

Executive Function Problems and Treatment in Children and Adolescents with Attention Deficit and Hyperactivity Disorder

Dikkat Eksikliği ve Hiperaktivite Bozukluğu Olan Çocuk ve Ergenlerde Yürütücü İşlev Sorunları ve Tedavisi

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder seriously affecting home, school, and social functioning of children and adolescent. In recent years, hypotheses have been revealed that the underlying cause of ADHD is related to executive function impairments. As a consequence of these hypotheses, executive dysfunctions shown in ADHD have started to be evaluated through both performance-based measures and scales based on parents and teachers. There are many methods for assessing executive function in ADHD. Also, there are several pharmacological and non-pharmacological treatment approaches available in the treatment of executive function problems among patients with ADHD. The aim of this article is to review the impact of executive function in ADHD and its treatment.

Keywords: Attention deficit and hyperactivity disorder, executive function, treatment.

Öz

Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) çocuk ve gençlerin evleri, okulları ve toplumsal işlevselliğini ciddi bir şekilde etkileyen nörogelişimsel bir bozukluktur. Son yıllarda DEHB'nin altta yatan sebebinin yürütücü işlev bozukluğu ile ilgili olduğu hipotezler ortaya konulmuştur. Bu hipotezlerin sonucu olarak hem performans dayalı ölçümlerle, hem de ebeveyn ve öğretmenlere dayalı ölçekler aracılığıyla DEHB'de hangi yürütücü işlev bozukluklarının görüldüğü araştırılmaya başlanmıştır. DEHB'de yürütücü işlev sorunlarının değerlendirilmesinde birçok yöntem bulunmaktadır. Ayrıca, DEHB'ye yürütücü işlev sorunlarının eşlik ettiği durumların tedavisinde uygulanan bazı ilaç ve ilaç dışı tedavi yaklaşımları mevcuttur. Bu yazının amacı, DEHB'de yürütücü işlev sorunları ve tedavisini gözden geçirmektir.

Anahtar sözcükler: Dikkat eksikliği ve hiperaktivite bozukluğu, yürütücü işlevler, tedavi.

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ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) is a heterogeneous neuropsychiatric disorder characterized by inattention, hyperactivity and impulsivity, incompatible with age and development level, early onset and persistent in life (American Psychiatric Association 2013). Clinical symptoms can change with development in individuals with ADHD. ADHD, commonly known as childhood disorder, is a developmental disorder. The disorder continues in adulthood after childhood and adolescence (Tannock 1998). Parents of children with ADHD diagnoses often state that their children are hyperactive from the time of their infancy (Bussig et al. 2006). It has been reported that children with ADHD during school age are more likely to have impaired academic functioning, lower school achievement, and higher grade repetition rates than those without ADHD (Biederman et al. 1999).

ADHD is common disorder in childhood and it has been reported rates ranging from 1.0% to 20.0% in worldwide studies. Worldwide combined prevalence of ADHD was 5.29% in systematic review and meta-regression analysis of ADHD epidemiology studies conducted worldwide between 1978 and 2005 (Polanczyk et al. 2007). The prevalence of ADHD in Turkey has found 13.4% (Ercan 2010). In addition, studies have shown that ADHD is seen more frequently in males than females. Community-based studies have shown that the ratio of boys / girls changes between 1/1 and 3/1, whereas clinical-based studies show that this ratio increases to 9/1 (Skounti et al. 2007).

It is known that many genetic, environmental, and biological factors play a role in the etiology of ADHD (Öncü ve Şenol 2002). The leading role in etiology has been shown to play a role in genetic factors and to be highly inheritable in the formation of ADHD (Akgün et al. 2011). In imaging studies, prefrontal cortex, caudate nucleus, globus pallidus, corpus callosum, and cerebellum volume were found to be decreased in individuals with ADHD (Castellanos et al. 2001). Although ADHD is one of the diseases with high inheritability, it has been suggested that environmental factors also contribute to the development of impairment. Responsible environmental factors include prenatal substance exposure, heavy metal / chemical exposure, nutrition, and psychosocial factors (Froehlich et al. 2011). In studies, it was found that there was a significant relationship between low birth weight, fetal alcohol exposure, maternal smoking, and polychlorinated biphenyl (PCB) exposure of the child and ADHD, but no significant relationship was found between other environmental factors and ADHD (Banerjee et al. 2007).

Structural MRI studies on ADHD have shown that there is a reduction in volume of splenium, corpus callosum, and right caudate nucleus, total or right cerebral, posterior or inferior cerebellar including several prefrontal regions. Subcortical limbic areas such as insula, amygdala and thalamus were found to have cortical thickness and gray matter abnormalities. It has been shown that impairments in the fronto-striatal and fronto-cerebellar connections leading to executive dysfunction in the patients (Rubia et al., 2014).

In this article, it is aimed to evaluate the results of the studies conducted on the diagnosis, evaluation and treatment of executive function in ADHD. In addition to the core symptoms defined in the diagnostic guidelines in ADHD cases, evaluation in terms of difficulties in executive functions may also contribute to the management of cases.

Executive Functions

Executive functions (EF) are an encompassing term that represents the entirety of interrelated processes that are responsible for target-specific and purposeful behaviors. These executive processes are necessary to integrate external stimuli, personally important goals and shaping methods of accessing those objectives, preparation for action, and examination of actions and plans while appropriately implementing them. The processes associated with EF are diverse, but the most important elements are; anticipation, goal selection, planning, initiation of activity, self-regulation, mental flexibility, deployment of attention, and utilization of feedback (Barkley 2012).

Within EF, "planning" includes decision-making, judging, evaluation and reponses of one's own behaviors and the behaviors of others. "Verbal fluency" is the ability to produce and recall words related to a certain category or starting with a certain letter. "Work memory" is the place where information is temporarily stored and used. "Response inhibition" is the ability to reject an automatic tendency in a given situation. "Set shifting" is the ability to make changes between tasks, processes, and mental setups (Chung et al., 2014). "Working memory" allows keeping the information in mind and using it for individual goals. There are two types of working memory, namely, the spatio-temporal working memory and the verbal working memory. Time memory, language skills, mathematical perception, cognitive flexibility, and thinking based on suggestions are realized through working memory. "Cognitive flexibility" is the ability to change thinking about a phenomenon, to produce different ways to solve the problem, and to look at events from a different perspective. Cognitive flexibility is very much related to creativity, task and set shifting. "Fluid intelligence", which enables the establishment of causality, is the ability to reason, problem solve, and to see patterns or relations among items. The establishment of the causality relationship is accepted by various researchers as a high level executive function (Diamond 2013).

