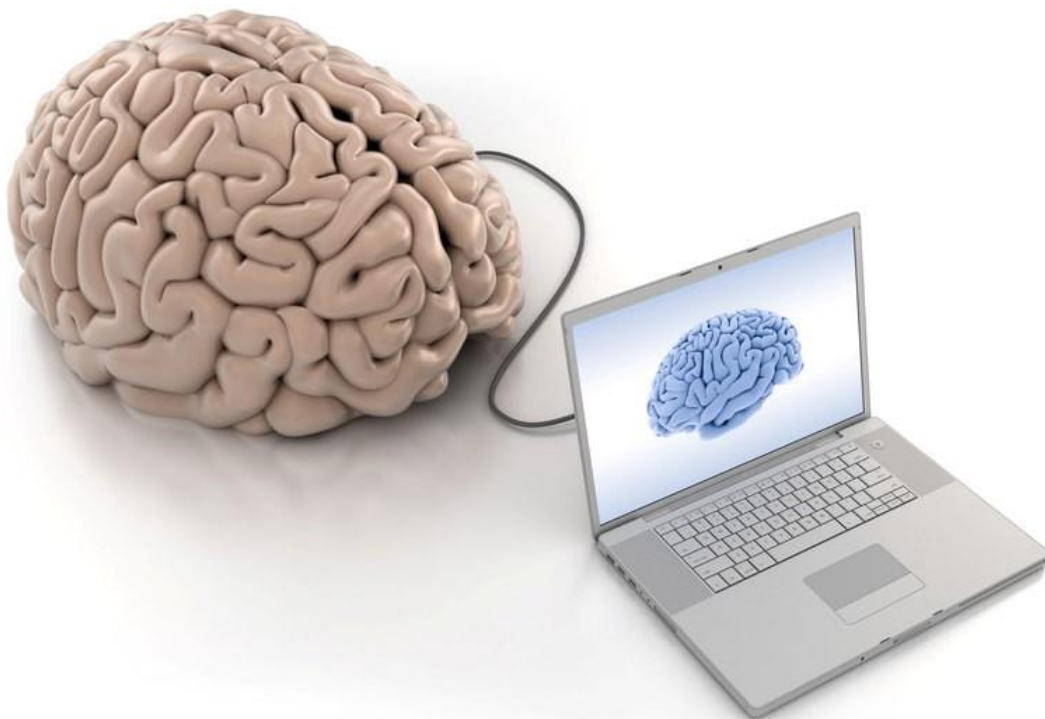


Cognitive Training in Children and Adolescents With Attention Deficit/Hyperactivity Disorder (ADHD)

PhD Thesis



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Preface

This PhD project was conceived and conducted at the Child and Adolescents Psychiatric Services in Augustenborg, Aabenraa, Kolding and Odense in the Region of Southern Denmark.

This dissertation is based on two clinical, controlled, randomized trials conducted with children and adolescents with Attention-deficit/hyperactivity disorder (ADHD). The first trial was a pilot project aimed at testing a new cognitive intervention for adolescents with ADHD and comparing the effect of the intervention with the effect of the computer game Tetris. The participants were recruited at the Child and Adolescents Psychiatric Services Augustenborg, Denmark. The second trial tested another cognitive training intervention developed for children with ADHD and compared the effect of this intervention with the effect of treatment as usual. For the second trial, children with ADHD were recruited from three Danish sites: Augustenborg/Aabenraa, Kolding and Odense.

The PhD study was financially supported by grants from the Region of Southern Denmark's Psychiatry Research Foundation, the Region of Southern Denmark's Ph.D. Foundation, the TrygFonden and the University of Southern Denmark.

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List of papers

This PhD-thesis is based upon the following papers:

- Paper 1: Bikic A., Leckman J., Bilenberg N., Christensen T.Ø. & Dalsgaard S. A Double-Blind Randomized Pilot Trial Comparing Computerised Cognitive Exercises to Tetris in Adolescents with Attention-Deficit/Hyperactivity Disorder. Submitted to Trials Journal.
- Paper 2: Bikic, A., Leckman, J.F., Lindschou, J., Christensen T.Ø. & Dalsgaard S. Cognitive computer training in children with attention deficit hyperactivity deficit disorder (ADHD) versus no intervention: study protocol for a randomized trial. *Trials*. (2015) 16: 480.
- Paper 3: Bikic, A., Leckman, J.F., Christensen T.Ø., Bilenberg, N. & Dalsgaard S. Cognitive computer training versus treatment as usual in children with Attention Deficit-Hyperactivity Deficit Disorder (ADHD): Results from a randomized, controlled trial. Submitted to *Journal of Attention Disorders*

Abbreviations

ADD:	Attention Deficit Disorder
ADHD:	Attention-deficit/hyperactivity disorder
ADHD-C:	Attention-deficit/hyperactivity disorder, Combined Type
ADHD-H:	Attention-deficit/hyperactivity disorder, Predominantly Hyperactive-Impulsive Ty
ADHD-I:	Attention-deficit/hyperactivity disorder, Predominantly Inattentive Type
ADHD-NOS:	Attention-deficit/hyperactivity disorder, Not Otherwise Specified
ADHD-RS:	Attention Deficit / Hyperactivity Disorder-Rating Scale
APQ:	Activity Perception Questionnaire
BLC:	The Big/Little Circle
BRIEF:	Behavior Rating Inventory of Executive Functions
CANTAB:	Cambridge Neuropsychological Test Automated Battery
DMS:	Delayed Matching to Sample (DMS)
DSM-5:	Diagnostic and Statistical Manual of Mental Disorders, 5 th Edition (DSM-5)
fMRI:	Functional Magnetic Resonance Imaging
HRC:	Hyperkinetic Reaction of Childhood
IBBS	Integrated Brain, Body, and Social
ICD-10:	International Classification of Diseases, 10 th Revision
IED:	Intra-Extra Dimensional Set Shift
IQ:	Intelligence Quotient
MOT:	Motor Screening Task
MTA:	Multimodal Treatment of ADHD study
MTS:	Match to Sample Visual Search
MRI:	Magnetic Resonance Imaging
RVP:	Rapid Visual Information Processing
SBT:	Scientific Brain Training
SMD:	Standardized Mean Difference
SOC:	Stockings of Cambridge
SSP:	Spatial Span
SWM:	Spatial Working Memory
TAU:	Treatment as Usual
WISC:	Wechsler Intelligence Scale for Children
WFIRS:	Weis's scale of disability-Parent Report

English summary:

Background: Many individuals with attention deficit hyperactivity disorder (ADHD) continue to experience impaired cognitive functions despite medical treatment. Inadequate medical compliance and uncertain long-term effects of treatment make it necessary to explore supplementary treatments for ADHD. Lately, several trials have shown that training with cognitive computer programs can reduce severity of symptoms and improve cognitive functions.

Method: This dissertation investigates the effects of cognitive training conducted at home in children and adolescents with ADHD. The effect of cognitive training was investigated in two randomized and controlled clinical trials with a focus on specific cognitive aspects, severity of symptoms, and functional outcomes.

Design:

Trial 1: In a pilot study, 18 adolescents with ADHD were randomized to cognitive training or active placebo treatment. They received the interventions for 7 weeks and were assessed at baseline and after the intervention.

Trial 2: In the second trial, 70 children with ADHD were randomized to an intervention targeting broader cognitive functions or a treatment-as-usual control group. Assessments were performed at baseline, after 8 weeks of intervention, and after 12 and 24 weeks of follow-up post-intervention.

Outcome measures: Participants' cognitive functions were assessed with the Cambridge Neurocognitive Automated Battery (CANTAB), and with symptom and behavioral measures before and after the intervention. The first study also focused on the feasibility of the intervention. The first trial was exploratory and based on these results the primary outcome measure in the second trial was chosen to be sustained attention.

Results: In the pilot trial with adolescents with ADHD, we found that it was feasible to use the intervention at home, but that the adolescents did not perceive the specific intervention as very interesting. There were no significant group differences in terms of cognitive and ADHD symptom measures after the intervention. Pre-post intra-group measurement showed that the intervention group had a significant, beneficial effect on sustained attention, while the active placebo had significant, beneficial effects on working memory, both with large effect sizes.

In the second trial, we found no significant differences on our primary or secondary outcome measures indicating no effects on sustained attention, ADHD symptoms or executive functions ratings by parents and teachers. In our exploratory analysis we found a significant difference on an objective measures of planning ability that was sustained at both follow-up points. Additionally we found some interesting effects at the subgroup level regarding the age of participants, ADHD subtypes, and the number of training sessions completed.

Conclusions: We found no additional beneficial effects of cognitive training in our trials for the broader ADHD population. However our results indicate that certain subgroups of patients with ADHD, like older individuals and the ADHD inattentive subtype, may benefit more from cognitive training than others. Additionally the effect of broader cognitive interventions on ability to plan should be investigated further. These hypotheses need to be tested in future trials.

Dansk resumé:

Baggrund: ADHD er en af de hyppigst diagnosticerede psykiatriske tilstande indenfor børne- og ungdomspsykiatrien. Inadækvat compliance og usikre langtidseffekter af farmakologisk behandling, har gjort det nødvendigt at undersøge andre behandlingstilgange for ADHD.

Metode: Denne afhandling undersøger effekten af hjemmebaseret kognitiv computer-træning hos børn og unge med ADHD. Effekten af kognitiv træning blev undersøgt i to randomiserede og kontrollerede kliniske forsøg med fokus på effekten på specifikke kognitive funktioner, symptomer og funktionsniveau.

Design:

Forsøg 1: I et pilotforsøg blev 18 unge med ADHD randomiseret til 7-ugers kognitiv træning eller aktiv placebobehandling.

Forsøg 2: I det efterfølgende forsøg blev 70 børn med ADHD randomiseret til intervention med ACTIVATE™, der træner flere kognitive funktioner, eller sædvanlig behandling. Udfaldsmål blev uret indt inden og efter 8 ugers intervention og 12 og 24 ugers efter interventionens afslutning.

Resultater: I pilotforsøget med unge med ADHD fandt vi, at interventionen var anvendeligt hjemmefra, men at de unge ikke oplevede den som særlig interessant eller værdifuld. Der var ingen signifikante gruppe-forskelle på kognitive og ADHD symptomsmål efter interventionen. Pre-post intra-gruppe målinger viste, at interventionsgruppen havde en signifikant, gavnlig effekt på vedvarende opmærksomhed, mens den aktive placebo, udviste signifikante forskelle i forhold til arbejdshukommelsen.

