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NEUROPSYCHOLOGICAL TESTING OF AD/HD SUBTYPES AS AN INDICATOR FOR NEUROMETRICS AND THERAPY: CURRENT STATE AND FURTHER CONSIDERATIONS

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SUMMARY

Background: The research presented in this chapter reflects some current trends in neuropsychological research on AD/HD children, with the goal of exploring the structure of the mental deficits that shape the clinical picture. The purpose of this research was to ascertain the specific nature of the disturbances of mental function in various subtypes of AD/HD, and on that basis to reach some conclusions regarding the differentiation of the neuronal basis.

Material/ Methods: We examined 132 children, 9 to 12 years of age, divided into two groups. The first group, which included children with the combined subtype of AD/HD, consisted of 64 children, 59 boys and 5 girls; the second group, with the inattentive sub-type, consisted of 21 children, 17 boys and 4 girls. There was also a control group, made up of 47 children (40 boys and 7 girls) without AD/HD symptoms. For our research we used the neuropsychological instruments most often applied in AD/HD, so that the results could be compared and discussed.

Results: We found different dimensions of functioning which can be used to characterize children with combined-type AD/HD, i.e. with manifest symptoms of inattentive, impulsive, and hyperactive behavior. Deficits in the inhibition of a motor response after a stop signal, when the response has already been evoked by a stimulus; deficits in the inhibition of a response to a stimulus that should not evoke any reaction (over-reactions); reduced readiness (preparation) for motor response; deficits in maintaining attention; in inhibiting a cognitive response; reduced concentration, deficits in divided attention and working memory; deficits in planning and monitoring motor performance. This list of characteristics suggests that children with combined-type AD/HD show differentiated deficits in behavior control.

Conclusions: Fuller cooperation is necessary between neuropsychologists and psychophysiologists, which will help the latter in understanding the problems of a person with AD/HD, and help the former evaluate the results of new programs of neurotherapy.

Key words: neurodiagnosis, psychometrics, neurometrics, quantitative EEG, ERPs

INTRODUCTION

Attention Deficit Hyperactivity Disorder (AD/HD) is a common neurobehavioral disturbance in the course of development. If ICD-10 criteria are applied, AD/HD occurs in from 1 to 3% of the population (Remschmidt, 2005), or from 4 to 8% if the more liberal DSM-4 criteria are applied (Pennington et al., 2009). In spite of the high frequency of occurrence and the fact that AD/HD has been diagnosed by professionals for decades, the accuracy of diagnosis is a subject of considerable debate and discussion (Faraone, 2005). Some of the criticism begins with the very fact that AD/HD is listed as a functional disorder, whereas some critics believe that it is merely a very extreme expression of normal behavior, caused by the natural energy of the child, a boring environment, or the excessively stressful influence of parents and teachers (Baughman, 2001, cited by Faraone, 2005). Children with a particular temperament, called "difficult," are likewise often classified as AD/HD (Lipowska, 2003; Wolanczyk et al. 1999). On the other hand, even if AD/HD is perceived as a pathology, some argue that its source is to be found in the negative influence of the social environment, which in turn underlies the criticism of pharmacological therapy, as an inappropriate response given the mechanisms that give rise to the symptoms.

These and other doubts and hesitations are prompting scientists to look for irrefutable evidence that would support:

- the very existence of this syndrome as a distinct and specific nosological entity;
- the existence of etiological factors and mechanisms operating on the biological level that would account for the clinical symptoms.

The formal diagnosis of AD/HD is primarily symptomatic, which is to say that the child is diagnosed on the basis of how parents and teachers evaluate the child's behavior, along with the diagnosing clinician's own observations of the child's behavior. The diagnosis is based on the appearance of a certain number of diagnostic criteria listed in the DSM-4-TR (APA, 2000) in the child's behavior. These symptoms have been divided (some would say: arbitrarily) into three groups:

- inattention;
- hyperactivity;
- impulsiveness.

The alleged arbitrariness of this classification results from the fact that these three categories have not been proven to be associated with any neuropsychological or neurobiological pathomechanisms. This results from the fact that there still exists no objective method of psychological or biological evaluation that would give us a profile of results pointing unambiguously to AD/HD, and serving also as differential criteria. Much of the biological and neuropsychological research currently being conducted on AD/HD reflects a common effort to distinguish an endophenotype, i.e. specific, pathognomonic characteristics of AD/HD that would be based on an analysis of neuropsychological symptoms (identifiable

deficits of mental functions) and their neurological correlates, rather than relying solely on behavioral symptoms.

The group of children now diagnosed clinically on the basis of behavioral symptoms is heterogenous. The symptomatic diagnosis of AD/HD according to DSM-IV-TR distinguishes two subtypes, depending on the dominant symptoms of inattentive or hyperactive-impulsive behavior. Thus on the level of behavioral analysis we are already confronted with the fact that the children diagnosed with this syndrome do not constitute an homogenous group (Borkowska, 2008a).

Tests performed using psychophysiological instruments, such as EEG or ERP (event-related potentials), have also demonstrated that the AD/HD population is diverse. Specific profiles of brain wave activity can used to classify children with AD/HD into groups. Barry et al. (2001) achieved some very interesting results, which are exemplary for this approach. They looked for EEG clusters in 186 boys with combined (inattentive and hyperactive-impulsive) AD/HD, and found three:

1) increased slow wave and reduced fast wave activity;
2) increased high-amplitude theta waves with reduced beta activity;
3) expansion of the group of beta waves.

These research results suggest that even the group with combined-type AD/HD is not homogeneous in terms of psychophysiological parameters. This is an essential fact, which must be kept in mind whenever attempts are made to use EEG, ERP, or other psychophysiological methods for the differential diagnosis of AD/HD compared to healthy controls (Borkowska & Tomaszewski 2008; Clark et al. 2003; Kropotov et al. 2005; Kropotov, 2009; Kropotov & Mueller, 2009; Barry et al., 2009). The lack of homogeneity of results in psychophysiological procedures probably reflects the differentiation of the underlying neuronal causes of AD/HD.

A more complete picture of the dysfunctions of brain activity associated with AD/HD symptoms could make it possible to develop more precise and specific neuropsychological diagnostics for disturbances of cognitive, emotional, and behavioral processes, as well as more effective therapy for these disturbances, which on the principle of feedback will support the reduction of the symptoms occurring in AD/HD (Kropotov, 2009; Kropotov & Mueller, 2009; Pachalska et al. 2012a; 2012b; 2014).

AD/HD, like any other developmental disorder, can be described on three levels:

- *on the behavioral level*, as a syndrome constituting a certain constellation of difficulties in the cognitive, emotional, and social spheres, including the diagnostic criteria considered pathognomonic for AD/HD, as well as other, secondary and concomitant disturbances;
- *on the level of neuropsychological mechanisms,* i.e. deficits in mental functions: attention, inhibition of impulses, and other associated executive functions;
- *on the neurobiological level*¸ which involves brain systems, whose disordered work causes distinct categories of neuropsychological deficits.