The development of EF is parallel to brain development. Babies aged under nine-month have difficulty suppressing the reactions they have already learned, but learn to suppress certain behaviors and to change these behaviors with new reactions until twelve months. Although suppression of instinctive behavior can be learned up to the age of three in early childhood, repetitive errors can be seen. Speed and accuracy in impulse control tasks is observed up to 6 years of age. There may be an impulsive increase for a short period around the age of 11, but children aged 9 years and older can well follow and regulate their actions. Increase in response rate and verbal fluency begins to be observed between 3-5 years. Processing speed and fluency continue to develop until mid-childhood. Significant increase in processing speed is observed between 9-10 and 11-12 years. Development in cognitive activity and fluency occurs in adolescence. In general, after 15 years of age, it is considered that there is very little gain in information processing (Anderson 2002).

EF are managed by dopaminergic, noradrenergic, serotonergic and cholinergic inputs in the prefrontal cortex. It is accepted that responses to EF and environmental changes are mediated through these molecules and changes in neurotransmitter systems have significant effects on EF (Anderson 2002).

The medial prefrontal cortex (mPFC) and the orbitofrontal cortex (OFC) take inputs from dopamine, noradrenaline, serotonin and acetylcholine neurotransmitter systems. Response inhibition is impaired in orbitofrontal cortex lesions, but it is not an

effect of medial prefrontal cortex injury. Attention systems are impaired in medial prefrontal cortex injuries, and orbitofrontal cortex injuries have no effect on attention systems. The set shifting is impaired in the medial prefrontal cortex lesions. Reverse learning ability is impaired in orbitofrontal cortex damage. Therefore, the mPFC is responsible for attention process and set shifting; the OPC is responsible for reverse learning and response inhibition skills (Logue and Gould 2014).

Assessment of Executive Functions

It is suggested to measure the working memory, fluency/reconstitution, set shifting/switching, and planning/problem solving skills in the assessment of EF (Henry and Bettenay 2010). It will be summarized the scales and batteries that can be used for the evaluation of EF in children and adolescents in this section.

The Delis-Kaplan Executive Function System (D-KEFS) is used assessment of EF in children from 8 years older and there is reliability and validity for 8-15 aged children. In this battery, letter, category fluency is used to measure the verbal field. On the other hand, the task of changing between the categories is carried out through the verbal fluency test (Delis et al. 2004).

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is used EF, working memory and planning abilities. This battery can be used for children between 4 and 12 aged. The battery consists of Spatial Working Memory, Stop Signal Test, Intra-Extra Dimensional Shift, Stockings of Cambridge tests. These four tests have been reported to be more appropriate for evaluating the visual-spatial domain of EF (Luciana 2003).

The Test of Everyday Attention- Children's Version (TEA-Ch) is primarily a battery designed to measure attention. This battery minimizes the contributions of memory, reasoning, task comprehension, motor speed, verbal ability and perceptual acuity. TEA-Ch is used for children 6 and 16 aged and consists of Walk/ Don't Walk, Creature Counting, Opposite Worlds, Sky Search Dual Task. It has been reported that the Opposite Worlds in this battery measures the ability to inhibition (Manly et al. 2001).

The Behavioural Assessment of the Dysexecutive Syndrome in Children (BADS-C) is used for children between 8-16 years. Planning is measured using several tests (Water, Key, Zoo Map, Six Part). The battery also includes the Dysexecutive Questionnaire for Children (DEX-C) (Giona et al. 2000). It has been reported that the external validity of the data obtained with the BADS-C battery is high and may reflect the difficulties with EF in daily life (Anderson 2002).

Inhibition ability can be assessed through the Animal-Stroop test which can be applied to children aged 3-16 years. In this test, it is presented cartoon style images to children in the first situation and is wanted naming these shown animals, then animal heads and bodies are jumbled up, but children still name the body of the animal (Wright et al. 2003).

Set shifting can be measured by the Wisconsin Card Sorting Test (WCST). WCST is a test that requires pairing cards with very few instructions. Cards contain different representations of shape, color, and transparency, and require matching of one of the four "base" cards that change in the same size. The correct mapping category is listed as color, shape, quantity for each bundle, and when the participant correctly

matches 10 times in the same category, the next category is passed. The participant receives feedback as to whether the reaction is true or false after each reaction. The test is terminated when all six categories are completed or when both decks are exhausted. This test can be used in individuals aged 6 to 89 years (Henry and Bettenay 2010).

Executive function assessments of preschool children focus on working memory, response inhibition, set shifting, and attention shifting tasks (Garon et al. 2010). Evaluation of basic working memory is assessed by response delay, number/ letter sequence and block sequence tests. Response delay can be applied to children over 5 months. During this task, an object is hidden from one place to another, and after waiting for a while, the child is asked to find the object. In the Number/ Letter Sequence test, the child is asked to repeat the letters or numbers on the list. This test can be applied to children aged 3 years and over. In the Corsi Block Series test, the practitioner touches the blocks in a certain pattern, and then the participants are asked to touch the blocks in such a way as to conform to this pattern. This test can be applied to children over 3 years of age (Garon et al. 2008).

Attention shifting skill is assessed by Dimension Change Card Sort (DCCS) and Bear Teddy test. Child is shown cards with colored shapes in the DCCS test. After the child maps the cards in one size, the size of the cards is changed. The Teddy Bear test is the same as DCCS except that the rules of the child are not explicitly stated. The child is expected to understand the rule change through feedback. These two tests are applicable to children over 3 years of age (Garon et al. 2008).

ADHD Theories about Executive Functions

In the executive function model proposed by Russell Barkley, it is suggested that there are deficiencies in behavioral inhibition in ADHD and the four executive functions associated with it. EF consists of working memory, self-regulation of affect-motivation-arousal, internalization of speech, and reconstitution. Behavioral impairment and associated 4 executive dysfunctions are also thought to affect motor control, fluency, and syntax (Barkley 1997) (Figure 1).

Thomas Brown's executive function model suggests that there are deficiencies in the field of six executive functions in ADHD. These areas consist of activation, focus, effort, emotion, memory and action (Brown 2005).