I det andet forsøg sammenlignede vi virkningen af et computer program som var rettet mod flere kognitive funktioner, ACTIVATE™, med den sædvanlige behandling for børn med ADHD. Der var ingen signifikante forskelle på vores primære eller sekundære resultatmål, hvilket indikerer ingen effekt på vedvarende opmærksomhed, ADHD symptomer eller forældrenes og lærernes vurdering af eksekutive funktioner. I vores eksplorative analyse fandt vi en signifikant forskel på et objektivi mål for planlægningsvnen. Derudover fandt vi nogle interessante effekter på subgruppe niveau i forhold til børnenes alder, ADHD subtype og antallet af gennemførte træningssessioner.

Konklusion: I vores to forsøg fandt vi ingen gavnlige virkninger af kognitiv træning for børn og unge med ADHD. Vores resultater peger dog på, at visse undergrupper af børn med ADHD, såsom de ældre og de med ADHD uopmærksom type, måske kan drage større fordele af kognitiv træning end andre. Endvidere bør nye studier også undersøge effekten af kognitiv træning på planlægningsvnen. Disse hypoteser bør testes i fremtidige forsøg.

Introduction and Background

Attention deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by symptoms of inattention and/or hyperactivity, and impulsivity. A diagnosis of ADHD commands the presence of a number of symptoms, depending on which diagnostic system is used. In research and in the United States, the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)[1] is widely used, while the International Classification of Diseases, 10th Revision (ICD-10) [2] is used widely in Europe and the rest of the world. To fulfill an ADHD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition -Text Revision (DSM-IV-TR)[3], the patient must show at least six out of nine inattention or six out of nine hyperactivity/impulsivity symptoms or six symptoms each from both categories for at least six months. The symptoms are required to be disruptive and inappropriate for the child's developmental stage, at a maladaptive level, and presented in two or more settings involving clinically significant impairment in social, academic, or occupational functioning [3]. Additionally, it is required that some of these symptoms were apparent before the age of seven. If the symptoms occur exclusively in connection with autism spectrum disorder, schizophrenia or another psychotic disorder, or if they are caused by another mental disorder, ADHD cannot be diagnosed according to the DSM-IV-TR [3]. In the DSM-IV-TR, three subtypes of ADHD are defined, depending on which category of symptoms is fulfilled: a) Combined Type (ADHD-C) requires the presence of at least six inattentive and also six hyperactive-impulsive symptoms; b) Predominantly Inattentive Type (ADHD-I) requires at least six inattentive, but less than six hyperactive-impulsive symptoms; and c) Predominantly Hyperactive-Impulsive Type (ADHD-H) requires at least six sufficiently hyperactive-impulsive symptoms, but under six inattentive symptoms. In case, that not all criteria are fully met, ADHD Not Otherwise Specified (ADHD-NOS) is an option in the DSM-IV-TR.

The current version of the DSM, the DSM-5, was introduced in 2013, some time after we started enrolment of our participants. Hence, the DSM-IV-TR criteria are used in this dissertation. The most important changes in the DSM-5 compared with the DSM-IV-TR are that age of onset has been increased to 12 years, the number of required symptoms has been reduced to five for individuals above age 17, and there is no requirement that symptoms cause functional impairment in two or more settings. Additionally, the requirement of clinical

impairment has been changed to interference with or quality reduction in social, academic, or occupational functioning. Pervasive developmental disorder is no longer an exclusion criterion for the diagnosis of ADHD. The ADHD subtypes are renamed to presentations, and the DSM-5 requires a specification of the severity level of ADHD as Mild, Moderate, or Severe. ADHD-NOS is now called Other Specified ADHD and Unspecified ADHD [4].

The term ADHD is not used in the ICD-10, where the diagnosis is called Hyperkinetic Disorder, Disturbance of Activity and Attention (F90.0)[2]. The diagnosis is similar to that of ADHD, but the ICD-10 requires the presence of all clusters of symptoms: inattentive, hyperactive, and impulsive, so that it is most equivalent to an ADHD-combined type according to the DSM-IV-TR. In the ICD-10, the ADHD-Inattentive subtype is often diagnosed as Inattention Without Hyperactivity (F98.8C). Compared with the DSM-5, the ICD-10 is somewhat more restrictive in requiring the symptoms to be present before the age of six years. Except requiring that the symptoms are present in at least two settings, like home and school, the ICD-10 also requires that the symptoms are observable at the clinic.

ADHD is one of the most prevalent psychiatric conditions in child and adolescent psychiatry with an estimated prevalence of approximately 5% [5-7]. A description of attention disorders resembling what we today know as ADHD is mentioned for the first time in a medical textbook from 1775 by the German physician Melchior Adam Weikard [8]. In 1798 the English physician Crichton added that this disorder was often heritable [9]. Both Weikard and Crichton noted that the disorder usually had its debut in childhood and that it persisted into adulthood only in some cases. However, a later description by George Still of “an abnormal defect of moral control in children” has been cited as the first discovery of ADHD for decades [10]. After an epidemic of meningitis in 1918/19, many children developed behaviors similar to those described by Stills, and the disorder was named Minimal Brain Damage, which was changed in the 1960s to Minimal Brain Dysfunction [11]. In 1968, the DSM-II introduced the diagnosis Hyperkinetic Reaction of Childhood (HRC) [12], which was understood within a psychodynamic frame as a reaction to a dysfunctional environment. In 1980 the DSM-III renamed the diagnosis into Attention Deficit Disorder (ADD) [13], as the earlier descriptions relied only on the hyperkinetic symptoms, but not on the inattentive ones. With the revision of the DSM-III in 1987, the diagnosis Undifferentiated Attention Deficit Disorder was introduced for the diagnosis without

hyperactivity [14]. Finally, the ADHD diagnosis was introduced in 1994 with the DSM-IV [15]. In Denmark, Hyperkinetic Disorder was introduced with the ICD-10.

Etiology of ADHD

The etiology of ADHD is still unknown, but it is likely to be the result of a complex interaction between multiple genes and environmental risk factors [16]. The etiology and underlying pathophysiology of the disorder is probably not the same for all individuals with ADHD [17]. ADHD is a highly heritable disorder with a mean heritability estimate of 76% across 20 twin studies [18]. Molecular genetic studies show a complex picture of ADHD and were not able to identify genes with moderately large effects. Although several genome-wide scans studies have identified a number of chromosomes likely to be involved in ADHD, no genome-wide significant associations were found [19]. A number of meta-analyses identified an association between ADHD and several candidate genes coding for dopamine receptor subtypes D4 and D5, DA beta-hydroxylase, the synaptosomal-associated protein 25, the serotonin transporter, and the serotonin 1B receptor, indicating that specific genetic factors are involved in the etiology of ADHD [18].

The genetic risk factors are interacting with a number of environmental factors. A number of pre- and perinatal risk factors have been identified including maternal smoking [20] and to some extent also psychosocial stress [21], maternal alcohol consumption [22], maternal exposure to lead [20], maternal iodine deficiency [23], and birthday in September indicating a possible effect of a maternal seasonal viral infection in the first trimester [24]. Perinatal factors include preterm birth and low birth weight [25], young age of the mother, Cesarean delivery [26], and oxygen deficiency at birth [27]. Among postnatal factors, ADHD is associated with iron deficiency [28, 29] and a number of viral and bacterial infections [30].

ADHD at the neurobiological level

Empirical studies shown structural and functional abnormalities in the brain of individuals with ADHD [31-33]. ADHD is also considered to be a neurodevelopmental¹ disorder affecting the organization and configuration of neural circuits [35].

Structural studies

There is evidence of a global brain volumetric reduction in subjects with ADHD. A meta-analysis of structural findings found that a number of brain structures are reduced in volume: the posterior inferior cerebellar vermis, the splenium of the corpus callosum, the right caudate, and the total and right side cerebral volume are most decreased [36]. As the medical status was not recorded in a number of studies, it remains unknown which role medication for ADHD plays in these deficits. In a longitudinal 5-year study comparing 163 children with ADHD (8.9 years) and 166 controls, Shaw et al. [37] found that children with ADHD had a global thinning of the cortex (mean reduction -0.09mm, $p=.02$), most prominently in the medial and prefrontal regions. The children with a worse 5-year outcome showed stable, decreased cortical thickness in the left medial prefrontal and cingulate cortex at baseline probably affecting attention. Children with a better outcome showed normalization of the right parietal cortex, which may be compensatory. These deficits can partly be caused by delayed cortical brain maturation expressed as reaching the peak cortical thickness [38]. There is evidence for a mean delay of approximately 3 years of brain maturation in subjects with ADHD compared with typically developing children; and in some parts of the brain, like the middle prefrontal cortex, the delay is around 5 years [39]. These delays mostly affect prefrontal regions thought to be important for control of cognitive processes including attention and motor planning [31]. Additionally the brain maturation trajectories seem to be heterogenic across children with ADHD. Children diagnosed with ADHD in childhood do not always fulfill the diagnosis in adolescence [40]. Adolescents, with remitting as well as persisting childhood ADHD, show deficits in perceptual sensitivity and response variability and fidgetiness, which suggest an enduring subcortical impairment, whereas executive function deficits are only characteristic in persisting childhood

¹ Neurodevelopmental disorders are a group of disorders in which the development of the central nervous system is disturbed. This can include developmental brain dysfunction, which can manifest as neuropsychiatric problems or impaired motor function, learning, language or non-verbal communication (34).

ADHD relative to controls. These findings may suggest a maturation-related process of recovery in the prefrontal cortex in some children [40]. Future research has to uncover if this may be due to arbitrary heterogeneity or distinct, but overlapping subgroups.

Functional studies

Functional cerebral dysfunctions are usually determined with the help of functional Magnetic Resonance Imaging (fMRI) by observing cerebral activation patterns in regions of interest while participants are engaged in a particular task, often a test of cognitive functions like e.g. working memory or response inhibition. In line with the heterogenic structural findings in the brains of individuals with ADHD described previously, there is evidence of functional problems in multiple neural systems. A meta-analysis of 16 fMRI studies found significant hypoactivity² in the following regions of the brain: anterior cingulate, dorsolateral prefrontal, and inferior prefrontal cortices, as well as related regions including basal ganglia, thalamus, and portions of parietal cortex [41]. These findings indicate a possible primacy of deficits in frontal-based neural circuitry in ADHD. However, these conclusions are not warranted as the included studies predominantly used tasks designed to isolate executive processes, which are supported by fronto-striatal and fronto-parietal neural networks.

A subsequent meta-analysis of 55 fMRI studies found that individuals with ADHD exhibited hypo- and hyperactivation patterns different from those typically developing in controls and that these activation patterns differed between children and adults with ADHD [42]. Hypoactivation in children was predominantly seen in systems involved in executive function (frontoparietal network) and attention (ventral attentional network), while the frontoparietal system was most affected in adults. Hyperactivation of certain brain areas, thought to reflect compensatory mechanisms of the brain, were evident in the default, ventral attention, and somatomotor networks of children and in the visual, dorsal attention, and default networks in adults [42]. Thus, fMRI studies show dysfunctions in brain regions belonging to multiple neuronal networks involved in higher-level cognitive and sensorimotor functions [42].

