification and discrimination, the complex association of the olfactory pathway with other brain regions such as the amygdala, hypothalamus, hippocampus, inferior frontal, lateral and medial temporal areas and indirectly the thalamus is necessary (Kareken *et al.* 2003). These connections allow the olfactory perceptions to influence cognitive, visceral and emotional behavior.

Morphological differentiation of the olfactory system takes place during early embryonic development. Axons of olfactory receptor neurons reach the olfactory bulb by the end of the first trimester and formation of mitral cell synapse has been found by the 17th week of gestation (Turetsky *et al.* 2009). Regarding its early development, the olfactory system is in utero vulnerable to disruption by physical and chemical teratogens (Farbman 1991). Abnormal development of the olfactory system, which may include abnormalities of the nasal cavity; disruptions in the olfactory pathways; or malformations of cortical olfactory areas, may result in a lifelong inability to smell – in congenital anosmia (Karstensen & Tommerup 2012). Congenital anosmia may occur as an isolated abnormality (no additional symptoms) or can be connected with a specific genetic disorder, such as Kallmann syndrome (the combination of anosmia with hypothalamic hypogonadism). Kallmann syndrome may be associated with moderate-to-severe intellectual disability and there is one case report on a patient with Kallmann syndrome and paranoid schizophrenia, who underwent extensive genetic analyses (Verhoeven *et al.* 2013). However, it has not yet been clearly demonstrated whether congenital anosmia or Kallmann syndrome could increase the risk for psychiatric disorders.

The sense of smell has long been thought to be almost nonfunctional in newborns and young infants and thus almost useless in their everyday lives. Despite relative prenatal maturity of chemoreceptive structures of the nose, their functionality in the fetus was not expected for a long time, because of obstructed nostrils, nasal pathways filled with stagnant fluid, or absence of effective airborne stimuli. At present, it is known that the human sense of smell develops in utero, the fetal olfactory system is already functional, odors are delivered to the fetus within the amniotic fluid (Schaal *et al.* 2000, 2004). Evidence for nasal chemoreception in the human fetus was obtained by tracing of the main olfactory tract with the olfactory marker protein – OMP (Chuah & Zheng 1987), which is uniquely associated with mature olfactory receptor neurons (Margolis 1980). Demonstration of immunohistochemical reaction for OMP in the olfactory receptor cells at later gestational stages suggests that fetal olfaction should be effective from around 29 weeks post-conception (Chuah & Zheng 1987), although trigeminal chemoreception may already be functional at an earlier time. The odor of amniotic fluid and various flavor compounds (e.g. anise, garlic or alcohol) transferred into the amniotic compartment from the mother's diet, induce later appetitive responses in the term-born infant (Schaal *et al.* 2000). The prenatally acquired odor memory can be manifested immediately after birth (0.5–8 hours) or later (from 1–4 days to 5–6 months). Other facts showing olfaction to be functioning in fetus come from observations in preterm infants. These observations revealed that preterm neonates regularly respond to olfactory stimuli after the 28th week of gestation (Sarnat 1978). The aim of olfactory perception in the fetus is not quite clear, but it probably conditions the fetal brain to sensory discrimination not only for olfaction but also for other sensory stimuli in the postnatal period (Sarnat *et al.* 2017).

Newborns are able to discriminate the intensity and quality of wide variety of odorants (even so-called non-human odors, such as acetic acid, phenylethyl alcohol or anise oil (Engen *et al.* 1963) and odors produce behavioral responses in them. Olfactory abilities are constantly developing between the age of 3 and 12 years (Monnery-Patris *et al.* 2009), particularly the identification and discrimination of odors. In general, the more stimulating and diverse the environment, the higher the olfactory ability of children (Nováková *et al.* 2018).

The ability of olfactory identification increases further during adolescence and the range of identifiable odorants expands, both due to increasing verbal abilities to name them and due to gaining new experiences (Hudson 1999). Adolescence is the period of development, when individuals are subjected to numerous socio-biological changes and this life stage directly precedes the peak of human olfactory ability. During this period of life, there are significant biological changes in the human body including odor emission and perception as well as changes in psychosocial functioning. For these reasons, adolescence appears to be an important period of olfactory development, when various environmental factors can significantly affect olfactory abilities (Oleszkievicz *et al.* 2016). Most studies point out that olfactory identification ability develops until the second decade of life, when it reaches the highest level (Sorokowska *et al.* 2015).

Research also focuses on determination the contribution of genetic and environmental influences of olfactory perception. The results of quantitative genetic analysis in twins indicate moderate heritability for odor identification and perceived intensity, however, genetic influence on odor detection and perceived pleasantness of odors was not confirmed (Finkel *et al.* 2001). Analyses further revealed that the relationship between odor identification and verbal abilities is primarily genetically mediated. This suggests that odor identification and verbal ability in general concern the same cognitive domain.

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