On each of these levels there is an interaction between intra-psychic factors and the environment. Thus it is difficult to expect that there would be a simple cause-and-effect relationship among the biological factors, the deficits in mental processes, and the observed behaviors; however, the search for the complex relations among all these factors is the primary aim of most neuropsychological research (Barry et al., 2009). It is difficult to produce a fully justified division into subtypes either phenomenologically, on the basis of observed symptoms, or solely on the basis of psychophysiological tests (Kropotov, 2009). Nor can it be done entirely on the basis of neuropsychological testing (Pachalska, 2008).

There is an urgent need, then, to integrate neuropsychological and neurophysiological research, and to take full advantage of accurate neurometric and psychometric data bases, where an important role is played by case studies (Kropotov & Pachalska, 2010).

Neuropsychological diagnosis of AD/HD subtypes

The pathomechanisms of AD/HD seem to lie in the general area of disturbances in the course of attention-related processes, and in functions that could be the source of impulsive and hyperactive behaviors, i.e. in deficits of inhibition and executive functions (Kropotov, 2009). A precise recognizance of the organization of behavior in AD/HD children would make possible a more effective diagnosis, as well as an understanding of the brain mechanisms involved in the realization of behaviors typical for AD/HD. The pursuit of this knowledge requires an interdisciplinary approach. Our research fits within the latest trends of neuropsychological research, integrating psychological, psychophysiologial, neurological, and psychiatric perspectives on the problems of children with AD/HD.

The differential neuropsychological diagnosis of a child with functional disturbances is intended to develop a systematic picture of the disturbed and undisturbed functions, and to reach conclusions based on the type of brain dysfunction that is the cause of interference in the normal development of the child (Herzyk, 2000). In the case of children with AD/HD, it is extraordinarily important to specify the brain mechanisms associated with the behavioral disturbances; however, as Kropotov (2009) quite correctly remarks, in the case of the mature brain there exist models that more or less adequately explain the brain-behavior relationship, while in the case of a developing brain, the formulation of this type of correlation meets many obstacles. Kropotov also argues that the child's brain is an organ in the process of growing, i.e. maturing and shaping its functions, as an effect of the interaction of biological and environmental variables (cf. also Brown, 2001, 2002).

There is still a great deal of debate about the basic characteristics of the developing brain, such as plasticity, which is the foundation for the possibility of compensation for deficits, and the range and level of functional specialization of particular brain regions. Knowledge derived from developmental psychology has demonstrated that there is considerable individual differentiation in the tempo and rhythm of the child's psychomotor development, which reflects differences in the pace of development of the brain as a whole, and of specific parts of the brain.

In developmental neuropsychology, specialized neuropsychological tests and experimental techniques are used, sensitive to the state of the child's brain. The detailed analysis of the results of these tests gives a basis for reaching conclusions regarding brain functions in normal and pathological conditions. It also allows us to describe the disorganization of the brain mechanism underlying the observed difficulties (Kaczmarek, 1987). Clinical and behavioral symptoms, i.e. the results obtained by performing particular tests, are correlated with the state of the brain, measured primarily by structural or functional neuroimaging. In this way we can not only show the location of the damage and the disorders of function, but also describe the brain mechanism that has been disturbed, and interpret how the brain compensates for the pathology that has arisen. However, new research on AD/HD children is being conducted around the world, and the results may well make it possible to draw more unambiguous conclusions regarding the essence of their functional difficulties (Barry and Clark 2009; Kropotov 2009).

The research presented in this chapter reflects some current trends in neuropsychological research on AD/HD children, with the goal of exploring the structure of the mental deficits that shape the clinical picture. The purpose of this research was to ascertain the specific nature of the disturbances of mental function in various subtypes of AD/HD, and on that basis to reach some conclusions regarding the differentiation of the neuronal basis.

MATERIAL AND METHODS

We examined 132 children, 9 to 12 years of age, divided into two groups. The first group, which included children with the combined subtype of AD/HD, consisted of 64 children, 59 boys and 5 girls; the second group, with the inattentive sub-type, consisted of 21 children, 17 boys and 4 girls. There was also a control group, made up of 47 children (40 boys and 7 girls) without AD/HD symptoms.

For our research we used the neuropsychological instruments most often applied in AD/HD (Frazier et al., 2004), so that the results could be compared and discussed. These included the following:

- the Change Task, which requires the child to change her response when a signal is sounded (computerized);
- simultaneous addition;
- successive subtraction of 3, beginning from 100, without an external auditory distraction;
- successive subtraction of 3, beginning from 100, with an external auditory distraction;
- a Stroop-based task to measure susceptibility to distraction;
- the Stop Signal Task, which requires the child to stop an activity when a signal is heard (computerized);
- The Kagan Matching Familiar Figures Test (MFF, cf. Matczak, 1992);
- the "Labyrinth" subtest from the Wechsler Intelligence Scale for Children;

- the Trail Making Test (TMT), A and B;
- the Continuous Performance Test (CPT), a visual, computer-based test.

As can be observed, this list of methods includes both standardized tests (e.g. the MFF), elements of larger neuropsychological and clinical batteries (the TMT, the Labyrinth subtest), and experimental and clinical methods, typical for neuropsychological evaluation, developed for testing based on the principles of Lezak (1983) and Sergeant et al. (1999).

The methods we used made it possible to evaluate the following dimensions of the functioning of these AD/HD children:

- inhibiting motor response in a situation when there is a stimulus that should not prompt any reaction;
- inhibiting motor responses in a situation when the stimulus is signalizing a need to react, but another simultaneous signal should inhibit the reaction;
- inhibiting a pre-learned motor response and replacing it with another, when a particular signal is received;
- inhibiting automatic responses and initiating intentional reactions in their place (control of interference);
- inhibiting cognitive reactions, resulting in a tendency to an impulsive, rather than reflective cognitive style;
- planning motor activities and inhibiting motor reactions that are inconsistent with visuo-spatial information;
- divided attention;
- resistance to the operation of external distracters (selectivity of attention);
- maintaining attention;
- shifting attention;
- working memory.

These selected dimensions of the functioning of AD/HD children are not isolated and separate functions. They often act in mutual interaction or are mutually dependent (Nebel et al., 2005). For example, from the perspective of experimental neuropsychology, the clinically accepted methods involve different components of attention and test them in the context of other, often complex cognitive functions (Domanska, 2004). In the literature one can find highly diverse interpretations of the processes involved in performing the tasks of a particular method. Especially if one assumes that a given method is testing primarily the ability to inhibit a response (i.e. the experimental task constructed on the basis of the Stroop test), the ability to concentrate is always an essential element of performance.

Many mental process are engaged in performing neuropsychological tests, due to the complex structure of the tasks. The results obtained by persons tested in particular tasks thus make it possible to reach conclusions about not one, but several of the dimensions of behavior.