Activation: It is responsible for organizing tasks and materials, estimating time, prioritizing tasks, and getting started on work tasks. Individuals with ADHD make chronic difficulty with excessive procrastination. They often put off getting started on a task even a task they recognize as very important to them. They can not start task until the urgency for the task is established.

Focus: It involves focusing, sustaining focus, and shifting focus to tasks. Individuals with ADHD are easily distracted by external stimuli and their own thoughts. Words are generally understood as they are read but often have to be read over and over for the meaning to be fully grasped and remembered. They have difficulty in maintaining focus. While driving, they can get away from the places they go when they listen to music.

Effort: It consists of regulating alertness, sustaining effort, and processing speed. Many people with ADHD report can perform short-term projects well, but they have much more difficulty with sustained effort over longer periods of time. They have

difficulty completing tasks on time. Many have difficulty in regulating sleep and wakefulness. They sink into deep sleep and have problems with getting up in the morning.

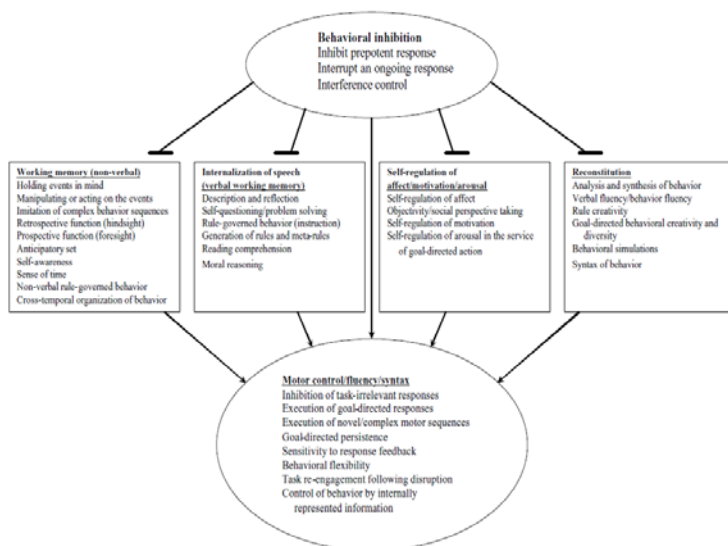


Figure 1. Russell Barkley's executive function model (Barkley 1997)

Emotion: It involves managing frustration and modulating emotions. Although the DSM-IV does not meet diagnosis criteria, many with this disorder describe chronic difficulties managing emotions. It is also reported that when they experience intense emotion, they cannot control their thoughts and are influenced by emotions of logical thinking skills. Because of these emotions, they cannot direct their attention to the other side. They have difficulty in assessing and controlling feelings in context and keeping up with the required reference.

Memory: It consists of using working memory and accessing recall. People with ADHD very often report that they have adequate and good memory for things but they have difficulty recalling information where necessary. They have difficulty holding other things in mind while attending to other tasks. They may not be able to reveal the knowledge when they need it.

Action: It consists of monitoring and regulating self-behavior. Many individuals with ADHD, even those without problems of hyperactive behavior, go through chronic problems in regulating their behaviors. They often are too impulsive in what they say or do and they arouse their minds into action very quickly without thinking about the results. They fail to notice when other people are puzzled, hurt, or annoyed and thus fail to modify their behavior in response to environment. They experience difficulty in regulating the pace of their actions, do tasks fast or slowly (Brown 2008).

When theories of EF in ADHD are evaluated, it is clear that both Barkley's theories in 1997 and in Brown in 2005 remain valid. When examined with the methods used in the studies in which Efs were assessed in ADHD, the studies focus on the

theories the two theoreticians evaluate (Goldberg et al, 2005, Lawrence et al, 2004, Skogli et al.2005; Wu et al. 2002).

Studies on Executive Dysfunction in ADHD

Children with ADHD have executive dysfunction during both real-life activities and during neuropsychological tests (Lawrence et al. 2004). It has been shown that performances of cases with diagnosed ADHD are worse than controls when the response inhibition is assessed by Stroop, do/ stop and stop signal tasks. In studies evaluating planning skills with Hanoi tower tests, it was determined that individuals with ADHD were impairment compared to controls. Studies evaluated the set shifting skill using the WCST showed that individuals with ADHD performed worse than the control group (Goldberg et al. 2005).

In studies, it was determined that individuals with ADHD have functional deficits in working memory (Goldberg et al. 2005). In a study investigating the effect of ADHD and Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) comorbidities on executive dysfunctions, the areas of planning, working memory and verbal fluency were assessed. It was determined that in comorbid ADHD and ODD/ CD presence, executive dysfunctions were not due to ODD/ CD, and these deficits were due to ADHD in this study (Oosterlaan et al., 2005).

In another study investigating the neuropsychological differences between ADHD subtypes, response inhibition, visual working memory, planning, cognitive flexibility, and verbal fluency were evaluated. In this study, it was found that ADHD combination type differed from controls in terms of the inhibition abilities and there was no difference in the neuropsychological profile between ADHD combined type and ADHD predominantly inattention type (Geurts et al. 2005). In a study comparing executive function performance in individuals with comorbid anxiety disorder, ODD and CD with ADHD, continuous performance test, Conners' Continuous Performance Test, WCST, Tower of London, Finger Windows and Self Ordered Pointing tests were used in evaluating executive function. It has been shown that those with comorbid anxiety disorder perform worse in Conners' Continuous Performance Test and children with CD obtained lower scores on WCST (Ter-Stepanian et al. 2017).

In a study comparing the performance of EF between ODD with and without ADHD and healthy controls, it was used trail making test to evaluate set shifting; self-ordered pointing task to evaluate working memory; Hanoi tower test to evaluate planning ability; continuous performance test and Stroop test to evaluate attention skills; door opening test to evaluate perseveration of responses and delay of gratification task to evaluate delay aversion. There were no differences in working memory, planning, inhibition and impulsivity among the three groups in this study. The ODD/ADHD group was worse than the healthy control group in set shifting. In addition, both the ODD alone and ODD/ADHD groups performed worse on a response perseveration task (van Goozen et al. 2004).

