

Attentional Dysfunctions and its Pharmacological Modulation in Childhood Psychiatric Disorders: Evidence from Neuropsychological Studies

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Summary:

Attention plays a critical role in normal cognitive, emotional and social development. Attentional deficits could affect schooling or vocational education. Attention is, however, a broad concept. There are well-defined attentional functions or processes which need to be differentiated. For example, current concepts of attention generally distinguish between selectivity and intensity of attention. In addition, a distinction is made between so-called ‘focused attention’, ‘selective attention’, ‘alertness’, and ‘sustained attention’, whereas deficits in attentional function are thought to be related to problems in inhibitory processes which are guided by a proper functioning of prefrontal areas in the brain. The majority of studies in Attention-Deficit/Hyperactivity Disorder (ADHD) have shown that children with ADHD have attentional deficits.

Through the years, psychopharmacological approaches have proven to have beneficial effects not only on behavior but also on cognitive functions. Typically, psychotropics like methylphenidate (MPH) are used to improve attentional functions in children and adolescents. However, the literature is not unambiguous and the precise effects of MPH on cognitive functions are less clearly described. There are only a limited number of formal neuropsychological studies on cognitive deficits in disruptive behavior disorders (DBD) or emotional disorders. Furthermore, hardly any investigations exist on how the typical psychotropic agents actually impact attentional functions in children and adolescents with DBD. This is a serious problem due to the high comorbidity between the disorders and possible interaction effects.

Therefore, the aim of this thesis was to learn more about attentional dysfunctions in children and adolescents with psychiatric disorders and about the possible influence of psychotropics on attentional functions. An improvement in diagnostic processes and an objective tool to measure cognitive changes caused by psychotropics may make it possible to improve the efficacy of psychopharmacological treatment. This is why attentional functions in children and adolescents with ADHD, ADHD with comorbid DBD, anxiety disorder and depression were examined. Furthermore, the thesis investigated how the psychotropic agents typically used for the different disorders influenced cognitive functions.

The thesis consists of two parts. Part I (chapters 2 and 3) investigates neuropsychological deficits in children with ADHD, ADHD with comorbid DBD, anxiety disorder and depression. Part II (chapters 4 to 8) examines the influence of various psychopharmacological agents (methylphenidate, sertraline and risperidone) on attention, verbal memory and motor activity.

Chapter 9 compiles and subsequently discusses the results described in the various chapters of the thesis.

Chapter 2 examines verbal memory and aspects of attentional control in children and adolescents with anxiety disorders or depressive disorders. It has been suggested that emotional disorders may be associated with impairments in neurocognitive functioning. However, it still remains unclear today whether neurocognitive abilities are disturbed when objective measures of attention and memory are applied and, if so, which cognitive impairments are specifically associated with either anxiety disorders or depression in childhood. Consequently, *chapter 2* aimed to examine basic performance in attention and memory tasks in treatment-naïve children and adolescents with anxiety disorder or depressive disorder under drug-free conditions. A total of 34 children between 6 and 17 years of age with an anxiety disorder, 31 children with a depressive disorder, and 33 healthy controls were assessed with five different computerized attention tasks and the Auditory-Verbal Learning Test. *Chapter 2* provides evidence for undisturbed attentional performance in both patient groups and a dissociation in memory functioning between anxious and depressed children. Memory impairment was found to be specifically associated with childhood depression.

The age differences for impulsivity and sustained attention deficits in ADHD with and without DBD are examined in *chapter 3*. Attention and executive function deficits are described for ADHD and ADHD +DBD. However, it seems that the described deficits are not specific to any one clinical group and evidence from research on neuropsychological deficits in ADHD or ADHD+DBD is based primarily on children under 12 years of age. Some studies suggest that attention and executive function deficits in children with ADHD change with age, possibly due to brain development. Therefore, *chapter 3* aimed to analyze attention and inhibition differences between children and adolescents with ADHD and ADHD+DBD. Two age groups within each clinical group were compared: children between 8 and 11 years of age and adolescents between 12 and 17 years of age. The results indicate that children with ADHD have more attentional problems than children with ADHD+DBD and that the ADHD+DBD group is more impulsive than the ADHD group. The differences between young ADHD, ADHD+DBD and normal controls in the used neuropsychological tasks were not detectable with higher age. The performance of adolescents with ADHD+DBD, ADHD or NC is comparable.