RESULTS

Children with combined-type AD/HD

The following problems in different dimensions of functioning can be used to characterize children with combined-type AD/HD, i.e. with manifest symptoms of inattentive, impulsive, and hyperactive behavior:

- deficits in the inhibition of a motor response after a stop signal, when the response has already been evoked by a stimulus;
- deficits in the inhibition of a response to a stimulus that should not evoke any reaction (over-reactions);
- reduced readiness (preparation) for motor response;
- deficits in maintaining attention;
- deficits in inhibiting a cognitive response;
- reduced capacity to inhibit automatic responses, and difficulties with initiating an intentional response (disturbance of inhibition of interference);
- reduced concentration on the task;
- deficits in divided attention and working memory;
- susceptibility to the effect of external distracters;
- deficits in shifting attention and visual search;
- deficits in planning and monitoring motor performance.

This list of characteristics suggests that children with combined-type AD/HD show differentiated deficits in behavior control.

In order to make some inferences in regards to the neurological correlates, i.e. the neuronal regions and systems that are dysfunctional in these children, we should refer to the results of research indicating the involvement of specific areas in the process of behavior control. The most general assumption is that the prefrontal cortex in the right hemisphere of the brain, along with its connections to subcortical and posterior brain regions, is the crucial structure for inhibiting responses, and participates actively in the regulation of behavior (Lee et al., 2001; Fuster, 2000; Aron et al. 2004; Aron & Poldrack, 2005). Particular emphasis is given to the importance of the cortical-subcortical circuits that connect the dorsolateral cortex, the orbital cortex, the medial frontal lobes, and the anterior cingulate gyrus. Discussions have arisen among researchers as to the varying importance of the various parts of the prefrontal regions. Most authors have stated that inhibitory processes are fundamentally associated with the activity of the ventrolateral (inferior) frontal regions (Aron & Poldrack, 2005; Lee et al., 2001), but others, such as Casey et al. (1997), state that activation during the realization of inhibitory functions is dispersed between the dorsolateral and orbital parts of the prefrontal cortex.

Various inhibitory tasks activate various areas and neuronal systems. Accordingly, the results we obtained with these combined-type AD/HD children will be discussed in reference to particular types of inhibition.

1. It has been shown that the process of inhibiting responses in stop signal tasks specifically activates the ventrolateral (inferior) frontal cortex (Brodmann areas 15 and 16/21) on the right side. The great importance of this region for stopping a motor response has been confirmed by the results of neuropsychological research on patients with focal damage to the inferior frontal cortex in the right hemisphere (Aron et al, 2004). Thus, in children with combined-type AD/HD, who have confirmed deficits in inhibiting motor responses when a stop signal intercedes after prior arousal by a stimulus, it can be concluded that there are abnormalities in the activity of the inferior prefrontal cortex on the right side.

This conclusion is confirmed by the results of neuroimaging in AD/HD children, who, while making more errors in inhibition tasks, showed less activation in the inferior frontal gyrus in the right hemisphere. Since the morphometric data suggest that the dimensions of these structures are smaller in AD/HD children, one can speak of an association between deficits of inhibiting motor responses in AD/HD with functional and structural changes in the lower right frontal region (Bunge, 2002).

2. The second type of task that requires inhibition of motor response is a change of response caused by a signal. The inhibitory processes that condition a change of motor response also activate the right frontal cortex: the dorsolateral region and the inferior frontal cortex, and sometimes also the left inferior frontal cortex (Lee et al., 2001). In this case also, however, a particular role is assigned to the right hemisphere. The processing costs of changing the response, in the form of protracted reaction time in patients with right-hemisphere damage, have been correlated with the size of the lesion. Thus the difficulties experienced by AD/HD children with inhibiting a motor reaction and changing the response upon a signal may also be associated with a dysfunction of the inferior prefrontal cortex in the right hemisphere, but also in the left hemisphere and the dorsolateral region. There are also indications of bilateral activation of the regions of the frontal axes (Brodmann area 10) in maintaining in memory the first goal of action, while secondary goals are being processed simultaneously, e.g. in a task where it is necessary first to make a decision as to whether something is the same or different (the first-order goal), and then to say the opposite (secondary goal). In realizing secondary goals, the dorsolateral cortex is active (BA 9/46 on the right side, and BA 9 on the left) (executive anticipation and cognitive control). In the case of the task of changing the response after a signal, inhibiting the previously learned response to the stimulus activates the frontal axes, while the performance of an altered reaction to the signal is conditioned by the activity of the dorsolateral prefrontal cortex (Lee et al., 2001). In the case of the difficulties experienced by our children with combined-type AD/HD in the realization of the task of changing the motor response to a signal, there are clearly problems in the functioning of the frontal axes bilaterally and the dorsolateral prefrontal cortex.

3. Cognitive inhibition activates the areas of the dorsolateral cortex. The presence of deficits in inhibiting cognitive responses in the children we tested suggests altered activity in these regions.

4. The inhibition of interference requires the activity of the inferior prefrontal cortex in the left hemisphere, though it has also been suggested that the right hemisphere has a certain role to play (Aron et al, 2004; Aron & Poldrack, 2005). Patients with lesions in the left inferior and central frontal gyrus showed increased interference of premature responses. This type of dysfunction can cause difficulties in inhibition, in the from of overreactions, i.e. performing motor activity inappropriate to the stimulus. These types of reactions were seen in our group of children with combined-type AD/HD, which suggests disturbance of the functions of the inferior and central prefrontal gyrus in the left hemisphere.

5. Monitoring and cognitive control of actions being performed (known as cognitive executive control) involves the participation of the anterior cingulate gyrus. MacDonald et al. (2000) have stated that cognitive control is a dynamic process represented in the brain by neuronal networks involving: 1) the dorsolateral prefrontal cortex, controlling the “top-down” pathway of behavior according to the requirements of the task, and 2) the anterior cingulate gyrus , which is engaged in value-related processes, indicating when the control process should be more engaged. Bilateral activation of the anterior cingulate gyrus is probably associated with performance, but also monitoring of conflict by “discovering” competitive responses (as for example in the Stroop test). In view of the fact that activation also occurs when the responses are correct, it seems that the cingulate gyrus recognizes the conditions in which errors may occur, and not the errors themselves. The posterior cingulate gyrus in the left hemisphere is associated with inhibiting previously learned rules and with monitoring accidental errors, which is essential in inhibiting habitual responses. It would seem, then, that the difficulties experienced by children with combined-type AD/HD in the performance of tasks requiring the inhibition of automated responses and the initiation of intentional responses may result from changes in the activity of both the anterior and posterior parts of the cingulate gyrus.

From these data it can be inferred that different regions of the prefrontal cortex participate in the realization of different elements of the inhibitory function, but they also cooperate with each other, integrating the various constituent elements of this process. The prefrontal cortex in the left hemisphere is involved in maintaining the goals of action, the cingulate gyrus in detecting conflicts, e.g. when the stimulus does not fit with the intended goal, while the inferior prefrontal cortex in the right hemisphere is engaged in inhibiting an improper motor response. Depending on the context, the inferior prefrontal cortex restrains reactions by a subcortical pathway, e.g. the hypothalamic nuclei or the brainstem, and can act directly on the motor cortex, or inhibit memories, for example, by connections with temporal regions.