In a study comparing the EF performance of individuals diagnosed with ADHD with and without learning disability, it was used color test in Stroop, times score in contingency naming test, motor control time in sky search score to evaluate for speed of processing; attention score in sky search test and Stroop interference score to evaluate selective attention; time and error scores in the third and fourth subset of contingency

naming test for switching attention abilities. It was found that children with ADHD have slower verbal responses and sustained attention deficit. Impairments in selective attention and attentional capacity was shown were largely related to the presence of learning disabilities. It was also shown that no specific deficit associated with ADHD or the comorbidity of LD was identified in switching attention, impulsiveness, planning, and problem solving. This study revealed that ADHD is not a general deficit in EF but impairments in the certain areas of EF occur in ADHD (Wu et al. 2002).

The effects of gender on EF in individuals with ADHD investigated in a study. In this study, parents were asked to evaluate their children by giving Behavior Rating Inventory of Executive Function (BRIEF). EF was evaluated by letter-number sequencing test, color-word interference test, trail making test, design fluency test, tower test and letter fluency test in children. The BRIEF evaluates areas of inhibition, shift, emotional control, initiate, working memory, planning, organization of materials and monitor. In this study, it was determined that children with ADHD had impairment compared to controls in all areas of the BRIEF test, but no significant difference was found between boys and girls with ADHD. In evaluating the executive function applied to children, it was shown that children with ADHD had significant low scores in all tests except for the tower test comparing to control group. EF difference could not be determined in direct applied tests between boys and girls with ADHD in this study (Skogli et al. 2013).

Executive function differences between individuals with ADHD and those with comorbid ODD were investigated in a study conducted in China. This study was assessed by measures based on BRIEF scale and performance. It was used Stroop test for inhibition, trail making test for scrolling, numerical sequence test for verbal working memory, Hanoi tower test for planning. In this study, it was found that the ADHD and ODD/ ADHD had worse performance than the control group in Stroop and trail making test. In these groups, it was also found that BRIEF scores were worse than the control group. While there was no difference in performance-based tests between ADHD and ADHD/ ODD groups, the ADHD/ ODD group were worse than ADHD group in the BRIEF scores and the significant difference between these groups was observed in the subtest tests of inhibition, shift and emotional control (Qian et al.2010).

In a study of EF differences between ADHD combined (ADHD-C) and ADHD predominantly inattention type (ADHD-I), the stop task, tower of London, Stroop task, trail making test, and output speed measures were used. It was found that both subtypes were impairments in the output speed and boys with ADHD-C had more difficulties in stop test than boys with ADHD-I, but there was no difference in stop test between the two subtypes in girls. In this study, it was also found that the ADHD-C had a deficit in planning. Although the ADHD subgroups were slower than the control group during the Stroop test, it was found that neither ADHD group had a deficit in interference control per se (Nigg et al. 2002).

In an another study comparing ADHD-C and ADHD-I, it was used Stroop test for interference control, continuous performance test and BRIEF for inhibition, trail making test for set shifting, London tower test for planning and WISC-3 for processing speed. In this study, no significant difference was found between the two ADHD subtypes in terms of EF performance tests. When girls were excluded and only

boys were considered, a significant difference was found in the Stroop test and it was found that boys with ADHD-I had lower scores than children with ADHD-C. A significant difference was found only in the subgingival dimension in the BRIEF scale, children with ADHD-C were found to have more problems with this subscale, and a significant difference was also observed when girls were excluded (Riccio et al. 2006).

In a study investigated the effect on EF of ADHD according to gender and subtype, the Stroop test, the matching familiar figures test, the trail making test, the London tower test and the WCST were used. In this study, it was determined that there was no effect of gender on EF, and the difference between the control group and the ADHD group was seen in Stroop test and WCST. It was also determined that the ADHD-C showed impairment in more parameters than ADHD-I and that the difference in impairment was more significant (Houghton et al. 1999). Studies with children with ADHD found that the working memory was also impairment and that the size of the impairment varied according to the method used in the measurement. In a meta-analysis study, it was determined that there was a large scale in the spatial working memory and a medium scale in the verbal working memory (Martinussen et al. 2005).

In the 10 studies assessing inhibition skills of individuals with ADHD were measured by the Stroop test, it was determined that the individuals with ADHD were impairment comparing to control group. However, there was no difference between the two groups in two studies. It was observed that there were differences between the ADHD and the control group in the 17 of the 26 studies conducted with WCST for the ability to set shifting, and it was determined that the significant difference was associated with younger age groups. In two studies using self-ordered pointing test to measure working memory, the group with ADHD had a worse performance than the control group. Five of the studies of Hanoi tower or London tower tests to measure planning skill showed that there was a difference between ADHD and control group, no difference was found between the two groups in the two studies. Six of the studies used letter fluency; it was found that ADHD performed worse than control group, no difference was found between two groups in three studies. In two of the studies using category fluency, there was a difference between the groups and in seven studies, it was determined that there was no difference between the ADHD and the healthy control group (Sergeant et al. 2002). Measurement of working memory, emotion regulation and inhibition skills was found to be the most sensitive measures of ADHD different from the control group (Berlin et al. 2004).

In a study of adolescents with ADHD compared with healthy controls in terms of BRIEF scores and performance-based measurements, it was compared with the tasks of inhibition, working memory, set shifting, and planning. In this study, it was observed that there was a difference between the two groups in the BRIEF filled by both the teachers and the parents and in the performance-based measures (Toplak et al. 2009). It is suggested that EF evaluation with rating scales is not related to performance-based measures and that the measured structures are different (Toplak et al. 2013).

Treatment of Executive Dysfunction in ADHD

Non-Pharmacological Treatment Approaches

Cognitive training programs including many areas of EF have been investigated as a

potential ADHD non-pharmacologic treatment (Rapport et al. 2013). Given the current data on neuroplasticity, rehabilitation and cognitive training may be considered to be able to strengthen key brain networks associated with ADHD and to support cognitive processes through controlled exposure to information processing tasks (Vinogradov et al. 2012). Therefore, it is asserted that cognitive training can reduce ADHD symptoms and improve functioning by targeting neuropsychological deficits thought to mediate ADHD pathophysiology (Cortese et al. 2015). Cognitive training approaches have targeted a range of deficits such as attentional control, working memory, inhibitory control. Sonuga-Barke and colleagues examined the efficacy of non-pharmacologic treatments in ADHD in their meta-analyzes in 2013. Consequently, it was shown effects of cognitive training on ADHD symptoms calculated using unblinded ratings. However, this effect dropped substantially and became statistically no significant when blinded assessment were used (Sonuga-Barke et al. 2013). In a meta-analysis conducted in recent years, cognitive training has been shown to be effective in all subtypes of ADHD in non-blind measures, and when the measurements are made by blinded evaluators, the effectiveness is significantly reduced. In addition, while it was shown that cognitive training had a significant effect on the working memory measured in the laboratory and the EF scores assessed by the families; no effect on academic performance was shown in this study (Cortese et al. 2015).