² Hypoactivity is referring to abnormally diminished or decreased activity.

Cognitive deficits in ADHD

As individuals with ADHD exhibit a wide range of structural and functional deficits, they are also characterized by prominent, heterogenic cognitive impairments to varying degrees [43]. A number of different cognitive functions are impaired in individuals with ADHD, but the most prominent and consistent differences in impairments are seen in response inhibition, working memory, planning, and vigilance (see Table 1.) [44, 45]. The marked impairment of several of these functions has led to proposals that some of these deficits may qualify as endophenotypes for ADHD [46]. Endophenotypes are measurable, quantitative traits intermediate between gene function and behavior, which are influenced by one or more susceptibility genes [46]. The cognitive functions that have received most attention in ADHD research will be described in detail in the following:

Table 1 Cognitive tasks reviewed by Nigg (2005) and Willcutt et al. (2005)

Nigg (2005)		Willcutt et al. (2005)	
Spatial working memory	1.14 to 0.75	Spatial working memory	0,63
Response suppression (Stop Task)	0.94 to 0.61	Stop task	0,61
Signal detection (CPT)	0,72	CPT omissions	0,64
		CPT commissions	0,51
Stroop naming speed	0,69		
Full scale IQ	0,61		
Set shifting (Trials B)	0.55 to 0.75	Trials B	0,55
Planning (Tower tasks)	0.51 to 0.69	Tower of London	0,51
		Tower of Hanoi	0,69
Mazes	0,58	Porteus Mazes	0,58
Verbal working memory	0,51 to 0,41	Verbal working memory	0,55
Fluency	0,27		
Decision speed (Go task)	0,49		
WCST perseverations	0.36 to 0.53	WCST perservations	0,46
		R-O copying (Organization)	0,43
Stroop interference	0,25		
Covert VP orienting	0,2		

Note: Impairment in different cognitive functions in individuals with ADHD as compared with typical developing individuals: results from two reviews. Numbers represent effect sizes that are defined as the difference between the ADHD and non-ADHD controls, expressed in standard deviation units (Reprinted from Swanson, Baler & Volkow, 2011)[47].

Attention

Clinical observations of deficits in attention are an essential part of the diagnostic criteria of ADHD (e.g. poor attending to details, sustaining attention, and ignoring extraneous) and are also seen in cognitive performance tests. Attention is thought of as the appropriate allocation of processing resources to relevant stimuli [48]. Posner and colleagues [49, 50] proposed three attention networks, that are different but related: 1) alerting, involved in acquiring and maintaining readiness to react; 2) orienting, involved in orienting attention to sensory stimuli; and 3) executive attention, involved in conflict resolution. Evidence from behavioral, neurobiological, and genetic data supports this triadic framework [51]. These three interrelated attention networks can be individually assessed and measured and are enabling the acquisition of skills in other areas with other neural networks that depend on these skills [52]. When comparing individuals with ADHD with typically developing controls, the most impaired attention process is vigilance/sustained attention where effect sizes are moderate to large [44, 45]. Selective attention, attention switching, and processing speed are impaired, but effect sizes are mostly moderate [38, 53-55]. These functions are also associated with the executive control system [56-59].

Executive functions

The term executive functions is an umbrella term referring to higher-order processes allowing goal-directed behavior and adaptive responses to novel environment. Executive functions have been suggested as one of the prime candidates for endophenotypes. It has been proposed that ADHD symptoms may arise from a primary deficit in executive functions [60]. Executive functions incorporate a number of cognitive functions like the ability to plan, response inhibition, working memory, set shifting, abstraction, organization, aspects of attention, and fluency and the effect sizes of many of these executive functions were reported to be moderate to large in two large meta-analysis (see Table 1.) [44, 46].

Working memory

Working memory is considered an executive function by some [61] and has been defined by Baddeley [62] (p.556) as “a brain system that provides temporary storage and manipulation of the information necessary for...complex cognitive tasks”. The most influential working memory model is a three-component system proposed by Baddeley and Hitch [62, 63]. The core part of

working memory is a control system called the central executive component, which enables subjects to focus and to divide their attention between concurrent tasks. The central executive component has limited attentional capacity and is controlling and manipulating the information held in two anatomically distinct, short-term memory stores: the visual sketchpad and the phonological loop, both storing visual and auditory information, respectively. The central executive component is also called the working component of working memory and it has no memory/ storage functions itself. When the remembered information exceeds the capacity of the two temporary storage components, the central executive component provides support [63]. The working memory model has been expanded with reference to a fourth component, an episodic buffer [64]. The episodic buffer refers to a separate storage system of limited capacity linking working memory to long term-memory, enabling the integration of information into complex multi-modal representations. Working memory is impaired with medium to large effect sizes (Table 1.) in children with ADHD. Specifically, large impairments are evident in the central executive component [65] and these impairments seem to be functionally associated with inattention [66].

Response inhibition

Response inhibition refers to the ability to withhold a pre-potent response to a stimulus and it is impaired with moderate to large effect sizes in individuals with ADHD. Response inhibition is also a part of the diagnostic criteria referred to as impulsivity and it has been proposed for a possible ADHD endophenotype [67]. Generally, the existence of ADHD endophenotypes is negated by several strains of evidence: When comparing individuals with ADHD with typically developing controls, the differences in executive functions are much smaller ($d = .46-.69$) than the differences in ADHD symptoms ($d = 2.5-4.0$) between these two groups. Children with ADHD display significant impairment in executive functions compared with typically developed controls as a group; but only 50% of the individuals exhibit significant impairment at the individual level [68, 69]. Correlations between ADHD symptoms and executive functions are significant, but with small effect sizes [70], and no evidence supports the hypothesis that impairments in executive function contribute to the etiology of ADHD or are a sufficient characteristic of the disorder [44, 45].

Reaction time variability

Variability in reaction time, defined as moment-to-moment fluctuation in task performance and inconsistency in individual speed of responding, is another cognitive function that has been considered a possible stable core feature of ADHD. It has been indicated that children with ADHD are slower and more inconsistent in their responses. A meta-analysis [71] evaluated 319 studies of reaction time and concluded that children and adolescents with ADHD exhibit large variability in reaction time with almost large magnitude effect size (Hedges' $g=0.76$) when compared to typical developing children. Reaction time impairments are somewhat smaller in adults ($g=0.46$) than in children. However, individuals with ADHD do not show slower processing speed after accounting for reaction time variability, which indicates that they can be described as displaying much inter-individual variability, but not as slower than controls. This variability is primarily rooted in a subset of abnormally slow responses, and it is not due to continuous inconsistency throughout a single task. The meta-analysis by Kofler et al. [71] found no significant differences when adolescents and adults were compared with other clinical groups; only children with ADHD were minimally more variable than clinical control children ($g=0.25$). Variability in reaction time is a stable feature of ADHD, but it is not specific to the disorder and cannot be used as a diagnostic marker [71].

Summary

Cognitive deficits are prevalent and marking features of ADHD. Recent years have seen a shift in the literature from a focus on a single core deficit theory in the frontal lobe functions in ADHD to multiple deficit theories. Although many cognitive functions are affected, a specific ADHD cognitive profile cannot be identified [43]; and no laboratory or clinical measure has so far been devised with sufficient predictive power to diagnose ADHD [72, 73].

Functional outcomes in ADHD

ADHD is a lifelong disorder and has been shown to severely impair academic performance and psychosocial functioning [74, 75]. ADHD is associated with a range of adverse outcomes in life like school drop-out [75, 76], increased risk of other psychiatric disorders [77-

79), substance abuse [80, 81], criminality [82, 83], adverse health events [84], and premature death [85].

Cognitive functions are also associated with functional outcomes. Thus, compared with children without ADHD, children with ADHD and associated executive dysfunctions are more likely to have poorer academic outcomes and they are more likely to have need for tutoring, and to be placed in special classes or to discontinue education [86]. Also attention ability has been identified as an important predictor of academic success [87]. An abundance of literature on other psychiatric populations shows that cognitive dysfunctions are strongly related to the ability to cope in everyday life (functional outcome), and the training of cognitive functions can have an effect both on cognition and on long-term functioning [88, 89].

Pharmacological treatment and cognitive functions

Stimulant medication is the first-line evidence-based treatment for ADHD. It has a positive effect on symptoms with large effect sizes [90, 91]. However, stimulant medication treatment is not a cure as the effect is short-termed and the symptoms return immediately after treatment discontinuation [92]. Although effective in the majority of affected individuals, pharmacological treatment is associated with inadequate compliance [93], parental reluctance towards long-term drug treatment of children [94, 95], and adverse side effects [96-98]. Moreover, the mechanisms behind partial or no response to pharmacological treatment [99] and its long-term effects are both understudied and relatively unknown [100]. The longest follow-up study to date (n=579), the Multimodal Treatment of ADHD study (MTA) [101], was investigating four different treatment combinations and showed that pharmacological treatment was superior to behavioral treatment for children with ADHD over a period of 14 months. Pharmacological treatment had a superior effect on behavior and cognition (test of achievement on reading and math), but the clinically optimal dose varied across individuals and 20% needed an increased dose to maintain full efficacy. All significant differences dissipated already after 3 years and were no longer significant [102]. In a prospective observational follow-up study no significant differences could be longer observed and only 32.5% of the participants were taking medication after 8 years [100].

Several studies indicate that many individuals with ADHD continue to have a certain degree of difficulty with cognitive functions despite receiving optimal pharmacological treatment [103, 104]. In a meta-analysis of 40 randomized trials, Pietrzak et al. [105] found that pharmacological treatment had a positive effect on cognition in 63.5% of subjects, while an improvement in divided attention and working memory was present only in 50% of trials. An investigation of the effect of methylphenidate on cognition in 75 drug-naïve boys showed a significant improvement of some tasks without a major executive function component like complex reaction time, spatial recognition memory reaction time, and delayed matching to sample [104]. Methylphenidate had no effect on executive functions including inhibition, working memory, strategy formation, planning, and set shifting. At four weeks, follow-up showed a significant behavioral response to medication and additional, significant effects on visual memory tests, but not on the executive function tests, except the Go-NoGo task [106].