Our analysis of the results we obtained in testing attention processes showed that:

1. Concentration of attention engages a broad expanse of brain regions, primarily in the right hemisphere. These neuronal networks include dorsolateral and ventrolateral frontal structures, superior and inferior parietal regions, and

the anterior cingulate gyrus. Neuroimaging shows that when attention is divided, which entails higher cognitive demands, there is increased activation in these areas, which is also manifest in homologous areas of the left hemisphere (Nebel et al., 2005). When the task of concentrating attention becomes more difficult, e.g. increased differentiation of visual stimuli without including another task (i.e. without divided attention), there is increased activation in the visual cortex (the right cuneus, the left inferior occipital gyrus, the left and right central occipital gyri, and the right superior occipital gyrus), but not in prefrontal or parietal structures. Thus concentration and divided attention are largely dependent on the functioning of the same neural structures. The differing proportions of involvement of the prefrontal and parietal cortex especially result from the level of involvement of attention, the difficulty of the task, and the necessity to engage cognitive control.

Reduced concentration on the task and difficulties with dividing attention were characteristic for our children with combined-type AD/HD, which points to disturbances in the functioning of dorsolateral and ventrolateral prefrontal structures, and the superior and inferior parietal regions.

2. The brain structures involved in orienting attention towards a stimulus include the precentral gyrus in the frontal lobe and the posterior superior parietal cortex, primarily in the right hemisphere (Corbetta, 1998). There is also frontal activation in the visuomotor region. Stronger activation of the superior lateral surface of the frontal lobes has been observed contralaterally to the localization of the stimulus (Nobre, 2001). Moderate activity has been observed in the cingulate region and the supplementary motor cortex, regardless of the localization of the stimulus. Subcortical activation is manifest in the pulvinar thalamic nucleus in the left hemisphere (Nobre, 2001). Data from animal research indicates that there are common neural structures engaged in explicit and implicit orientation, including the parietal cortex, the frontal visuomotor fields, and several subcortical structures, such as the superior colliculi and the thalamus.

The superior colliculi are associated with the act of switching attention, while the thalamus is thought to be part of the route by which the parietal and frontal regions make contact with the ventral pathway of object identification. The pulvinar is involved with concentrating attention on an object. Neuroimaging research has shown that if attention is directed by motor actions, fronto-parietal structures in the left hemisphere are engaged. The parietal activity takes in the lower parietal lobule and the intraparietal sulcus (Nobre, 2001).

Our children with combined-type AD/HD did not display any difficulties in orienting or directing attention, or in shifting attention to another stimulus.

3. Maintaining a state of alertness is conditioned by the effective course of many cognitive functions. This is accomplished with the essential participation of the fronto-parietal regions in the right hemisphere, both in the presence of a stimulus and in the situation of waiting for it to appear (Pardo et al., 1991). The activation is lateralized to the right, regardless of the modality of the stimulus (auditory or visual) or the laterality of the anticipated reaction (Belin et al., 1998).

In the continuous performance tasks that evaluate this aspect of attention, the increase in errors over time is greater in the case of patients with right-hemisphere damage than in those with left-hemisphere damage. The former are not only generally less alert, but their alertness deteriorates over time (Rueckert & Grafman, 1996). Alertness can be aroused by both conscious intention (voluntary maintenance of attention) and external stimuli. The frontal lobes are probably the generator of internal signals of alertness, whereas the effect of alertness to exterior stimuli is achieved with the help of the thalamus (Fernandez-Duque & Posner, 2001).

Both of these two effects, the volitional warning effect (endogenous, accompanied by a particular effort) and the automatic effect (exogenous, without effort), are also dependent on the functioning of the right parietal lobe. Damage to this part of the brain brings about a reduction in alertness and a deterioration of orientation functions, which means that these patients present with symptoms, not only of a deficit in maintaining a state of alertness, but also in shifting attention.

Our children with combined-type AD/HD displayed deficits in maintaining attention, which can be interpreted to indicate abnormalities in the fronto-parietal cortex in the right hemisphere.

4. Many of the tasks that evaluate concentration also involve working (or "operating") memory. In the course of describing attention processes, then, it is necessary to discuss this cognitive function also. Research data indicates that various neuronal circuits mediate the realization of verbal, spatial, and object working memory. Spatial working memory involves the right hemisphere, while verbal and object working memory engages the left hemisphere. The difference in lateralization is more quantitative than qualitative. What is specific for spatial working memory only is the activation of occipital regions and the inferior frontal region. It is only in the case of object working memory that the temporal lobe is involved, and in the case of verbal memory, Broca's area.

In verbal memory (regardless of modality, visual or auditory) there are separate components responsible for storing and rehearsing material. The posterior parietal cortex (primarily in the left hemisphere) is responsible for storage, while frontal structures (primarily Broca's area, the premotor area, and the supplementary motor area) are responsible for rehearsal. In spatial memory there are similar distinctions: storage engages the posterior parietal region in the left hemisphere, while rehearsal involves the premotor area, mainly in the right hemisphere, but also in the left (Baddeley, 2003; Smith & Jonides, 1997; Gruber & Cramon, 2001; Martinessen & Tannock, 2006).

The process of manipulating the contents of working memory is mediated by the dorsolateral prefrontal cortex, especially when the material is temporally coded, and not merely stored.

In our own research, the tests we used measured verbal working memory, and in the children with combined-type AD/HD we found poorer performance than in the healthy controls. The inference from this would be that the posterior parietal cortex in the left hemisphere and the dorsolateral prefrontal cortex are working less effectively.

Various and diverse executive processes, such as monitoring the contents of working memory, changing the mental processes being performed that make demands on working memory, applying complex rules that must be actively maintained in working memory, planning a series of movements in a problem-solving task – all of these activate the dorsolateral prefrontal cortex. There is probably some functional diversity within this area, but contemporary neuroimaging methods (even fMRI) are not able to detect these differences. Another interpretation would be to assume that all these activities have a common component, which is a metacognitive process that monitors task performance through working memory, or a process that maintains the structure of the goal.

Children with inattentive-type AD/HD

Our group of children with inattentive-type AD/HD were characterized by the following:

- normal inhibition of motor reaction in response to a stop signal when the response has already been aroused by a stimulus;
- normal inhibition of cognitive responses;
- selective difficulties in inhibiting automated responses in favor of intentional responses (interference control), manifested in abnormal performance but without protracting the time needed to perform the task;
- deficits in inhibiting responses to stimuli that should not evoke a response;
- deficits in maintaining attention;
- deficits in divided attention, working memory, and concentration on a cognitively difficult task;
- high susceptibility to external distracters;
- deficits in shifting (selecting) attention;
- deficits in planning and controlling (inhibiting) a motor response according to the spatial requirements.

The group of inattentive children differed from the children with combined-type AD/HD primarily in respect to the task of inhibiting a response in reaction to a stop signal. The inattentive children were much better in performing this task than were the children with combined-type AD/HD. This suggests proper functioning of the right ventrolateral (inferior) prefrontal cortex in the inattentive children, which is much in contrast to the combined-type children. The inattentive children also had no problems with cognitive inhibition, so that it would seem that the dorsolateral prefrontal areas involved in this function are working normally. The fact that the inattentive children had less difficulties than the combined-type children in performing tasks that require interference control, restraining automated reactions and replacing them with intentional reactions, may result from less dysfunction of both the anterior and posterior cingulate gyrus.