One of the non-pharmacologic approaches is the Cogmed Working Memory Training (CWMT). The CWMT is a computerized training program designed to improve working memory over a five-week training period. Three age-specific software applications were created for preschool children, school children and adults. The program has been developed aiming at the storage and manipulation of the components of verbal and non-verbal working memory. The CWMT can be applied where there is internet access (eg home, school, etc.). This feature may be more common than other interventions. (Roche and Johnson 2014). However, it may be controversial whether the CWMT has improved the working memory (Klingberg 2010). CWMT program designed initially to improve the documented visuospatial span deficits in children with ADHD uses an adaptive algorithm that continuously adjusts the task difficulty by repeatedly experimenting to match the capacity of the individual work memory to the individual (Klingberg et al. 2002, Westerberg et al. 2014). CWMT consists of intensive daily practice (30–45 min per day) for 5 days per week for 5 weeks, during which time the practitioners consistently perform the task working memory tasks and are organized according to the correctness of applying feedback and rewards for each trial. There are many studies evaluating the efficacy of CWMT in ADHD. When these studies are examined, it seems that the findings are inconsistent. In a study examining the effect of CWMT on children with ADHD, while the improvement in working memory and attention deficit scores evaluated by their families was observed, there was no difference in the hyperactivity and ODD symptoms rated by the parents and in the all subscales graded by the teachers (Beck et al. 2010). In addition, Green and colleagues' study in 2012 showed no difference in the ADHD symptoms rated by parents, although positive results were reported in the task of objectively assessed working memory of children with ADHD who received CWMT (Green et al. 2012). In another study, CWMT was found to have no effect on the ADHD rating, which was rated by both family and teachers (Gray et al. 2012). In a review of Chacko and colleagues evaluating the efficacy

of CWMT in young people with ADHD, the strengths and limitations of the studies reviewed suggest that CWMT is best defined as a possibly efficacious treatment for youth with ADHD (Chacko et al. 2013). In a study conducted with adult ADHD, it was found that the individuals applied CBCT improved in the capacity of verbal and visual spatial working memory and this progress continued for 6 months (Dentz et al. 2017).

Physical exercise is another non-pharmacologic approach that has been studied on EF in ADHD. Studies have shown that exercise modifies brain plasticity positively through neurogenesis, neuroadaptation and neuroprotective processes; increases dopamine, which plays an important role in ADHD, epinephrine and norepinephrine. It is recommended because these mechanisms may be beneficial in EF and inhibition. In addition, physical activity may also activate areas of cognitive activity, such as prefrontal and parietal regions (Dishman et al. 2006). Exercise may also increase the level of Brain-derived Neurotrophic Factor (BDNF), which facilitates attention, inhibition, learning, and progression of emotions. BDNF also helps release dopamine, which is frequently used in the treatment of ADHD (Hong et al., 2012). Thus, exercise and physical activity may directly or indirectly affect catecholamine levels, which are thought to play an important role in ADHD (Dishman et al. 2006). Smith and colleagues showed that continuous moderate-to-severe physical exercise, which lasted about 26 minutes each day during eight school weeks, made important changes in attention and response inhibition in young ADHD children (Smith et al. 2013). In another study conducted with children with ADHD, it was found that physical exercise consisting of progressive aerobic, muscular, and motor skills during 10 consecutive weeks, 3 times a week for 45-min periods in a school gymnasium, and supervised by a physical activity specialist had no significant effect on response inhibition (Verret et al. 2012). In a pilot study, twelve-week tennis exercise was shown to have an effect on the color-naming scores of the Stroop test in cases with ADHD (Chien-Yu et al. 2015). In a recent study, it has been shown that exercise program consisting 90-minute 24-session has positive effect on cognitive and behavioral inhibition of EF in 40 ADHD boys aged 7-12 (Memarmoghaddam et al. 2016).

Pharmacological Treatments

There are many studies evaluating the effects of stimulant (methylphenidate) and non-stimulant (atomoxetine, guanfacin) used in the treatment of ADHD on EF. These studies mostly examined the efficacy of methylphenidate. In a meta-analysis involving 36 studies investigating the efficacy of methylphenidate in children and adolescents, methylphenidate was found to be superior to placebo in all parameters including executive memory, non-executive memory, reaction time, reaction time variability, and response inhibition (Coghill et al. 2014). In another meta-analysis, the effects of methylphenidate on executive functioning in ADHD have been examined for age-related effects. It has been shown that methylphenidate have moderate and consistent effect on response inhibition, working memory and sustained attention test performance in individuals with ADHD, despite the wide age range of the samples studied and neuropsychological tests, dependent variables, and drug protocol diversity. In addition, when the response inhibition, working memory and sustained attention tests are analyzed separately, no relation with age has been shown. In conclusion, this study

showed that the efficacy of methylphenidate on EF was age-independent (Tamminga et al. 2016). In a study conducted by Yılmaz and his colleagues in our country, 30 healthy children and 30 children diagnosed with ADHD-C according to DSM IV diagnostic criteria between 7-12 years were included in the study and WCST and Stroop test were applied to the children. 4 patients were treated with immediate release methylphenidate (mean dose \pm sd: 0.54 \pm 0.17 mg/kg/day) and 26 patients were treated with osmotic controlled release methylphenidate (and 0.70 \pm 0.22 mg/kg/day) after the application of the first tests in ADHD group. After 1 month, the tests were applied to both groups for the second time. As a result, it was found that WCST (perseveration) and Stroop test (color naming) performances were worse in children with ADHD-C compared to healthy controls and the use of methylphenidate improves the color naming ability. Methylphenidate treatment resulted in improvements on the WCST (perseveration and conceptualization/reasoning) and Stroop test (color naming and interference effect) performances in the ADHD-C group (Yılmaz et al. 2013).