Chapter 4 examines the age-dependent neuropsychological deficits and effects of MPH in children with ADHD. The neuropsychological performance of pre-school and grade-school children with ADHD was compared. Attention deficits in both age groups were expected, especially in attention intensity and in the inhibitory system. Brain maturation processes might result in differences in the distribution of cognitive subtypes across age groups. A second aim was to evaluate MPH effects on computerized attention tasks and to compare pre-school and grade-school children. The pre-school group comprised 45 children aged 5-7 years; the grade-school group comprised 54 children aged 8-12 years. Children were tested on placebo and on MPH, employing tasks of alertness, sustained attention, focused attention, divided attention, and a cognitive conflict task. Both groups showed measurable attention deficits. While preschoolers were especially impaired in inhibitory functions, grade-schoolers most frequently exhibited deficits in attention intensity and selectivity. Positive MPH effects were documented for sustained attention in both age groups. Analysis of MPH effects in dependence of the type of attention impairment (supervisory functions vs. attention intensity / selectivity) revealed a positive relation between deficits in a specific attention domain and MPH effects. Age-dependent differences in attention dysfunctions might be due to brain maturational processes.

The focus of *chapter 5* is on the differential effects of MPH on attentional functions in children with ADHD. Little is known about the sensitivity and specificity of levels of MPH to attention tasks, and only a limited number of studies are available. Therefore, the aim was to investigate dose-dependent effects on different attentional functions using a theoretically based selection of six attention paradigms. A total of 60 ADHD children aged between 8 and 12 years completed a randomized, double-blind, placebo-controlled, within-subject crossover trial with two doses of MPH (0.25 and 0.5 mg/kg body weight) and placebo. A neuropsychological test battery was applied, including tests of alertness and sustained, focused, and divided attention as well as two executive tests, the stop-signal paradigm and a visual set-shifting task. Results indicate that attentional functions are influenced differentially by MPH: intensity functions are best influenced by higher doses, executive functions by moderate doses, and selectivity functions by variable doses.

Chapter 6 evaluates the subjective and objective changes in motor activity and attention in children with ADHD. Although several studies have examined drug effects on either subjective or objective measures of attentional and motor functioning in children with ADHD, little is

known about the relationship between these two areas of outcome measures. Studying the convergences and divergences of change in these two measures might provide a useful basis for optimizing MPH titration guidelines. Therefore, the aim of chapter 6 was to examine dose-dependent effects of MPH on motor activity and attention. A total of 44 ADHD children with the combined subtype completed a randomized, double-blind, placebo-controlled, crossover trial with 2 doses of MPH (0.25; 0.5 mg/kg body weight) and placebo. In each condition, computerized attention tasks were performed, teacher-behavior ratings obtained, and actigraph data collected, in both clinical and natural settings. The results revealed linear effects of MPH dose on actigraph data in the test session and at school as well as on sustained attention, while inhibitory control showed a quadratic dose-response curve. Multivariate regression analyses revealed that changes of both hyperactive-impulsive symptoms and inattentive symptoms could be explained by objective changes in motor activity. The results have implications for clinical practice, as the behavior ratings of ADHD symptoms appeared to be predominantly influenced by changes in motor activity.

Chapter 7 examines the influence of sertraline on attention and verbal memory in children and adolescents with anxiety disorders. Several studies demonstrate that sertraline is safe in the treatment of children and adolescents. However, their results for SSRI influence on cognitive functions, like attention and memory, remain contradictory. Thus, chapter 7 aims to investigate the effect of a 6-week course of sertraline treatment on verbal memory and attentional performance in children with anxiety disorders. Children with various anxiety disorders (social phobia, generalized and separation anxiety disorder; $n=28$), aged between 8 and 17 years, received a standardized computerized neuropsychological assessment before treatment and another six weeks after treatment onset with sertraline (daily dose range between 25 and 100 mg). The patient group was compared to healthy controls ($n=28$), who were matched for age and IQ and were also tested twice over a six-week period. Sertraline did not have any negative effects on attentional performance but did increase response speed in a divided attention paradigm. By contrast, performance in the interference part of a verbal memory task decreased. The described results also remained stable over a 12-week period after treatment onset. Thus, the cognitive side effects of sertraline seemed to differ slightly between pediatric patients and those described in adult patient groups, and should therefore be carefully assessed.