Reduced effectiveness in the remaining processes appears to be characteristic of both subtypes of AD/HD.

Comparison of neuropsychological results in the inattentive and combined subtypes of AD/HD

In all parameters of deficits in inhibiting responses, disturbances of attention, and other executive functions (planning activity and working memory), the group of children with combined-type AD/HD obtained worse results than the healthy controls, which points to differentiated and diverse deficits of mental functions.

Among the inattentive children, some of the types of response inhibition we used in the testing turned out to differentiate this group from the healthy controls, while others did not; thus this deficit occurs in a limited range. A similar conclusion can be reached in relation to interference control. The children with inattentive-type AD/HD did not need more time to perform an interference task, but they made more mistakes.

We did not observe dominant disturbances of attention among the inattentive children, as might have been expected based on the reported symptoms. To be sure, we did see disturbances of these processes somewhat more often than disturbances of inhibition, but the differences are not very distinct. When we take into account the severity and quality of inhibition disturbances, the inattentive children were significantly different from the combined-type children.

Many indications of deficit in inhibition were found in the children with combined-type AD/HD, whereas in the inattentive children there were no such indications. This pertains not only to motor and cognitive responses, but also to inhibition of automatic responses in favor of intentional reactions associated with the task. However, when we assessed attention processes, we found no differences between the two clinical groups, which would indicate that an attention deficit is common to all children with AD/HD. This does not mean, however, that the structure of the problems in attention processes among children with combined-type and inattentive-type AD/HD was just the same. To be sure, for both groups the most typical problems involved difficulties with concentrating on a task, working memory, and maintaining attention over a longer period of time, but problems with maintaining conscious effort in dealing with a cognitive task and susceptibility to external distracters occurred more often in the inattentive children. This differentiation of deficits, as well as the infrequency of their co-occurrence, may result from a differentiation of the neuronal basis for various aspects of the attention processes (Fernandez-Duque & Posner, 2001; Sterr, 2004; Mirsky, 1989), and from the fact that some subsystems are functioning properly, while others are not.

In characterizing the neuropsychological deficits in the group of children with combined-type AD/HD, we found both difficulties in inhibiting responses and attention deficits. It turned out, however, that depending on the type of situation that required the child to restrain a reaction and the type of response, the severity of particular problems was different. While more than half of the combined-type children were found to have at least one form of inhibition deficit, all forms co-occurred at the same time in less than one third of the group. Thus we cannot speak of a general inhibition deficit in children with the combined type of AD/HD.

It is essential to be more precise as to the specific nature of the problems each child must deal with.

This differentiation becomes visible if we compare the severity of the deficits. The inability to inhibit a motor response evoked by the wrong stimulus ("over-reactions") appeared at a level significantly less than average in the same percentage as children who were significantly worse than average in this respect. On the other hand, a below-average intensity of difficulties with inhibiting an already-evoked response when a stop signal is given was found in three times more children than severe deficits. Inhibiting an automatic response and replacing it with an intentional reaction was impaired in half these children, and disturbed in one-fifth.

The inattentive children also displayed differentiated inhibition deficits, but the frequency of their occurrence was lower than in the combined-type children. One-third of the inattentive children had difficulties in inhibiting a response evoked by a incorrect stimulus, while a greater tendency to overreactions was found in 20% of these children. Also, 30% of the children had greater than average problems with inhibiting an already-initiated action upon receiving a stop signal, and again, as in the previous case of inhibition, 20% of these children had a significant deficit. An increased susceptibility to distraction occurred in 40% of these children, whereas no child from this group was found to have profound disturbances in this respect. It should be emphasized that there was no co-occurrence of different types of inhibition deficits in the inattentive children. This results from the fact that this group displays predominantly single, selective, and less frequent difficulties with inhibition.

Inhibiting cognitive responses that were overly quick and not adapted to the demands of the task was not especially difficult for these children. In this respect we found no differences between the inattentive and combined-type children. A small percentage (10-15%) of both combined-type and inattentive children displayed below average capacities in this respect, while severe difficulties were found in only 5-9%. The inhibition of cognitive responses was thus not a major problem for most of these AD/HD children.

Disturbances in planning a motor response on the basis of visuo-spatial data and inhibiting responses inconsistent with these data occurred in over half of these children, and about 40% of the combined-type children had serious problems. Among the inattentive children these difficulties occurred less often, but they were measurable in about 40%.

As mentioned above, attention disorders are typical for the entire group of AD/HD children. Over 60% of the combined-type children and about half of the inattentive children displayed problems in the functioning of certain aspects of attention. In the combined-type group, the most frequently occurring problems were in the areas of concentration on the task and working memory (almost one-third had severe difficulties), while the largest percentage of the inattentive children had difficulties with maintaining attention on a long and monotonous task. These latter difficulties also occurred just as often among the combined-type children. Problems with engaging intentional effort in completing a task were

found somewhat more often among the inattentive children than in the combined-type children. Susceptibility to external distracters turned out to be more characteristic for the inattentive children than the combined-type children. The co-occurrence of disturbances of different aspects of attention was observed more often in the children with combined-type AD/HD than in the inattentive group.

In order to illustrate the frequency of occurrence of deficits in the inattentive and combined-type groups, we took under consideration several of the more important results obtained in our research by various methods.

Problems of inhibitions have been defined in many different ways. We distinguished the following factors:

- difficulties in inhibiting response to a stimulus that should not evoke any reaction (Inhibition 1);
- difficulties in inhibiting a response that has already been evoked by a stimulus, but should be restrained by a stop signal (Inhibition 2);
- difficulties in inhibiting cognitive responses: overly quick decisions, answering without prior thought, and making mistakes because of this (Inhibition 3);
- difficulties in inhibiting an automated response in favor of an intentional, conscious reaction, i.e. reduced resistance to interference (Inhibition 4);
- difficulties in planning a motor response on the basis of visuo-spatial data and restraining reactions that would be inconsistent with these data (Inhibition 5).

Attention deficits were also of varying nature, but the following factors seemed to be the most important:

- difficulties in maintaining intellectual exertion over a long period of time (Attention 1);
- difficulties in maintaining attention on the task over a long period of time when the situation is monotonous in terms of stimuli (Attention 2);
- difficulties in concentrating on an auditory task and in the functioning of working memory (Attention 3);
- problems with selectivity of attention, increased susceptibility to external distracters (Attention 4).

Results more than two standard deviations below the mean were taken to indicate disturbances. Fig. 1 presents the percentage of children from the inattentive and combined-type groups displaying deficits in each of the nine factors listed above.

Upon analysis of these selected deficits of attention and inhibition, we can see that a greater percentage of the combined-type children had inhibition deficits, while in the group of inattentive children serious attention deficits did not occur significantly more often than in the combined-type group. It is particularly important to note that, despite the occurrence of some AD/HD symptoms in every child, deficits of each particular function were diagnosed only in a certain percentage of the children. In other words, despite the clinical similarities, these children showed a differentiated profile of neuropsychological disturbances.