It can be concluded that pharmacological treatment is very effective for treating the core symptoms of ADHD, but its impact on cognition, particularly executive functions, is limited [104-106]. Considering the shortcomings and inadequate compliance characterizing pharmacological treatments, parental reluctance to choose pharmacological treatment, and the disappointing long-term effects, there is a genuine need for other treatment options in ADHD. As described above, ADHD is associated with many evident deficits at the structural and functional levels of the brain, showing a delay of maturation in children with ADHD. These deficits are also associated with cognitive functions. Because cognition is strongly associated with every-day functioning / functional outcome, there would seem to be ample grounds for exploration of cognitive training as a treatment option complementary to the current pharmacological treatment regimens. Cognitive training has been tested in relation to cognitive deficits in other psychiatric disorders, for example psychosis [88].

Cognitive training in ADHD

Cognitive training consists of repeated exercises that target specific cognitive processes. The aim of such training is to improve cognitive functions that are deficient in a particular population or an individual. Cognitive training is typically delivered in a computerized format. As described in the previous chapter, ADHD is considered to be a disorder involving heterogenic cognitive and

neurological dysfunctions. Attempts have been made to improve these dysfunctions using external stimulation, i.e. cognitive training, based on the theory of neuroplasticity. Cognitive training programs rest on two main assumptions: First, that executive functions and/or related attentional processes are significantly underdeveloped or impaired in children with ADHD; and, second, that the maturation and/or efficiency of the neural circuits of executive functions can be enhanced by training and practice [107].

Neuroplasticity

Cognitive training is historically rooted in cognitive rehabilitation and it is based on the concept that direct training can induce reorganization of neural functions. The concept of neuroplasticity refers to changes in neural structure and functions due to experience and environmental impact. Neuroplasticity allows the central nervous system to learn new skills, remember information, and reorganize neural networks in response to external stimulation [108]. The basic mechanisms involved are neurogenesis, programmed cell death, and activity-dependent synaptic plasticity. Childhood is a period during which the brain's anatomical structure and synaptic connections undergoes profound change. A child's brain is more susceptible to the environmental impact than the adult's brain due to increased plasticity [108]. Thus, injuries and certain diseases are overcome by children faster and easier than by adults. Several studies indicate that the brain's maximum plasticity in respect of overcoming some diseases is probably reached within the first 7 years of life [109]. In addition, musicians, who started playing before the age of 7, show major structural brain changes compared with those who started after this age [110]. This age appears to be a critical time window; and music training after this period seems not to have as strong or lasting effects on anatomical representations [110]. Although brain plasticity is assumed to be at its peak in childhood, the potential is assumed to be life-long. An fMRI study of young healthy adults shows that training with a working memory task resulted in an increased brain activity in the dorsolateral prefrontal and parietal association cortex, indicating plasticity of the neural system [111]. These cortical areas are overlapping the prefrontal regions, which are implicated in the pathology of ADHD [112, 113]. It seems that cognitive training has an effect on neural structures. Hoekzema et al. [114] found that 10 days of combined attention and executive functions training (45min/day) enhanced activity in neural structures closely related to ADHD pathology. An fMRI paradigm of

response inhibition task showed increases in the orbitofrontal, the superior frontal, and the middle temporal and inferior frontal cortex, while an fMRI paradigm for a selective attention task showed increased activity in the cerebellum correlating with improvement in scanner measures of attention [114]. The same kind of training also increases focal volumetric gray matter in the bilateral middle frontal cortex and the right inferior-posterior cerebellum [115]. These structures are often associated with volumetric reduction in ADHD, and the inferior posterior cerebellum is associated with progressive volume loss [115]. Cognitive training has also been shown to induce neurochemical changes at the synapse level in dopamine function after training [116]. These are preliminary indications that cognitive training possibly has an effect on some of the neuroanatomical deficits associated with the disorder.

Focus of cognitive training interventions

Several different cognitive training programs have been developed with the overarching aim of improving some of the deficient cognitive functions in ADHD considered to be most important. The aims of cognitive training are two-fold. One aim is to target functions inherent in the training task; another is to attempt to generalize from the trained function/s to the untrained ones, which is called transfer effect. Near transfer is demonstrated using tests that measure the trained construct, e.g. working memory, with one or several tests that do not resemble the task/s embedded in the cognitive training program. Near transfer is necessary to ensure that any improvement ascertained is associated with the training and not with task-specific factors due to practice or expectancy effects. Near transfer also helps validate the mechanisms responsible for potential transfer to distal transfer cognitive and behavioral outcomes [117]. Demonstrating far transfer is the most important objective in cognitive training, implicating, that successfully trained cognitive functions may have spillover effects to other, related cognitive functions, symptoms and functional outcomes. The improvement in far transfer depends on the degree of near transfer change and on how much the far transfer outcome is dependent on the trained functions [118].

A number of trials investigating cognitive training in ADHD have been conducted over the past 15 years. The field of cognitive training is very complex and diverse in terms of the focus and duration of interventions, the outcome measures used, the methodological design of the

trials, and the subsequent results. Cognitive training interventions can be divided into two large fields: attention training and executive functions training. Although the term executive functions, as previously described, encompasses a range of cognitive functions, the vast majority of studies focus solely on working memory. The different focus areas and some of the most influential trials will be outlined in the following. Thereafter the results of a number of narrative and systematic reviews and meta-analyses on cognitive training will be discussed.

Attention training

A number of trials have focused on training different aspects of attention assuming that training attention does not strengthen only the attention network itself but may also transfer to other cognitive skills and academic outcomes. Studies have focused on different aspects of attention training like alerting attention [119, 120], orienting attention [121], or combined aspects of attention [122-124]. Computerized progressive attention training in children with ADHD resulted in a significant improvement in trained and untrained attention and vigilance [121, 125, 126], i.e. non-trained measures of school performance, and in a significant reduction in parents' and teachers' observation of inattention [121, 125, 127]. Steiner et al. [119] found a significant improvement of inattentive, behavior, and ratings of executive functions. Tamm et al. [122] found significant effects of attention training on verbal working memory, inhibition, and attention.

Working memory training

Several research groups have studied working memory training, predominantly with the computer program Cogmed, invented and marketed by Klingberg and colleagues [128]. Cogmed consists of games focusing on remembering positions on a grid and replicating the grid. In their first study, Klingberg et al. [128] found that training of working memory improved problem solving / executive functions (working memory, response inhibition, and reasoning) in ADHD children, and they found far transfer effects to non-verbal intelligence tests (Raven) and inhibitory control tests (Stroop) [128]. In their second randomized, double-blind trial with 53 non-medicated children with ADHD, Klingberg et al. [129] found substantial effects of computerized working memory training on both parent-rated symptoms, such as inattention and response inhibition, and visuospatial working memory. These changes were maintained 3

months after completed training. These two trials were some of the first and most influential in the ADHD cognitive training field, and they set off an avalanche of trials focusing on working memory training. Subsequent trials could only partially confirm the results of the two Klingberg studies, which both had a pro-profit bias [130].

Beck et al. [131] (n=52) found significant improvements in parents' ratings of attention, number of ADHD symptoms, BRIEF initiative, planning/organization, and working memory; and teacher ratings on the initiative scale BRIEF were sustained at the 4-month follow-up. Two other studies found significant effects of working memory training on verbal and visual working memory and generalization effect on inhibition and attention measures [132, 133]. Remarkably, Green et al. [134] found significant improvements in task attention as measured by independent raters. However, several studies were not able to replicate these results and reported negative results [134-136]. Holmes et al. [130] found differential effects of medication and cognitive training on working memory, albeit in an uncontrolled study. Medical treatment enhanced visuo-spatial working memory significantly, whereas cognitive training led to significant changes in four working memory domains (verbal and visuo-spatial working and verbal and visuo-spatial short-term memory). The effect could be maintained in three domains for 6 months.

Broader executive functions

Less attention has been devoted to combined working memory and response inhibition training. Two such studies [137] found a significant reduction of the symptoms described by a significant other person (not a parent), and significant behavior changes in a larger group of children with ADHD [138]. In addition, there was significant improvement in spatial working memory, ignoring distracting stimuli, and sustained attention in the treatment group compared with the waiting list as rated by a parent and another adult [138]. Improvements were maintained 6 weeks after training.

To date, only two trials have explored the effects of cognitive training focusing on broader executive functions, both using the program "Braingame Brian" training visuospatial working memory, response inhibition, and cognitive flexibility [139, 140]. Van der Oord [140] found an effect on parent-rated executive functions compared with the waiting list control condition,

while Dosis et al. [139] found significant differences on measures of visuospatial short-term and working memory, inhibitory performance, and interference control as compared with active placebo.

In conclusion, evidence from cognitive training trials is somewhat mixed, and the results are strongly influenced by the methodology used, ranging from open trials to double-blind, active placebo trials. In the past couple of years, several systematic reviews and meta-analyses have been published on this subject, which has given us a clearer picture of the impact of cognitive training. These results will be presented in the following.

Meta-analysis and systematic reviews

Mixed populations, including ADHD

To date a number of meta-analyses [107, 141-144] and reviews [117, 145-147] have investigated the near and far transfer effects of cognitive training. As working memory training has been the primary focus of much of this research, it has also been the main focus of the first systematic reviews and meta-analyses. Because the number of studies with children with ADHD is rather small, the first systematic reviews focused on different diagnostic populations involving children, adolescents and adults, with and without pathology (ADHD, learning disabilities, cochlear implants, low working memory). Two such reviews reached positive conclusions on cognitive training [148, 149], but were both based on the same three studies with children with ADHD of which only two were randomized and controlled [128, 129]. Shipstead et al. [117] reviewed 11 studies of working memory training in different populations, six of which involved children with ADHD, but only three were randomized and controlled [128, 129, 131]. Shipstead et al. [117] adopted a more critical approach and concluded that working memory training could improve performance only on tasks that closely resembled the training task itself, indicating that this effect could be a reflection of task-specific experience and not an instance of near transfer. Additionally, no far transfer effects were seen on increased intelligence, improved focus, and attentional control, or on relief from ADHD [117] as claimed by the studies. Even though several studies reported far transfer to attentional control using the Stroop task, these conclusions were not warranted according to Shipstead et al. [117] as these studies measured attention using only incongruent trials from the Stroop task; but when congruent trials are excluded from the

analysis, working memory no longer predicts performance on the Stroop task. A subsequent meta-analysis [142] examined 23 studies involving children, adolescents, and adults with and without psychopathology, but again only two studies involving children with ADHD [128, 129], was in agreement with those conclusions. The meta-analysis [142] concluded that working memory training programs appear to produce short-term effects in verbal and visuospatial working memory tasks. The near transfer could not be sustained in the follow-up and specific training effects did not generalize to far transfer tasks [142]. Wass and colleagues [150] explored the relation between cognitive training, targeting working memory, or “mixed attention” (including one or more cognitive domains like sustained attention, selective attention, task switching, and inhibition). Also, they included a mixed sample with a wide age range (11 months to 96 years) with only four randomized, controlled studies including children with ADHD. They concluded that cognitive training is more effective for younger than for older individuals, and that the effect is stronger for working memory training than for mixed attention training. A newer review entitled “Cogmed WM Training: Reviewing the Reviews ” challenges the described results obtained by Melby-Lervåg [142] and Shipstead [117]. It should be noticed that this review, which has a more positive perspective on working memory training, was conducted by authors who are all affiliated with Pearson, the company that now owns and markets Cogmed [146].