The influence of risperidone on attentional functions in children and adolescents with ADHD and comorbid DBD is investigated in *chapter 8*. Risperidone is a well tolerated neuroleptic agent and has a place in the management of children with ADHD with associated severe DBD, when other treatments have proven unsuccessful. However, little is known about cognitive side effects in ADHD+DBD children with average IQ. Therefore, the study examines the influence of risperidone on attentional functions in children with ADHD+DBD with three different attention related tasks: (1) a sustained attention task to examine intensity aspects of attention; (2) a divided attention task to detect changes in selectivity aspects of attention and (3), a Go/No-Go task to examine inhibitory control as a measurement of impulsivity. Risperidone-treated children (n=23) with normal IQ and ADHD and severe comorbid DBD were compared with an age and IQ matched group of normal controls (n=23). Under risperidone medication, children with ADHD+DBD improved on the inattention-overactivity and aggressive behavior scales. No influence of the risperidone medication on the three attention tasks could be detected, neither as a positive enhancement nor as adverse side effects. Risperidone is useful for treating aggression in children with ADHD with comorbid severe DBD, and it has no negative impact on attentional functions. However, additional stimulant treatment seems to be necessary to treat the attentional deficits in children with ADHD+DBD.

Chapter 9 gives some concluding remarks on the findings from the experimental research described in the thesis and on some implications. The main conclusions of the thesis are:

- Childhood depression is associated with memory impairment, whereas no attentional performance deficits are detectable for anxiety disorders and depression in pediatric patients.
- Children with ADHD have more attentional problems than children with ADHD+DBD, and children with ADHD+DBD are more impulsive than children with ADHD.
- The performance of adolescents with ADHD or ADHD+DBD in attention tasks is comparable with that of age and IQ matched normal controls.
- Children under the age of six with ADHD show deficits in attention control processes, whereas older children have problems in the intensity and selective parts of attention.
- There is no specific difference between MPH effects in pre-school or grade-school children with ADHD.
- MPH significantly improves subjective and objective measures of ADHD symptoms. Hyperactivity reduces with dose level, whereas MPH has differential effects on attentional functions.

- Sertraline induces no deterioration of attentional performance in pediatric patients, whereas a negative impact of sertraline on verbal memory is detectable.
- Risperidone has no influence on attentional functions, neither as a positive enhancement nor as an adverse side effect.

Together, these conclusions suggest that in-depth neuropsychological assessment with cognitive neuropsychological measures has a major contribution to make to objectively evaluating attentional functions in children and adolescents in a psychiatric setting. For example, behavior ratings of inattentive symptoms are influenced more by objective measures of motor activity than by objective measures of attention. This puts into question the typical clinical practice of determining the response to stimulant treatment using only subjective measures, such as parental or teacher ratings. As a consequence, children who are less hyperactive while on MPH might be judged as generally improved while they may still suffer from inattentiveness. Depending on the predominant attentional deficit of a child, different doses might be necessary to improve attentional functions. Thus, it is not enough to examine the efficacy of psychotropic treatment with behavioral check lists: it is imperative that objective neuropsychological instruments with proven sensitivity, reliability, validity and theoretical background are used. The results of lists for behavioral observation are primarily linked to hyperactivity and impulsivity and are –generally– not very sensitive. Treatment with higher doses of MPH results in a reduction in hyperactive behavior which leads to an overestimation of the attentional functions of the child due to its calm behavior. It is not possible to measure inattention in an adequate manner with these behavioral scales because hyperactivity-impulsivity and inattention are two different entities.