The development and use of the most recent methods of neuroimaging have shown that in the combined subtype of AD/HD also there can be structural ab-

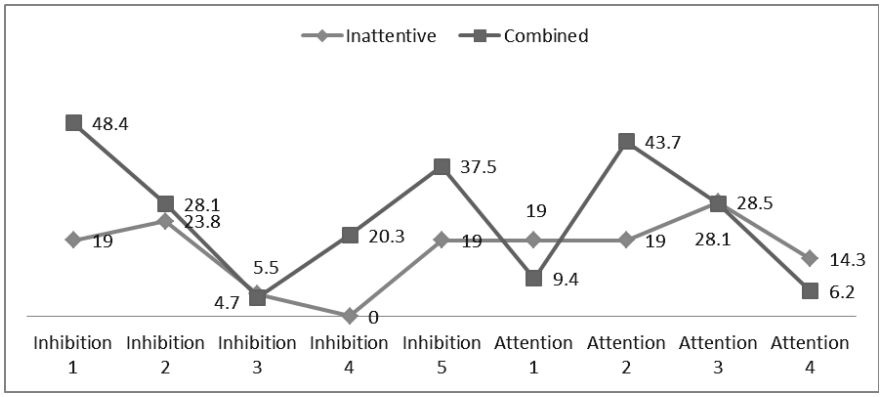

Fig. 1. Selected deficits of attention and response inhibition

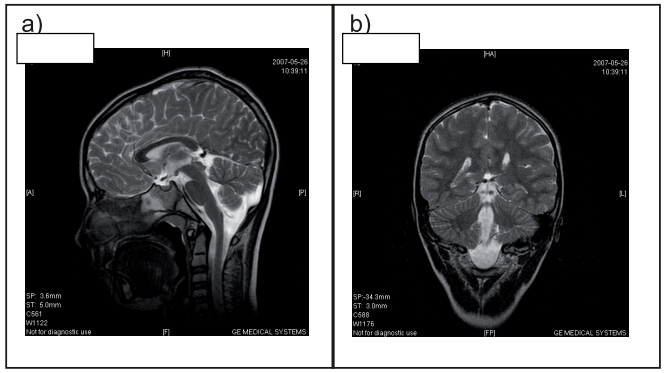

Fig. 2. Changes in the brain of a 14-year-old boy with combined-type AD/HD. (a) sagittal, FSE T2, hypoplasia of the lobe of the corpus callosum and the rostrum of the corpus callosum. (b) coronal, FSE T2, the Dandy Walker variant

normalities of the brain, including the corpus callosum and the structures of the posterior cranial cavity (see Fig. 2). While the changes in the corpus callosum may be associated with a combined-type AD/HD syndrome, the changes in the posterior cranial cavity may be an incidental finding. Accordingly, it is impossible to diagnose AD/HD on the basis of neuroimaging alone, without functional and clinical testing. The cooperation of many specialists is necessary in this respect (Pachalska & Kropotov, 2010).

The microgenetic theory of the formation of the symptom and the problem of AD/HD

In the children with combined-type AD/HD, the inhibition problems we observed may be associated with abnormalities in the following brain structures:

- ventolateral (inferior) prefrontal cortex in the right hemisphere;
- ventolateral (inferior) prefrontal cortex in the left hemisphere;

- dorsolateral regions in both hemispheres;
- anterior and posterior cingulate gyrus, primarily in the right hemisphere.

The disorders of attention seen in these children suggest changes in the functioning of the following structures:

- dorsolateral and ventrolateral prefrontal cortex in the right hemisphere;
- superior and inferior parietal cortex in the right hemisphere;
- anterior cingulate gyrus in the right hemisphere.

In the case of tasks requiring considerable resources of attention (as for example in divided attention tasks), the dysfunctional areas include homologous regions in the left hemisphere.

The difficulties we observed with the performance of tasks intended to measure attention, but including the activation of working memory, suggest abnormalities in the functioning of the posterior parietal cortex and the dorsolateral prefrontal cortex.

In the children with inattentive-type AD/HD, the disturbances of inhibition we observed could be connected with abnormalities in the:

- inferior prefrontal cortex in the left hemisphere;
- dorsolateral regions of the right hemisphere;
- anterior and posterior cingulate gyrus, primarily in the right hemisphere.

The attention disturbances suggest impaired effectiveness of the following areas:

- superior and inferior parietal cortex in the right hemisphere;
- anterior cingulate gyrus in the right hemisphere.

Again, in the case of tasks requiring considerable resources of attention (as for example in divided attention tasks), the dysfunctional areas include homologous regions in the left hemisphere. The disturbances in the performance of tasks that involve working memory suggest abnormal activity in the posterior parietal cortex and the dorsolateral prefrontal cortex.

In discussing the structure of neuropsychological deficits among these children, it should be stated that there were disturbances of motor and cognitive inhibition and various attention processes in both groups. The deficits appeared more often in the combined-type children, somewhat less often in the inattentive children. We observed a broad range of differentiation in the neuropsychological deficits associated with different subtypes of AD/HD.

An analysis of the neuropsychological mechanisms makes it possible to formulate the hypothesis that the inattentive subtype of AD/HD, when diagnosed from the cognitive side on the basis of DSM-4 criteria, seems to be only a “weaker version” of the combined type. It may be that symptomatic diagnostics of attention disorders according to DSM-4 guidelines does not enable us to identify children with qualitatively different disturbances of these processes.

Barry and Clark (2009) suggest that Figure 3 shows clear and unmistakable differences in absolute power between children with both types of AD/HD as compared to normally developing children, with smaller differences apparent between the two types. In the absolute measures (top panel), it is apparent that

the major correlates of AD/HD, in both types, are globally elevated delta and theta power, with globally reduced alpha and beta power. In general terms, all groups show a topography broadly similar to that described above for normally developing children, although there are some common group x topography interactions. In absolute delta, in terms of deviance from the normally developing controls, the data clearly indicate that the profiles of inattentive-type children are not as aberrant as those from children with combined-type AD/HD. With absolute theta, global increases are again common, and the combined type often shows a greater frontal elevation than that shown in Figure 3. In terms of deviance from the typically developing controls, the data again indicate that children with the inattentive type are not as aberrant as those with the combined type of AD/HD. Absolute alpha typically shows a greater posterior than frontal reduction in AD/HD compared with the controls, and the inattentive type appears to lie between the control children and those with the combined type. Broadly similar group differences are apparent in absolute beta.