A recent meta-analysis [144] looked exclusively on attention training across 15 studies with three different populations (ADHD, individuals with learning difficulties, and typically developing individuals) including adults. For the six studies of children with ADHD, the results showed that attention training improved attention significantly within a moderate range (Hedges $g=.52$). The effect was stronger for the ADHD population alone than for the ADHD population combined with individuals with learning disability and typically developing controls across ages (Hedges $g=.25$), and the effects of training significantly transferred to non-trained tasks (academic and cognitive skills) (Hedges $g=.24$). This meta-analysis also implied that the training was more effective when it was adaptive for younger individuals, and also more effective when targeting the orienting attention network.

It is difficult to make any specific conclusions about the effect of cognitive training on children based on the described reviews and meta-analyses because they include diverse

samples of disorders and also typically developing individuals, and because the age range studied is wide, including adults. As different psychopathologies have different etiological and neurobiological bases, these psychopathologies may also have very different neuroplasticity potential for improvement. Overall, there were very few randomized, controlled trials with children with ADHD included in the described reviews. Most of the meta-analysis and reviews were involving the two original Klingberg studies [128, 129], which had a pro-profit bias and why the conclusions of the reviews and any statements about their impact on children with ADHD are difficult to interpret. An interesting aspect of these early reviews is the emerging issue discussed between the authors whether working memory training, especially in Cogmed, is truly targeting the concept of working memory and if it has any impact on working memory. Several authors [107, 145] propose that working memory interventions, in reality, target short-term and not working memory, because their focus lies primarily on the short-term memory storage and rehearsal abilities with a minimal impact on the central executive component. These authors therefore consider these interventions short-term memory training. Adopting the criterion that working memory training should target the central executive component, it is argued that none of the reviewed studies targeted working memory. This is problematic in relation to the theoretical background of cognitive training, as short-term memory is not related to the majority of behavioral and functional outcomes in ADHD [151]. Additionally, most studies measured working memory with simple span tasks that in reality measure short-term memory. Simple span tasks often contain a series of verbal items (numbers or letters) or spatial objects (locations on a grid) that have to be reproduced in the same order [117]. If simple span tasks, like remembering a list of numbers, are presented forwards, but required reproduced backwards, then they can only measure working memory for younger children [152], but not for adults [153].

Children with ADHD

The first meta-analysis of cognitive training focusing solely on randomized controlled trials with children with ADHD was published in 2013 [143] and resulted in an analysis of only six out of 25 cognitive training studies published, three trials on working memory and three on attention training, all but one including probably blinded assessments. However, this meta-analysis was specifically interested in the effects of cognitive training on parent and teacher

ratings and did not calculate effect sizes on objective cognitive test. This approach is somewhat problematic as near and far transfer is more objectively measured by cognitive tests, while parents and teacher ratings are usually only partially blind and therefore probably biased. Sonuga-Barke et al. [143] concluded that significant treatment effects with moderate effect sizes (SMD=0.64, 95% CI=0.33-0.95) were observed when using the most proximal assessors, typically parents' assessments, who were not blind to the allocation and were invested in treatment. These effects were not longer significant (SMD=0.24, 95% CI=-0.24-0.72) when only probably blinded assessments were analyzed, typically teachers' assessments. This effect remained unaltered when the analysis was restricted to the three no- or low medication trials (standardized mean difference=0.26; 95% CI=-0.08, 0.60).

Sonuga-Barke et al. [143] mentioned that the effects of treatment may be inflated and thus biased by the status of the rater (blind or not) and that more evidence from blinded trials is required. This might be true; however, it is also important to acknowledge that parents and teachers tend to differ substantially in their perception of the child's symptoms when it comes to ratings of ADHD [154]. Parents' and teachers' ratings show only weak correlations for inattention and moderate correlations for hyperactivity/impulsivity symptoms, which are constant across child development paths over time [154]. Thus, the conclusion that the strength of effect is dependent only upon the probable blindness of the assessor is not sufficient to account for the differences.

Chacko et al. [147] investigated the effects of Cogmed in children and adolescents with ADHD (n=7) and reported mixed findings with some trials showing improvements in neuropsychological outcomes and parent-rated ADHD symptoms, while others did not. One trial found a significant result on a 15-min observation of behavior during an academic task by independent raters, but parent-rated ADHD symptoms did not reflect this change. However, these studies were all based on small samples; and Chacko et al. [147] concluded that cognitive training could be defined as a possibly efficacious treatment for youth with ADHD.

Other investigators [107] included a large sample of 20 randomized, controlled and five uncontrolled trials with children and adolescents with ADHD. Rapport et al. [107] found significant effects of short-term memory training on short-term memory with moderate effect

sizes ($d=0.63$). Three studies reported follow-up data and suggested that short-term memory training is associated with medium-magnitude improvements in non-trained tasks of working memory and that these tasks could be maintained across 3 to 6 months of follow-up, whereas attention training or mixed executive functions (mostly combined inhibition and short-term memory) or set-shifting training did not significantly improve the targeted functions. There was only one study of sustained and selective attention training that showed large near transfer effects [121]. Far transfer effects of cognitive training on academic functioning and blinded ratings of behavior were non-significant. Unblinded raters ($d=0.48$) reported significantly larger benefits than blinded raters, $p<.05$, indicating the likelihood of Hawthorne effects. However, far transfer effects on cognitive test were evident in 11 studies with small, but significant effects. A considerable weakness of this meta-analysis was the inclusion of uncontrolled studies and pooling across design types, why the results are difficult to interpret. Rapport et al. [107] agreed with Shipstead [117] that working memory training interventions in reality target short-term memory and that none of the studies analyzed targeted working memory. Rapport et al. [107] argued that there was a general incongruence in cognitive training interventions by not targeting the most significant, evidence-based cognitive impairments, like working memory, which are related to the behavioral and academic outcomes in ADHD.

The most comprehensive and largest meta-analysis to date [141] included 16 randomized controlled trials and investigated effects on a range of symptoms, cognitive functions, and academic outcomes. Overall, the results were strongest for total ADHD scores (standardized mean difference (SMD) = 0.37, 95% CI = 0.09-0.66), inattentive symptoms (SMD=0.47, 95% CI = 0.14-0.80), and ratings of executive functions with BRIEF (SMD=0.35, 95% CI = 0.08-0.61) when rated by individuals closest to the treatment setting, i.e. typically parents. The results from raters, who were probably blinded to participant allocation, were somewhat smaller for total ADHD scores (SMD= 0.20, 95% CI = 0.01-0.40) and inattentive symptoms (SMD= 0.32, 95% CI = -0.01-0.66). There were no significant effects on ratings of hyperactivity/impulsivity symptoms. Effects on objective cognitive outcome measures were significant for laboratory test of verbal working memory (SMD=0.52, 95% CI = 0.24-0.80) and visual working memory (SMD=0.47, 95% CI = 0.23-0.70). In accordance with the previous reviews and meta-analysis, Cortese and colleagues (2015) concluded that there were no effects of far transfer of working memory training on ADHD symptoms. On the other hand, interventions targeting a broad range of

cognitive functions had large effects on ADHD symptoms as rated by most proximal assessors (SMD=0.79, 95% CI = 0.46-1.12).

As described in the present chapter, a substantial number of systematic reviews and meta-analysis has been conducted on a relatively small number of good quality studies. This large number of systematic reviews and meta-analyses also reflects the controversy surrounding cognitive training. Working memory training has been heavily commercially marketed, initiated by the findings of large effects of the first studies of Cogmed [128, 129]. The literature indicates consensus on the issue of working memory training primarily having an effect on short term/working memory tasks, but far transfers to other cognitive functions or symptoms are generally not observed. Training of attention and a broader range of executive functions seem to offer more promising results; also considering that ADHD is not a single core deficit disorder, but rather a heterogenic disorder involving a broad range of cognitive deficits, which makes it interesting to explore the effects of the training of broader cognitive functions.

More recent studies of cognitive training

To address the studies that have not been covered since the last meta-analysis was performed, we conducted a search from the date of Cortese et al. (2015) search on 18 May 2014 to 12 May 2016 in the PsychInfo database using the same search terms as Cortese et al. [141] and Sonuga-Barke et al. [143]: cognitive training, attention training, working memory training, cognitive remediation, executive function training, and cognitive control and ADHD, attention deficit, and hyperkinetic disorder. The search was limited to children and adolescents, randomized controlled trials, and English language. We identified 107 studies of which 100 were excluded because they were not about cognitive training. Additionally, two studies of cognitive training were excluded because one was in Chinese [155] and another one in Dutch [156] ; thus, five relevant controlled and randomized studies remained.

Several new studies with larger sample sizes with children with ADHD have been performed with Cogmed. Van der Donk et al. [157] randomized 102 children (8 -12 years) to Cogmed or combined working memory- and executive-function-compensatory training called 'Paying Attention in Class.' with a 6-month follow-up. They observed only one treatment effect on visual spatial working memory favoring Cogmed, but none on other cognitive functions, academic

performance, ratings of behavior in class, behavior problems, and quality of life. Pre-post changes were found in each group for broad neurocognitive measures and parent and teacher ratings. Another study of working memory training, not CogMed [158], found no significant differences in any cognitive measures for 28 children receiving 25 sessions of working memory training over 6 weeks compared with a placebo program.

One study investigated an intervention consisting of a combination of visuospatial working memory, response inhibition, and cognitive flexibility training in a double-blind, placebo-controlled trial with three groups [139]; 1) the intervention group: trained all three aspects of cognitive functions, 2) a partly-active-condition: trained response inhibition and cognitive flexibility, but not working memory, which was in a placebo mode and 3) a full placebo-controlled condition. Only children in the full-active condition showed improvement on measures of visuospatial short-term and working memory. Inhibitory performance and interference control (response inhibition) improved only in the fully active condition and in the partially-active-condition. There was no impact on cognitive flexibility, verbal short-term and working memory, non-verbal complex reasoning or child-rated psychosocial health; nor for any parent or teacher-rated ADHD symptoms, BRIEF, motivational behaviors, or general problem behaviors.