The efficacy of atomoxetine in the treatment of ADHD on EF has been investigated in studies. In a study of the effect of atomoxetine on EF in ADHD with a computer-based continuous performance test combined with a motion-tracking device. 125 cases of ADHD were included in the study and 63 of these cases were started with 0.5 mg/kg/day atomoxetine and the target dose was increased to 1.2 mg/kg/day and 62 of these cases were given placebo. It was found that the number of micro-events (number of position changes greater than 1 mm per head during the test), the number of commission errors (response rate recorded when the stimulus did not reach the target), range of motion, omission error rate, reaction time (when the patient's head moved more than 1 cm/s), simplicity of motion, and normal variance of the response time were significantly reduced (Wehmeier et al. 2012). In another study examining the effect of atomoxetine on EF in young adults aged 18-30 years, 220 patients with ADHD were treated with atomoxetine 50 mg twice a day according to tolerability and safety interval for 12 weeks, 225 patients were given placebo for the same period. In the group receiving atomoxetine treatment, a significant improvement in EF was found according to placebo (Adler et al. 2014).

When examined in the literature, studies comparing methylphenidate and atomoxetine for EF problems in ADHD draw attention. Yıldız and colleagues compared the effects of atomoxetine and osmotic controlled release methylphenidate on EF in ADHD. Twenty-five cases were included in the study and 14 patients were treated with 1.28 mg/kg/day of atomoxetine and 11 patients with 1.07 mg/kg/day of osmotic controlled release methylphenidate treatment. It has been shown that after 12 weeks of treatment osmotic controlled release methylphenidate is more effective on Stroop-5 time and number of correction compared to atomoxetine and a significant reduction in the rate of perseverative errors in WKET (Yıldız et al. 2011). In another study, 54 mg/day of prolonged methylphenidate (n = 85), which started at 18 mg/day in ADHD, and 1.2 mg/kg/day atomoxetine were (n = 57) starting at 0.5 mg/kg/day compared with neuropsychological EF tests and behavioral assessment scales based on efficacy performance. Both methylphenidate and atomoxetine have positive effects on BDI compared to placebo, and methylphenidate has also been shown to develop significantly in all of the performance-based EF tests compared to atomoxetine (Yang et al. 2012). In a study conducted in our country, both long-acting methylphenidate (median dose: 1.31 \pm 0.37

mg/kg/day) and atomoxetine (median dose: 0.90-0.29 mg/kg/day), it has been shown to have beneficial effects on EF assessed with WCST and Stroop test (Inca Tasdelen et al. 2015).

When the studies on EF in ADHD were evaluated, the limitation of national studies is remarkable. Both national and international studies show EF problems in ADHD but do not mention a specific EF problem. In studies on the treatment of EF problems in ADHD, it is shown that while pharmacologic treatments' studies have been made both national and international while non-pharmacologic-based approaches are more concerned with international studies. Both stimulant and non-stimulant ADHD treatment approaches have been shown to have a positive effect on EF in ADHD.

Conclusion

Difficulties in executive functions have been reported in studies on children and adolescents with ADHD. However, these difficulties are not specific to ADHD, and may be detected in other neurodevelopmental disorders, as well as in all ADHD cases. Furthermore, there are executive dysfunctions in normal developmental children. There are many methods for evaluating executive function problems in ADHD. There are non-pharmacological and pharmacological treatment on EF problems approaches in ADHD, but further work in this area is required. Longitudinal studies can be used to identify both specific ADHD difficulties and differences between ADHD and normal developmental children in EF. In addition, treatment interventions to be made by identifying the specific EF difficulties to ADHD may be more effective.

References

- Adler LA, Clemow DB, Williams DW, Durell TM (2014) Atomoxetine effects on executive function as measured by the BRIEF-A in young adults with ADHD: A randomized, double-blind, placebo-controlled study. *PLoS One*, 9:e104175.
- Akgün GM, Tufan AE, Yurteri N, Erdoğan E (2011) Dikkat eksikliği hiperaktivite bozukluğunun genetik boyutu. *Psikiyatride Güncel Yaklaşımlar*, 3:15-48.
- American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5)*. Washington, American Psychiatric Association.
- Anderson P (2002) Assessment and development of executive function during childhood. *Child Neuropsychol*, 8:71-82.
- Banerjee TD, Middleton F, Faraone SV (2007) Environmental risk factors for attention-deficit hyperactivity disorder. *Acta Paediatr*, 96:1269-1274.
- Barkley R (2012) *Executive Functions: What They Are, How They Work and Why They Evolved*. New York, Guilford Press.
- Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull*, 121:65-94.
- Beck SJ, Hanson CA, Puffenberger SS, Benninger KL, Benninger WB (2010) A controlled trial of working memory training for children and adolescents with ADHD. *J Clin Child Adolesc Psychol*, 39:825-836.
- Berlin L, Bohlin G, Nyberg L, Janols LO (2004) How well do measures of inhibition and other executive functions discriminate between children with ADHD and controls? *Child Neuropsychol*, 10:1-13.
- Biederman J, Faraone SV, Mick E, Williamson S, Wilens TE, Spencer TJ, et al. (1999) Clinical correlates of ADHD in females: findings from a large group of girls ascertained from pediatric and psychiatric referral sources. *J Am Acad Child Adolesc Psychiatry*, 38:966-975.
- Brown TE (2005) *Attention Deficit Disorder: The Unfocused Mind in Children and Adults*. New Haven, Yale University Press.
- Brown TE (2008) ADD/ADHD and impaired executive function in clinical practice. *Curr Psychiatry Rep*, 10:407-411.
- Bussing R, Lebninger F, Eyberg S (2006) Difficult child temperament and attentiondeficit/hyperactivity disorder in preschool children. *Infants Young Child*, 19:123-131.
- Castellanos FX, Giedd JN, Berquin PC, Walter JM, Sharp W, Tran T et al. (2001) Quantitative brain magnetic resonance imaging in girls with attention deficit/ hyperactivity disorder. *Arch Gen Psychiatry*, 58:289-295.