In the relative measures (Figure 3, lower panel), it is apparent that the major correlates of AD/HD, in both types, are globally elevated relative theta, with glob-

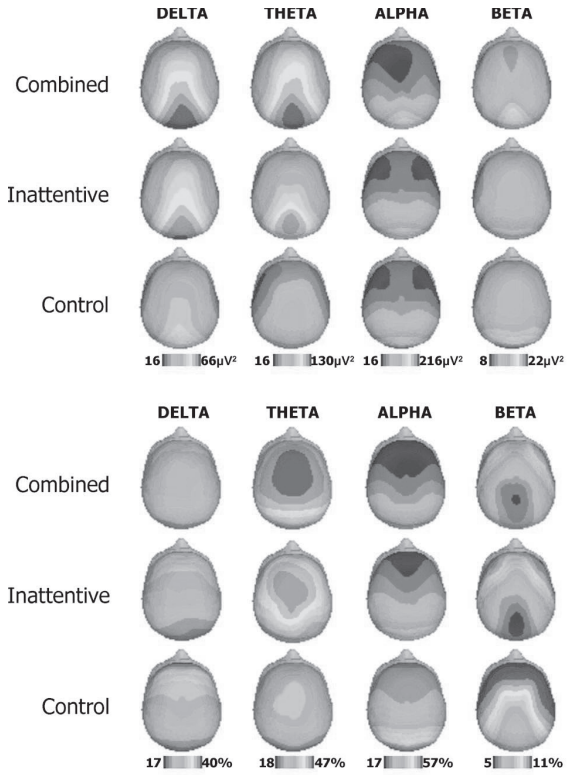

Fig. 3. Topographic head maps showing marked differences in absolute (top panel) and relative power (bottom panel) between children with both types of AD/HD versus typically developing controls [from: Barry and Clark 2009, with the permission of Journal of Psychophysiology Publishers]

ally reduced alpha and beta power. In general terms, all groups again show topography broadly similar to normally developing children, but there are some common group x topography interactions worth noting.

As indicated in the lower panel of Figure 3, relative delta shows more impaired frontal (compared with posterior) activity in AD/HD, which is greater in the combined than inattentive type. Relative theta in AD/HD shows substantially enhanced fronto-central activity, greater and more frontal in the combined compared to the inattentive type. Relative alpha shows a global reduction in AD/HD, which is somewhat more extreme in the combined type, particularly in posterior regions. Relative beta shows a marked global reduction in AD/HD, which is relatively larger frontally and in the hemispheres.

These decrements do not differ greatly between DSM-IV types.

Diagnostic power of independent components

The multi-centre study, carried out within the framework of the COST B 27 initiative, sponsored by the European Commission Research Foundation and included 5 countries: Switzerland (Andreas Mueller and his group), Austria (Michael Doppelmayr and his group), Norway (Stig Hollup and his group), Macedonia (Jordan Pop-Jordanov and his team), and Russia (Juri Kropotov and his lab) were included recordings of 150 ADHD children (24 girls), ranging in age from 7 to 12 years, and 168 ADHD adults, ranging in age from 18 to 50 years (see also: Kropotov and Mueller 2009).

Fig. 4 shows the results from the children's group for comparison between two age matched groups of healthy subjects (taken from the Human Brain Index reference normative database) and ADHD children recorded under the same task conditions.

Seven independent components, constituting around 90% of the signal, were separated from the collection of ERPs recorded in response to GO and NO GO stimuli. Four of them are presented in Fig. 4. As can be seen, only one component significantly (with a size effect of 0.43) discriminates the ADHD group from the control healthy group. This component is generated in the premotor cortex. Its reduction in ADHD reflects functional hypoactivation of the premotor area in inhibitory control in children with attention deficit (see also: Grin-Yatsenko et. Al 2010).

This result fits well with numerous fMRI studies on ADHD children performing GO/NO GO and Stop tasks. These studies showed a decrease of metabolic activity in the prefrontal cortex (also known as hypofrontality) in the ADHD population, in comparison to healthy controls (Rubia et al., 1999; Zang et al., 2005).

Impairment in response inhibition has been conceptualized as a core of ADHD by many authors, including Russel Barkley (1997), the leading figure in the field of ADHD. However, attempts to test this hypothesis in ERP studies have been controversial. In these studies the N2 NO GO wave was considered as an index of inhibition. The N2 is obtained when the ERP to a NO GO (or Stop cue) is con-

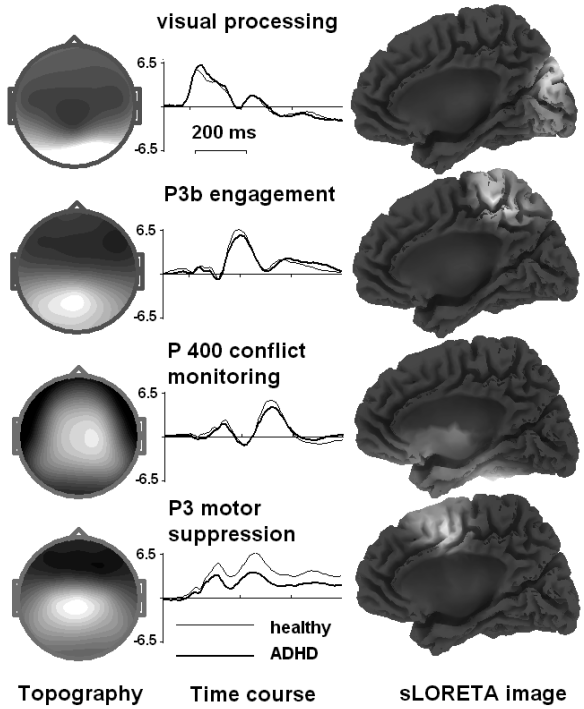

Fig. 4. Independent components of ERPs in response to NOGO cues in ADHD and healthy children. Components are computed for array of 300 individual ERPs for GO and NOGO task conditions in response GO and NOGO cues in the two stimulus GO/NOGO task. Four out seven independent components with largest variances are presented. Left – topography of the component. Middle – time dynamics to NOGO cues in ADHD (thick line) and healthy control children (thin line) of age for 7 to 12 years old. Right –LORETA images of the corresponding components

trasted to the ERP to a GO cue. An international team from the University of Goettingen in Germany and the University of Zurich in Switzerland (Banaschewski et al., 2004) recently reported a failure to find any deviations from normality in an ADHD group in the N2 component of ERPs in a variant of the GO/NO GO paradigm – the CPT-A-X task. In contrast, in a study at the University of Texas (Pliszka et al., 2000) ERPs in another variant of the GO/NO GO paradigm – the Stop signal task - showed a remarkable decrease of the N2 component in the ADHD group in comparison to healthy subjects. In response to all Stop signals, control participants produced a large negative wave at 200 msec (N200) over the right inferior frontal cortex, which was markedly reduced in ADHD children. The N200 amplitude was significantly correlated across subjects with the response–inhibition performance.

The inconsistencies of the N2 deficit in the ADHD population are probably due to the heterogeneity of the psychological operations involved in GO/NO GO tasks. Recently, ICA was applied to a collection of individual ERPs in response to GO and NO GO cues in two-stimulus visual GO/NO GO tasks. The selected

six independent components with different topographies and time courses constituted 87% of the artifact-free signal variance. Three of them were loaded into the frontally distributed N2 wave. According to S-LORETA, these three independent components were generated in the supplementary motor cortex (motor suppression component), left angular gyrus (sensory comparison component) and anterior cingulate cortex (conflict monitoring component). Consequently, the N2 effect in ADHD depends very much on the task, and on how these operations are involved in task performance (Kropotov and Mueller 2009).