Two studies investigated the effect of cognitive training as a part of a larger multifaceted intervention. Steeger et al. [159] combined Cogmed working memory training with behavioral parent training and randomized 91 adolescents and their mothers to one of four possible combinations of active and placebo Cogmed and active and placebo parent training for 5 weeks. Adolescents in both active Cogmed groups achieved higher backwards-working memory spans than did adolescent in the Cogmed control groups. No combined treatment effects were obtained with the active Cogmed and active parent training together. Combined treatment effects showed the greatest improvement on parent ratings for the group using active parent training and placebo Cogmed as compared with the three other groups for working memory deficit, behavioral regulation, and global executive deficit. There was no evidence that Cogmed either singly or in combination with behavioral parent training affected any domain of functioning. Also, Smith et al. [160] tested a multifaceted intervention program, the Integrated Brain, Body, and Social (IBBS) intervention. In a randomized, controlled trial, children with ADHD

or subthreshold ADHD used cognitive training in combination with behavior and physical training compared to treatment as usual (TAU). The results showed no significant differences between groups after the combined intervention on ADHD symptoms ratings by trained clinical assessors blinded to treatment condition, teachers or parents.

Consistent with the meta-analytic and review results, working memory training seems to have an impact on working/short-term memory, but not on other cognitive functions or behavioral or academic domains. Only few studies to date have investigated the effects of broader cognitive training on cognition, symptoms, and functional outcome, making it difficult to draw conclusions on their effects.

Aims and hypothesis:

As children and adolescents with ADHD have multiple cognitive dysfunctions, we hypothesized that computer programs targeting several cognitive function may have better impact on cognition and generalization to symptoms than interventions only targeting one single cognitive function. To investigate this hypothesis, we have conducted two trials in order to examine the effects of broader cognitive training on cognition and symptoms in children and adolescents with ADHD.

1. In the first trial we have examined the feasibility and efficacy of computerized cognitive exercises from Scientific Brain Training (SBT), compared to the computer game Tetris as an active placebo, in adolescents (age 14-17) with ADHD.
2. In the second trial we have investigated the effect of ACTIVATE™, a cognitive computer training program targeting multiple cognitive functions on cognitive functions, symptoms and functional outcome in children (age 6-13) with ADHD.

Methods

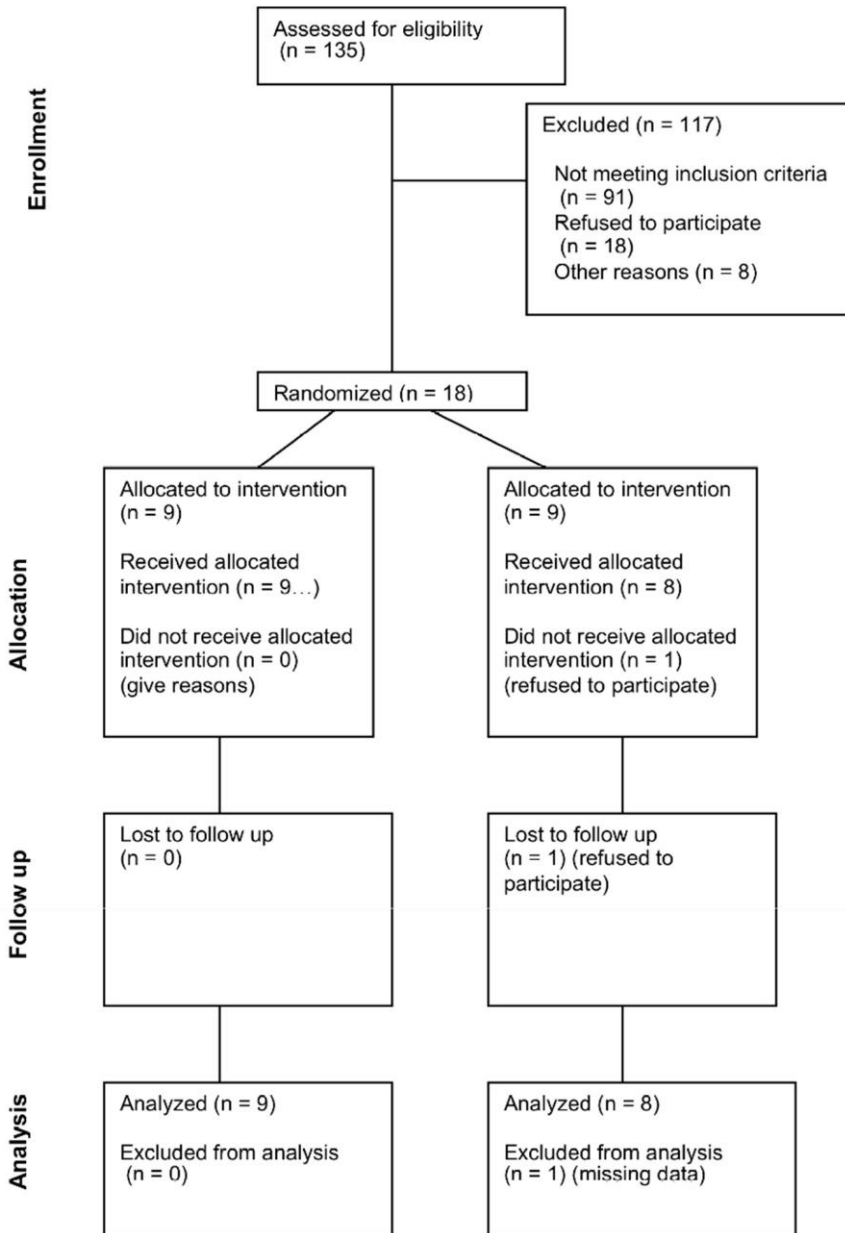
Study 1.

Setting and Sample

We recruited participants from the child and adolescent psychiatric department Augustenborg in the Region of Southern Denmark, in September 2010. The trial was conducted from October to December 2010. Participants were considered eligible for the trial if following inclusion criteria were fulfilled: 1) a clinical diagnosis of hyperkinetic disorder according to ICD-10 (F90.0, corresponding to ADHD combined type) [2]; 2) age between 14-17 years; 3) intelligence quotient (IQ) > 80. The exclusion criteria were: 1) pharmacological treatment other than methylphenidate, dexamphetamine and/or atomoxetine; 2) comorbid conduct disorder, autism spectrum disorders or major depression; 3) history of head trauma or verified neurological disease; 4) motor or perceptual disabilities which prevented the use of a computer; 5) medical illness that required treatment; and 6) no access to a computer and internet at home.

In Denmark clinical psychiatric assessments are performed using ICD-10 criteria [2]. We only included adolescents with the most narrow definition of Hyperkinetic Disorder (F90.0), which is a valid proxy for ADHD combined type in DSM-IV-TR [161, 162]. We identified 135 adolescents with ADHD in the clinic database, of which 91 were excluded due to exclusion criteria after a screening of case records. We sent information letters to the eligible 44 participants and their parents. Eighteen families provided written informed consent. Participants were all Caucasian with a mean age of 15.6 years (standard deviation (SD)=0.99) and 76.5 % were boys. All participants had a clinically estimated IQ with Wechsler Intelligence Scale for Children (WISC)-IV [163] higher than or equal to 80. The flow of participant inclusion can be seen in Figure 1.

Figure 1: CONSORT flow diagram



Legend for Figure 1: This chart shows the flow and number of adolescents with ADHD eligible, excluded, randomized, lost to follow-up and analyzed in trial 1

Measures

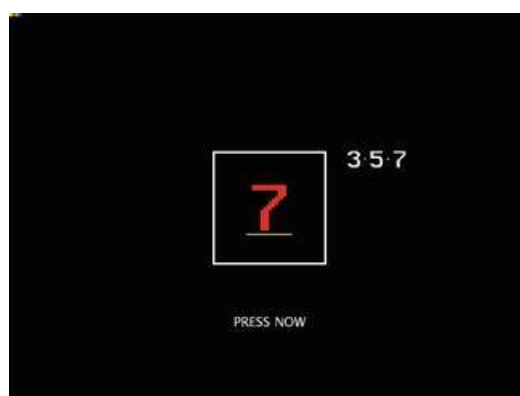
All participants were tested by a psychologist blind to group allocation with Cambridge Neuropsychological Test Automated Battery (CANTAB) [164, 165] before randomization and within one week after ended intervention. Parents, participants and teachers completed the Attention Deficit/ Hyperactivity Disorder-Rating Scale (ADHD-RS) [166] before randomization and a second time after seven weeks of intervention. Participants also filled out the Activity Perception Questionnaire (APQ) at the end of the intervention period [167] which was used to determine the feasibility of the treatment. APQ is measuring motivation, the perceived meaningfulness and value of the intervention. Parents asked the teachers to fill out the ADHD-RS questionnaire and they brought them back to the last appointment.

Cognitive functions were assessed with a number of tests from the CANTAB, a non-verbal computerized cognitive test battery with solid psychometric properties [164, 168, 169]. We choose a number of cognitive tests investigating those cognitive functions that we expected to be likely to be affected by the intervention. Prior to the use of the other tests, we used the Motor Screening Task (MOT) to screen for visual, movement and comprehension difficulties. In addition we used the Big/Little Circle (BLC) test to assess the participants' comprehension, learning and reversal.

Attention tests:

Rapid Visual Information Processing (RVP)(A' and probability of hit) is a test of sustained attention (similar to the Continuous Performance Task) (see Figure 2).

Figure 2: Rapid Visual Information Processing (RVP)

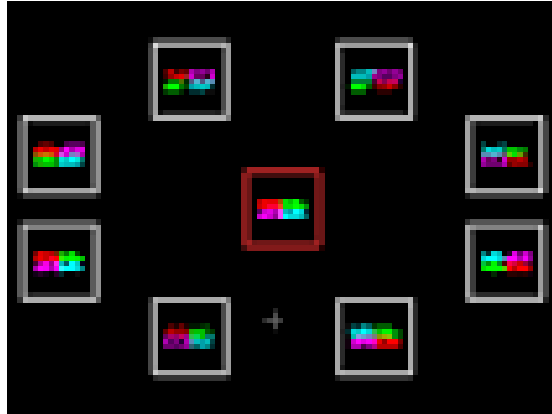


Legend for Figure 2: The task is to press the button each time the number 7 appears following the numbers 3 and 5 in a row.

Match to Sample Visual Search (MTS) (percent correct) is a matching test, with a speed/accuracy trade-off (se Figure 3). It is a simultaneous visual search task with response latency

dissociated from movement time. Efficient performance on this task requires the ability to search among the targets and ignore the similar distractor patterns.

Figure 3: Match to Sample Visual Search (MTS)



Legend for Figure 3: The task is to find the figure, which is identical with the figure in the middle and press it as quickly as possible.