- Chacko A, Feirsen N, Bedard AC, Marks D, Uderman JZ, Chimiklis A (2013) Cogmed Working Memory Training for Youth with ADHD: A closer examination of efficacy utilizing evidence-based criteria. *J Clin Child Adolesc Psychol*, 42:769-783.
- Chien-Yu P, Chia-Liang T, Chia-Hua C, Ming-Chih S, Chu-Yang H, Wei-Ya M (2015) Effects of physical exercise intervention on motor skills and executive functions in children with ADHD: A Pilot Study. *J Atten Disord*, 1-14.
- Chung HJ, Weyandt LL, Swentosky A (2014) The physiology of executive functioning. In *Handbook of Executive Functioning* (Eds S Goldstein, JA Naglieri):13-27. New York, Springer.
- Coghill DR, Seth S, Pedroso S, Usala T, Currie J, Gagliano A (2014) Effects of methylphenidate on cognitive functions in children and adolescents with attention-deficit/ hyperactivity disorder: evidence from a systematic review and a meta-analysis. *Biol Psychiatry*, 76:603-615.
- Cortese S, Ferrin M, Brandeis D, Buitelaar J, Daley D, Dittmann RW et al. (2015) Cognitive training for attention-deficit/hyperactivity disorder: meta-analysis of clinical and neuropsychological outcomes from randomized controlled trials. *J Am Acad Child Adolesc Psychiatry*, 54:164-174.
- Delis DC, Kramer JH, Kaplan E, Holdnack J (2004) Reliability and validity of the Delis-Kaplan Executive Function System: An update. *J Int Neuropsychol Soc*, 10:301-303.
- Dentz A, Guay MC, Parent V, Romo L (2017) Working memory training for adults with ADHD. *J Atten Disord*, 1:1087054717723987.
- Diamond A (2013) Executive functions. *Annu Rev Psychol*, 64:135-168.
- Dishman RK, Berthoud HR, Booth FW, Cotman CW, Edgerton VR, Fleshner MR et al. (2006) Neurobiology of exercise. *Obesity*, 14:345-355.
- Ercan ES (2010) Dikkat eksikliği hiperaktivite bozukluğunda epidemiyolojik veriler. *Türkiye Klinikleri Pediatrik Bilimler Dergisi*, 6:1-5.
- Froehlich TE, Anixt JS, Loe IM, Chirdkiatgumchai V, Kuan L, Gilman RC (2011) Update on environmental risk factors for Attention-Deficit/Hyperactivity Disorder. *Curr Psychiatry Rep*, 13:333-344.
- Garon N, Bryson SE, Smith IM (2008) Executive function in preschoolers: a review using an integrative framework. *Psychol Bull*, 134:31-60.
- Geurts HM, Verté S, Oosterlaan J, Roeyers H, Sergeant JA (2005) ADHD subtypes: do they differ in their executive functioning profile? *Arch Clin Neuropsychol*, 20:457-477.
- Gioia GA, Isquith PK, Guy SC, Kenworthy L (2000). The Behavior Rating Inventory of Executive Function. *Child Neuropsychol*, 6:235-238.
- Goldberg MC, Mostofsky SH, Cutting LE, Mahone EM, Astor BC, Denckla MB et al. (2005) Subtle executive impairment in children with autism and children with ADHD. *J Autism Dev Disord*, 35:279-293.
- Gray SA, Chaban R, Martinussen R, Goldberg H, Gottlieb R, Kronitz R et al. (2012) Effects of a computerized working memory training program on working memory, attention, and academics in adolescents with severe LD and comorbid ADHD: A randomized clinical trial. *J Child Psychol Psychiatry*, 53:1277-1284.
- Green CT, Long DL, Green D, Iosif A, Dixon F, Miller MR et al. (2012) Will working memory training generalize to improve off-task behavior in children with attentiondeficit/hyperactivity disorder? *Neurotherapeutics*, 9: 639-648.
- Henry L, Bettenay C (2010) The assessment of executive functioning in children. *Child Adolesc Ment Health*, 15:110-119.
- Hong CJ, Liou YJ, Tsai SJ (2012) Reprint of: Effects of BDNF polymorphisms on brain function and behavior in health and disease. *Brain Res Bull*, 88:406-417.
- Houghton S, Douglas G, West J, Whiting K, Wall M, Langsford S, et al. (1999) Differential patterns of executive function in children with attention-deficit hyperactivity disorder according to gender and subtype. *J Child Neurol*, 14:801-805.
- Ince Tasdelen B, Karakaya E, Oztop DB (2015) Effects of atomoxetine and osmotic release oral system-methylphenidate on executive functions in patients with combined type attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*, 25:494-500.
- Klingberg T (2010) Training and plasticity of working memory. *Trends Cogn Sci*, 14:317-324.
- Klingberg T, Forssberg H, Westerberg H (2002) Training of working memory in children with ADHD. *J Clin Exp Neuropsychol*, 24:781-791.
- Lawrence V, Houghton S, Douglas G, Durkin K, Whiting K, Tannock R (2004) Executive function and ADHD: a comparison of children's performance during neuropsychological testing and real-world activities. *J Atten Disord*, 7:137-149.
- Logue S, Gould TJ (2014) The neural and genetic basis of executive function: Attention, cognitive flexibility, and response inhibition. *Pharmacol Biochem Behav*, 123:45-54.
- Luciana M (2003) Practitioner Review: Computerised assessment of neuropsychological function in children: Clinical and research applications of the Cambridge Neuropsychological Testing Automated Battery (CANTAB). *J Child Psychol Psychiatry*, 44:649-