To sum up, it should be pointed out, that the most recent work in neuropsychology and psychophysiology provides several possible reasons for behavioral disturbances in children with AD/HD. These disturbances, according to Kropotov's and his team research and our own results (Kropotov, 2009; Kropotov and Mueller 2009; Kropotov & Pachalska, 2010; Brown & Pachalska, 2003; Borkowska, 2008a; Borkowska, 2008b; Pachalska, 2008) can very arranged very generally – in accordance with microgenetic theory – from dysfunctions of the lowest and phylogenetically oldest brain structures to those of the highest and youngest structures, as follows:

- lack of general cortical activation due to functional disturbances of the ascending reticular system of the brainstem (Sergeant, 2000);
- dysfunction of the cingulate gyrus, the effect of which is to increase the level of disquiet, emotional instability, and excessive arousal (Albrecht et al., 2010);
- functional disturbance of the prefrontal-striate-thalamic system due to structural abnormalities of the brain (Busch et al., 2009; Castellanos et Makarov, 2006) or increased dopamine uptake by the dopamine transporters in the striate nucleus (Krause et al., 2008);
- a focal lesion in strategic areas of the cerebral cortex, which despite the absence of clearly epileptic signals is impairing the processing of information, which in effect mimics an attention deficit (Aldenkamp & Arends, 2010);
- a genetically determined hyperactivity of the frontal lobes (Clarke et al., 2001; 2003), with particular attention to the premotor cortex, which is compensated by increased motor activity (Simmonds et al., 2007).

Microgenetic theory (Brown & Pachalska, 2003) makes it possible to interpret the results we achieved. This theory differs from other theories of brain function, in that it emphasizes:

- process and change, rather than data processors connected to each other by neural "cables," as though the brain were a computer;
- the creative nature of perception, which is not just a passive collection of stimuli, but a process of creating an image of reality;
- understanding the symptom as a segment of normal behavior that is revealed prematurely by pathology, and is not just a deficit, that is, the absence of the correct behavior;
- the development of mental processes that evolve on different scales of time, assuming that the laws of behavior are the laws of evolution expressed on another temporal plane;

- processing of information from whole to part, and not, as in standard theory, from “bits” to “stacks” of information.

In particular, a fuller understanding of the essence of AD/HD brings us closer to grasping the process of symptom formation.

In Fig. 5, the afferent pathways bring impulses received from the sense organs to the brainstem, which constitutes the oldest and most primitive part of the brain. The brainstem reacts with a general activation of the organism, which is transmitted upwards (A), to the limbic system and cerebellum. From these somewhat younger structures the activation signal becomes more complex (B), so that in the cortex it spreads to highly specialized areas. Signals from the cortex then travel by pyramidal pathways back down to the brainstem, and from there by efferent pathways to effectors in the musculoskeletal system.

Understanding this somewhat simplified diagram of activation makes it easier to interpret the mosaic of diverse disturbances that occur in children with AD/HD, associated with disturbances that are both structural (involving different areas and different levels of the brain) and functional (resulting from changes on the level of neurotransmission), as well as the resolution of these disturbances in the course of rehabilitation.

The process of symptom formation responsible for the heterogeneity and changeability of behavioral disturbances in AD/HD children is explained by Fig.

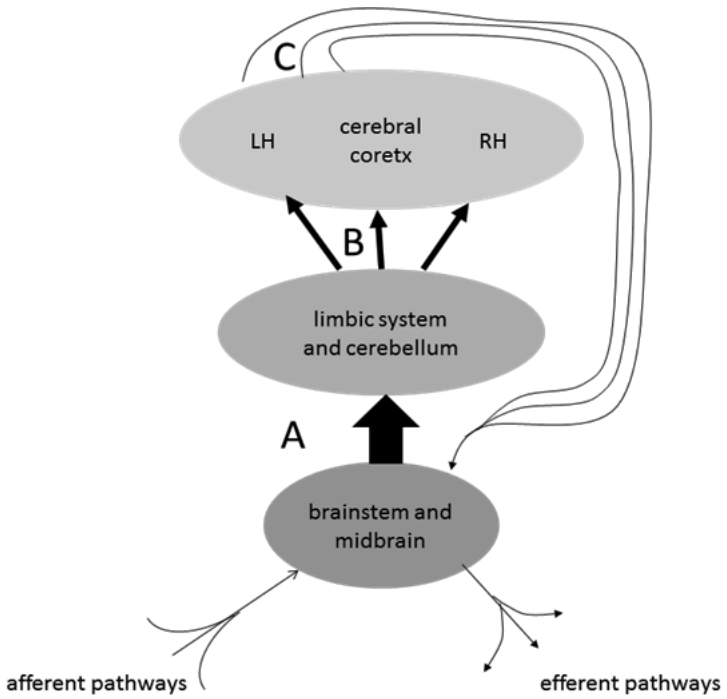

Fig. 5. Schematic diagram of the pathways and brain regions involved in behavior (Pachalska 2008)

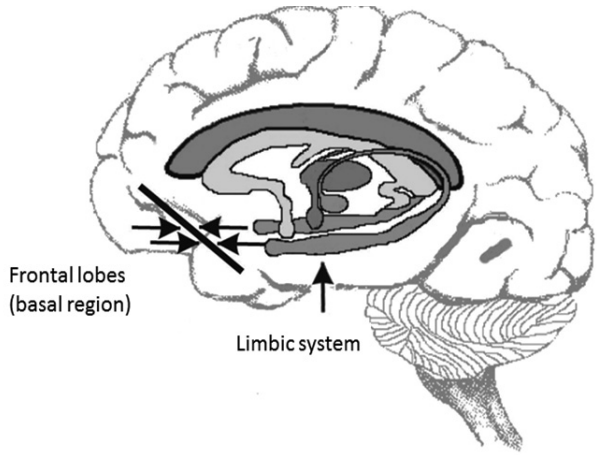

Fig. 6. The bidirectional transition from emotion to mentation and action – płaty czołowe (obszar podstawny) – frontal lobes, basal region, układ limbiczny – limbic system

6, which illustrates the bidirectional transition from emotion to mentation and action. The state of arousal in the mind, which in a healthy brain can be reinforced or inhibited by the executive functions, cannot be controlled in the brains of AD/HD children. Thus the behavior which these children exhibit can be diverse, variable, and capricious, depending on a whole range of factors both structural and functional in nature, which have been discussed in this chapter.

In response to suggestions by scientists from around the world regarding the future directions of research, which can also be supported by our research, work is now under way to modify the diagnostic criteria for AD/HD. The revised criteria will appear in DSM-5, which is already available online. One of the proposed changes involves the necessity of reintroducing the diagnosis of attention deficit disorder (ADD) as a distinct nosological entity. Research in genetics, as well as neuroimaging studies and neuropsychological research on this children, suggests that there are distinct reasons for the deficits in the inattentive children, as opposed to the hyperactive ones (cf. also Kropotov & Pachalska, 2010).

CONCLUSIONS

Fuller cooperation is necessary between neuropsychologists and psychophysiologists, which will help the latter in understanding the problems of a person with AD/HD, and help the former evaluate the results of new programs of neurotherapy.

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