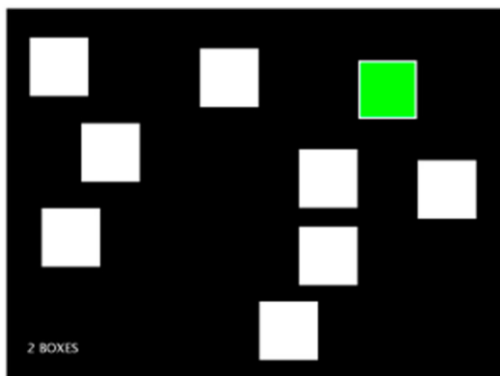
Visual memory:

DMS Delayed Matching to Sample (DMS) assesses forced choice recognition memory for novel, not verbalized patterns, and tests both simultaneous and short-term visual memory. It looks identical with figure 3., but the task is to look at all figures and remember them. Later on, only the figure in the middle is shown and the task is to find the identical, hidden figure.

Executive functions:

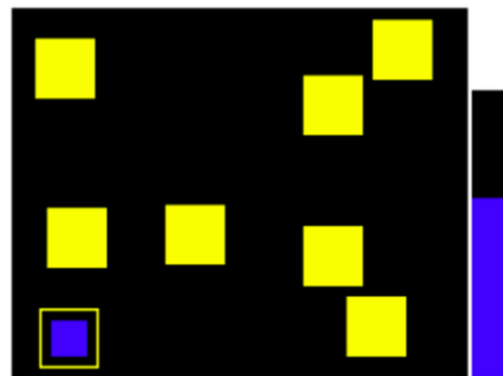
Spatial Span (SSP) (Span Length) assesses working memory capacity, and is a visuo-spatial analogue of the Digit Span test (see Figure 4). Spatial Working Memory (SWM) (between errors and strategy) is a test of the ability to retain spatial information and to manipulate remembered items in working memory.

Figure 4: Spatial Span (SSP)



Legend for Figure 4: The order of the green boxes lightening up has to be remembered and reproduced.

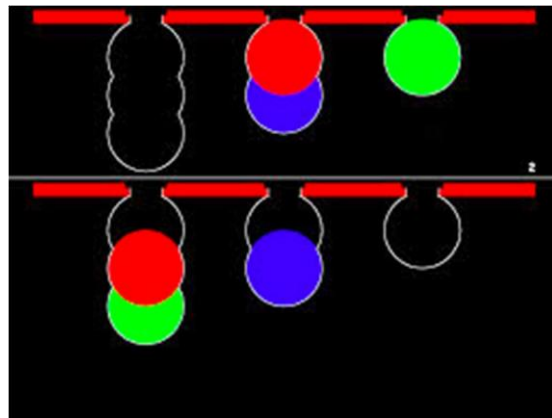
Figure 5: Spatial Working Memory (SWM)



Legend for Figure 5: The task is to find the blue box inside the yellow box without revisiting boxes.

Stockings of Cambridge (SOC) (problems solved in minimum moves) is a spatial planning test. The time used to complete the pattern and the number of moves required to master the task, are taken as measures of the user's planning ability.

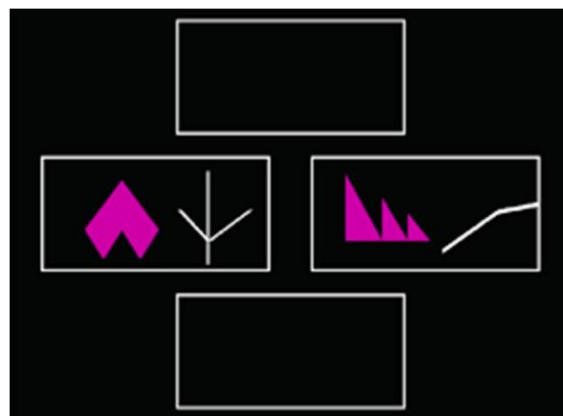
Figure 6: Stockings of Cambridge (SOC)



Legend for Figure 6: The task is to move the balls in the first row in minimum moves possible with the intent to reproduce the second row.

Intra-Extra Dimensional Set Shift (IED) (stages completed) is a test of rule acquisition and reversal. It features visual discrimination, attention set formation maintenance, shifting and flexibility of attention. This test is a computerized analogue of the Wisconsin Card Sorting test.

Figure 7: Intra-Extra Dimensional Set Shift (IED)



Legend for Figure 7: The task is to figure out the rule (choosing the right figure) and keep choosing it until the rule changes, thereafter the new rule has to be figured out.

Questionnaires:

Furthermore we wished to investigate the feasibility and the effect of intervention on ADHD-symptoms and used following rating scales: 1) Feasibility was measured by the Activity Perception Questionnaire (APQ) that measures different dimensions in a computer-related activity [167]: a) Interest (did you like the training, was it interesting); b) Value (was it useful to do the training) and c) Choice (was it your own choice to play). APQ consists of 25 questions that are rated on a Likert scale

from 1 to 7 (1 corresponds to “not true at all”, 4 corresponds to “somewhat true” and 7 corresponds to “very true”). 2) ADHD-Rating Scale (RS) is a 26-item symptom rating scale, comprising nine items on inattentiveness, nine items on hyperactivity/ impulsive behavior and eight questions on oppositional behavior [170]. ADHD-RS has been widely used in research and clinics and has been shown to be sensitive to changes induced by pharmacological treatment [171, 172].

Intervention

SBT Exercises.

A number of beta-exercises from Scientific Brain Training (SBT)-program [173], which is a commercially available program for adults was applied in the intervention group. We selected six out of nine cognitive exercises available at that time. The three exercises were excluded, as they were not considered age-appropriate. The following SBT exercises were used: Entangled Figures, Shapes and Colors, Under Pressure, Displaced Characters, Heraldry and Objects Where are You? All games included different difficulty levels and were adaptive to individual performance. Promotion to the next level occurred after 90 % accuracy three times in a row at one level. Accuracy under 60 % twice in a row implied returning to the previous level. Each week all participants played two selected games in a rotating manner.

Following exercises were used: 1) Entangled figures is targeting visual and spatial skills and working memory. The task is to identify and memorize characteristics of an object and then to transform the details into a whole. 2) Shapes and Colors is focusing on attention to detail, visual short-term memory and discrimination. The goal is to memorize several figures of various shapes and colors and then recognize them among similar figures. 3) Under Pressure targets sustained attention and vigilance. Three types of stimuli (a red circle, a black cross, and a letter) appear consecutively at different spots, anywhere on the screen. The aim is to decide quickly whether the red circle appears above or below the black cross. 4) Displaced Characters is addressing visual discrimination among visual shapes. After observing carefully figures in one list, the task is to find figures in a second list that do not appear in the first list. At the beginning of the task, both lists can be directly compared at the same screen and at later stages, they are on separate screens and the figures need to be remembered. 5) Heraldry is targeting sustained attention, visual and spatial memory and perception. First a coat of arms with all the elements that make up the heraldry has to be memorized, thus paying attention to shapes, colors, and patterns to distinguish between various details. The task is then to recreate the coat of arms with all its components. 6) Objects, Where are You? is targeting visual and spatial memory and perception. The task is to memorize the location of different pictures on a grid, and then recall them in the same spot.

Control intervention: Tetris.

The control group played a traditional version of the game Tetris. The goal of Tetris is to manipulate the function of game pieces called Tetriminos, built of four-square blocks as they fall down randomly into the playing field. Tetriminos can be manipulated by moving each one sideways and rotating by 90-degree units. The aim is to create a horizontal line of ten blocks without gaps, which then disappears, and the blocks above the deleted line fall down. Progress to a higher level requires that a certain number of lines is cleared. At each following level the Tetriminos fall faster, and the game ends when the stack of game pieces reaches the top of the playing field closing the possibility for new Tetriminos to enter. The version of Tetris that we used was non-adaptive so that the participants had to start on the lowest level each day.

Procedures

In this double-blinded trial 18 participants were randomized to either active intervention with SBT exercises or Tetris. For the randomization each participant was assigned a number, which was sealed and then chosen from envelope by a blind clinician unrelated to the trial. Participants were told that we expected one of the two treatments to be more effective than the other. Both groups were introduced to their assigned computer game at the clinic. All participants got an individual username and password in order to access the allocated computer game at a secure online web-based platform, designed for this trial. The interventions required the participants to play at home for half an hour a day, five days a week for seven weeks. Compliance was measured through registration of each login for both groups. The SBT homepage automatically closed down the program after 30 min of active playing. The amount of time spent and progress on games was only registered for the SBT group. In the control group participants and their parents used a timer to control for time. All participants and their parents received a daily text message reminder to their cell phone. Additionally the principal investigator contacted the parents and participants once a week to discuss compliance or possible problems.

Statistical Analyses

The intervention and placebo groups were compared before and after treatment using t-test and repeated measures analysis of variance (ANOVA) when the outcomes of interest were normally distributed, and non-parametric Wilcoxon-Mann-Whitney test otherwise. APQ scores were tested using two-sample t test with equal variances. Intra group correlations were measured using one-way ANOVA when the outcome of interest was normally distributed. The non-parametric version was used in case when the outcome of interest was not normally distributed (Friedman test). The

participant who dropped out of the trial was excluded from the statistical analysis. The level of significance was set at $\alpha > 0.05$ in all analyses, that were carried out using statistical program Stata version 11 [174].

Ethical Approval and Consent to participate

The trial was conducted in accordance to the Declaration of Helsinki and was approved by the Danish Data Protection Agency (2010-41-4970) and the Regional Scientific Ethical Committee for Southern Denmark (S-20100075). The written consent was obtained from all participants and their guardians prior to their participation in this trial.

Study 2:

Methods

Objectives

The primary objective of this trial was to investigate whether computer training with the computer program ACTIVATE™ (<http://denmarkstudy2.c8sciences.com/?language=da>) has a positive effect on specific cognitive functions. ACTIVATE™ was chosen because it targets a number of cognitive functions. The secondary objectives were to investigate a possible effect on ADHD symptoms and executive functions ratings. Furthermore our exploratory objectives were to investigate possible effects 12 and 24 weeks after the training and to investigate whether younger children benefit more from training than older children.

Trial sites

Participants were recruited from three sites in Southern Denmark: Child Psychiatric Departments Aabenraa (including Augustenborg), Kolding and Odense from January 2013 to October 2015. One site (Odense) is part of a university hospital and all three sites are part of the same organization, i.e. the Region of Southern Denmark. Referral from the treating physician or school psychologists is required for assessment and treatment at the Psychiatric Departments. No children treated by privately practicing child and adolescent psychiatrist were included in the study. The participants enrollment was done consecutively throughout the calendar year, mostly during the school year. Only a few participants were enrolled during school vacations, but as the intervention is home-based, this was not likely to affect the adherence.