- 663.
- Manly T, Anderson V, Nimmo-Smith I, Turner A, Watson P, Robertson IH (2001) The differential assessment of children's attention: The Test of Everyday Attention for Children (TEA -Ch), normative sample and ADHD performance. *J Child Psychol Psychiatry*, 42:1065-1081.
- Martinussen R, Hayden J, Hogg-Johnson S, Tannock R (2005) A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*, 44:377-384.
- Memarmoghaddam M, Torbati H, Sohrabi M, Mashhadi A, Kashi A (2016) Effects of a selected exercise program on executive function of children with attention deficit hyperactivity disorder. *J Med Life*, 9:373-379.
- Nigg JT, Blaskey LG, Huang-Pollock CL, Rappley MD (2002) Neuropsychological executive functions and DSM-IV ADHD subtypes. *J Am Acad Child Adolesc Psychiatry*, 41:59-66.
- Öncü B, Şenol S (2002) Dikkat eksikliği ve hiperaktivite bozukluğunun etiyolojisi: Bütüncül yaklaşım. *Klinik Psikiyatri Dergisi*, 5:111-119.
- Oosterlaan J, Scheres A, Sergeant JA (2005) Which executive functioning deficits are associated with AD/HD, ODD/CD and comorbid AD/HD+ODD/CD? *J Abnorm Child Psychol*, 33:69-85.
- Polanczyk G, De Lima MS, Horta BL, Biederman J, Rohde LA (2007) The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *Am J Psychiatry*, 164:942-948.
- Qian Y, Shuai L, Cao Q, Chan RC, Wang Y (2010) Do executive function deficits differentiate between children with attention deficit hyperactivity disorder (ADHD) and ADHD comorbid with oppositional defiant disorder? A cross-cultural study using performance-based tests and the behavior rating inventory of executive function. *Clin Neuropsychol*, 24:793-810.
- Rappoport MD, Orban SA, Kofler MJ, Friedman LM (2013) Do programs designed to train working memory, other executive functions, and attention benefit children with ADHD? A meta-analytic review of cognitive, academic, and behavioral outcomes. *Clin Psychol Rev*, 33:1237-1252.
- Riccio CA, Homack S, Jarratt KP, Wolfe ME (2006) Differences in academic and executive function domains among children with ADHD Predominantly inattentive and combined types. *Arch Clin Neuropsychol*, 21:657-667.
- Roche JD, Johnson BD (2014) Cogmed working memory product review. *J Atten Disord*, 18:379-384.
- Rubia K, Alegria AA, Brinson H (2014) Brain abnormalities in attention-deficit hyperactivity disorder: a review. *Rev Neurol*, 58:3-16.
- Sergeant JA, Geurts H, Oosterlaan J (2002) How specific is a deficit of executive functioning for attention-deficit/hyperactivity disorder? *Behav Brain Res*, 130:3-28.
- Skogli EW, Teicher MH, Andersen PN, Hovik KT, Øie M (2013) ADHD in girls and boys—gender differences in co-existing symptoms and executive function measures. *BMC Psychiatry*, 13:298.
- Skounti M, Philalithis A, Galanakis E (2007) Variations in prevalence of attention deficit hyperactivity disorder worldwide. *Eur J Pediatr*, 166:117-123.
- Smith AL, Hoza B, Linnea K, McQuade JD, Tomb M, Vaughn AJ et al. (2013) Pilot physical activity intervention reduces severity of ADHD symptoms in young children. *J Atten Disord*, 17:70-82.
- Sonuga-Barke EJ, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M (2013) Nonpharmacological interventions for ADHD: systematic review and meta-analyses of randomized controlled trials of dietary and psychological treatments. *Am J Psychiatry*, 170:275-289.
- Tamminga H, Reneman L, Huizenga H, Geurts H (2016) Effects of methylphenidate on executive functioning in attention-deficit/hyperactivity disorder across the lifespan: A meta-regression analysis. *Psychol Med*, 46:1791-1807.
- Tannock R (1998) Attention deficit hyperactivity disorder: advances in cognitive neurobiological and genetic research. *J Child Psychol Psychiatry*, 34:65-99.
- Ter-Stepanian M, Grizenko N, Cornish K, Talwar V, Mbekou V, Schmitz N et al. (2017) Attention and executive function in children diagnosed with attention deficit hyperactivity disorder and comorbid disorders. *J Can Acad Child Adolesc Psychiatry* 2017; 26:21-30.
- Toplak ME, Bucciarelli SM, Jain U, Tannock R (2009) Executive functions: performance- based measures and The Behaviour Rating Inventory of Executive Function (BRIEF) in adolescent with ADHD. *Child Neuropsychol*, 15:53-72.
- Toplak ME, West RF, Stanovich KE (2013) Practitioner Review: Do performance-based measures and ratings of executive function assess the same construct. *J Child Psychol Psychiatry*, 54:131-143.
- van Goozen SH, Cohen-Kettenis PT, Snoek H, Matthys W, Swaab-Barneveld H, van Engeland H (2004) Executive functioning in children: a comparison of hospitalised ODD and ODD/ADHD children and normal controls. *J Child Psychol Psychiatry*, 45:284-292.
- Verret C, Guay MC, Berthiaume C, Gardiner P, Beliveau LA (2012) Physical activity program improves behavior and cognitive

- functions in children with ADHD: An exploratory study. *J Atten Disord*, 16:71-80.
- Vinogradov S, Fisher M, de Villers-Sidani E (2012) Cognitive training for impaired neural systems in neuropsychiatric illness. *Neuropsychopharmacology*, 37:43-76.
- Wehmeier PM, Schacht A, Ulberstad F, Lehmann M, Schneider-Fresenius C, Lehmkuhl G, et al. (2012) Does atomoxetine improve executive function, inhibitory control, and hyperactivity? Results from a placebo-controlled trial using quantitative measurement technology. *J Clin Psychopharmacol*, 32:653-660.
- Westerberg H, Hirvikoski T, Forssberg H, Klingberg T (2014) Visuo-spatial working memory span: a sensitive measure of cognitive deficits in children with ADHD. *Child Neuropsychol*, 10:155-161.
- Wright I, Waterman M, Prestcott H, Murdoch-Eaton D (2003) A new Stroop like measure of inhibitory function development: Typical developmental trends. *J Child Psychol Psychiatry*, 44:561-557.
- Wu KK, Anderson V, Castiello U (2002) Neuropsychological evaluation of deficits in executive functioning for ADHD children with or without learning disabilities. *Dev Neuropsychol*, 22:501-531.
- Yang L, Cao Q, Shuai L, Li H, Chan RC, Wang Y (2012) Comparative study of OROS-MPH and atomoxetine on executive function improvement in ADHD: A randomized controlled trial. *Int J Neuropsychopharmacol*, 1501:15-26.
- Yıldız O, Sismanlar SG, Memik NC, Karakaya I, Agaoglu B (2011) Atomoxetine and methylphenidate treatment in children with ADHD: The efficacy, tolerability and effects on executive functions. *Child Psychiatry Hum Dev*, 423:257-269.
- Yılmaz A, Gökçen C, Fettagolu EÇ, Ozatalat E (2013) The effect of methylphenidate on executive functions in children with attention-deficit hyperactivity disorder. *Klin Psikofarmakol Bulteni*, 23:162-170.

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