Assessments of eligibility

All children, who were newly referred with ADHD symptoms to one of the sites or were already in treatment with ADHD-medication, were invited to participate in the trial. We offered individual

information sessions, after which the legal guardians could decide regarding the participation. A total of 164 families provided informed consent and were invited to participate in the assessment. The diagnostic assessment was done in a 2-step model: In Step 1 parents, a teacher and children over 11 years of age, completed an online questionnaire, including the Strength and Difficulties Questionnaire (SDQ) [175, 176] in conjunction with the psychiatric diagnostic interview Development and Well-being Assessment (DAWBA). DAWBA is a valid hybrid between a structured and a semi-structured interview for the diagnosis of child and adolescent psychiatric disorders according to both ICD-10 and DSM-IV [176, 177]. DAWBA's sensitivity is 92% in a clinical sample and specificity 89% for all psychiatric diagnoses in a community sample [177]. The DSM-IV criteria for ADHD, conduct disorder, autism spectrum disorder, depression and schizophrenia were assessed for this trial. DAWBA was filled out by the parent (s), by the child if older than 11 years and in the majority of cases also a teacher. If parents failed to complete the DAWBA online within 10 days of invitation, they were contacted and reminded to do so by the principal investigator. Of 164 invited families 122 participated in the DAWBA interview, which was then rated by one of two medical doctors (residents for child and adolescent psychiatry), trained as clinical DAWBA-raters. To ensure a high inter-rater reliability, the first 10 interviews assessed by each rater were also assessed blindly by a child psychiatrist (S. Dalsgaard), who has extensive clinical experience and was trained as a clinical DAWBA-rater by the developer of the instrument, Professor Robert Goodman. Overall, the inter-rater-reliability test showed a high composite agreement percentage of 87.5% (95% CI 60.4-97.8%) and an overall Cohen's Kappa of 0.75. According to Landis & Koch [178] a value of 0.61-0.80 corresponds to a substantial agreement. Inconsistencies between ratings in these initial interviews were discussed and a consensus about diagnoses was reached.

Participants meeting full or sub-threshold criteria for an ADHD diagnosis in DAWBA (n=86) proceeded to Step 2 and were invited to a clinical interview by one of three trained psychologists, to confirm the ADHD diagnosis, using the ADHD section of the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) [179]. K-SADS is a semi-structured clinical interview of parents and is the most widely used psychometric instrument for the diagnostic investigation of children in clinical research. To ensure inter-rater reliability for the K-SADS, the first 10 cases of each of the three psychologists were videotaped and also rated by an experienced K-SADS rater (N. Bilenberg or A. Bikic). After the parent(s) completed the K-SADS interview, the intellectual level of participants was tested by a trained psychologist, using the Reynolds Intellectual Assessment Scales (RIAS) [180] to ensure that all participants had an IQ above 80. Finally, children were included in the trial, if they complied with the following inclusion and exclusion criteria:

Inclusion criteria

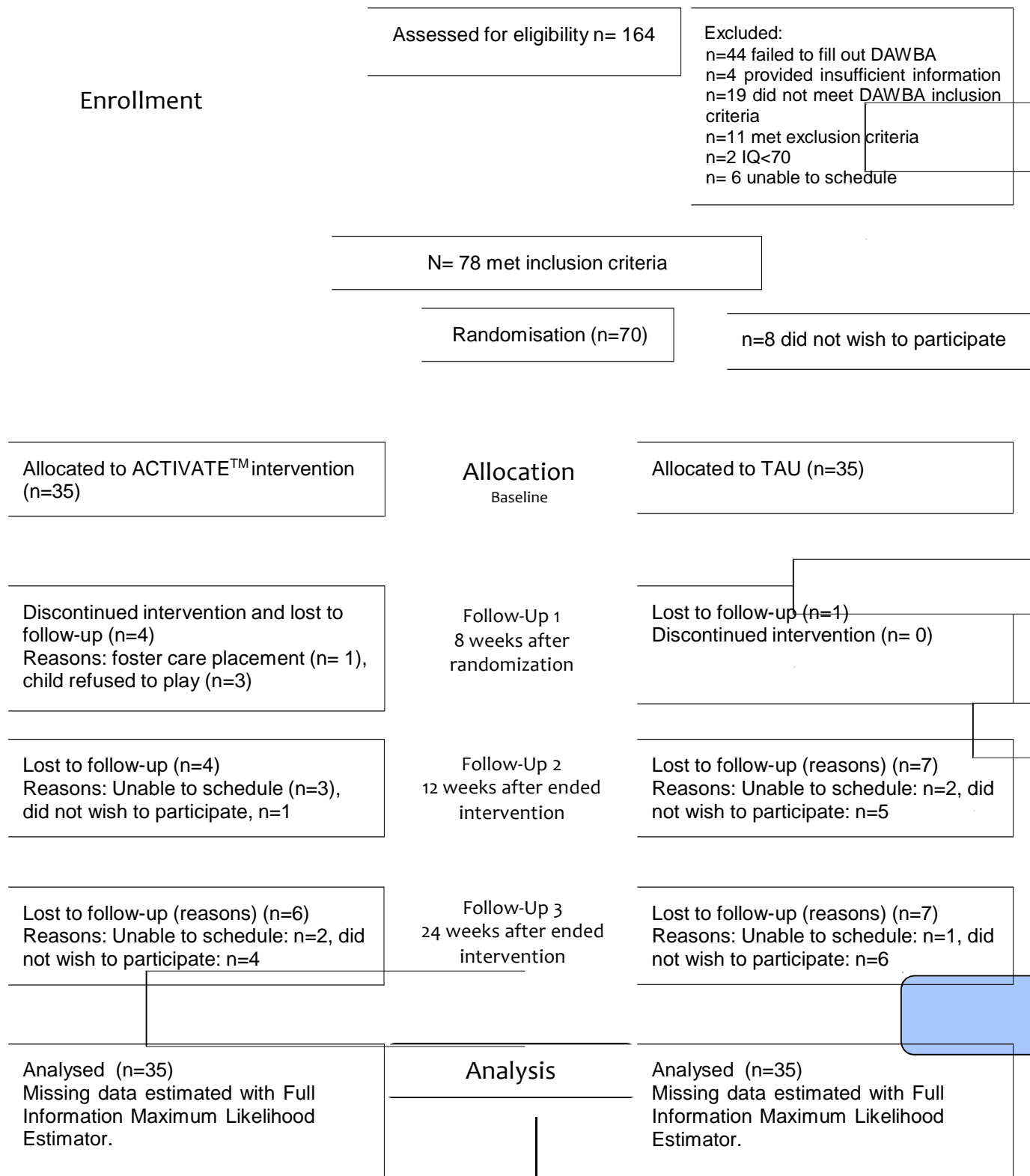
Following criteria were required for inclusion: ADHD diagnosis after DAWBA interview [177] and verification with clinical interview K-SADS, ADHD section parent interview [179]; age between 6-13 years, both inclusive; access to a computer and the internet; informed consent

Exclusion criteria

Following exclusion criteria were applied: comorbid conduct disorder, autism spectrum disorders, depression or schizophrenia; head injury or verified neurological disease; IQ <80; motor or perceptual handicaps preventing computer use; medical condition, requiring primary treatment, and no informed consent from custody.

Finally, 78 participants met the required criteria and were considered eligible for the trial. Eight families decided not to participate for various reasons (lack of time, change of mind, starting medication treatment, and/or family difficulties) hence 70 participants were randomized. Participants were informed not to change their medication status during the 8 weeks of intervention. Anyway two participants (one in each group) choose to start medication after randomization during the intervention period. They were, like all other participants in pharmacological treatment, required not to take their medication 24 hours prior to the cognitive test.

Figure 8: CONSORT 2010 Flow Diagram



Legend for Figure 8: This chart shows the flow and number of children with ADHD eligible, excluded, randomized, lost to follow-up and analyzed in trial 2.

Interventions

Both the intervention group and the control group received treatment as usual (TAU). TAU involved both clinical assessment and treatment. Clinical assessment at the three sites is typically involving anamnestic interviews with the parents, observations of the child at school and clinic, IQ and other cognitive testing, parents and teacher questionnaires about ADHD symptoms and executive functions. Treatment is involving advising of parents and teachers, network meetings, parent training and for some children medication. Parallel to the trial all of our participants underwent clinical assessment and/or treatment. The treating clinical specialist, who was unrelated to the trial, decided with the family on pharmacological treatment. All medicated trial participants were required not to change their medication during the intervention period.

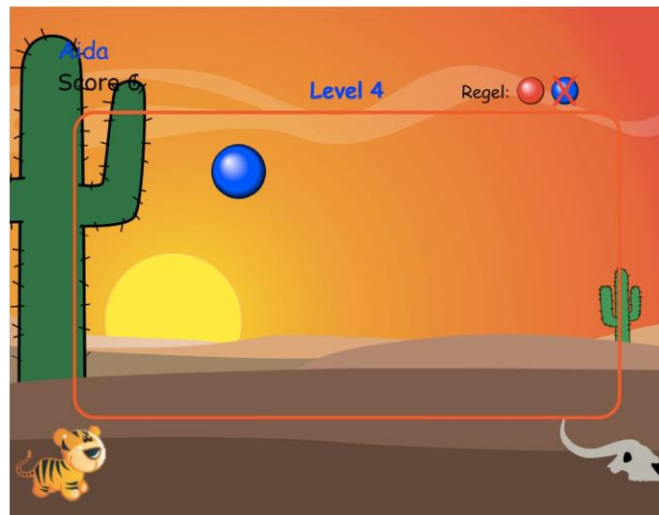
Intervention group

In addition to TAU the intervention group used the computer program ACTIVATE™ (<http://denmarkstudy2.c8sciences.com/?language=da>). ACTIVATE™ includes three engaging games that target following multiple cognitive functions simultaneously: sustained attention, working memory, speed of information processing, response inhibition, cognitive flexibility, category formation, pattern recognition and multiple simultaneous attention. Following three games are part of ACTIVATE™: 'Catch the Ball', 'Butterflies' and 'What Comes Next'.

1. Catch The Ball: The aim of this game is that the child uses the computer mouse to chase a moving ball on the screen (see Figure 8). The child has to put the arrow on the ball and click every time the ball turns red in order to catch the ball. Every time a child succeeds in catching the ball, the child is rewarded with a nice sound and points. If the child waits too long to click or clicks outside of the ball, s/he will miss the ball and the computer will make a different sound. In order to get as many points as possible, the child has to observe the ball constantly. The moving speed of the ball increases after a number of balls are caught. In case that the child misses some balls, the moving speed slows down and it becomes easier to catch them. The target – red balls or blue balls – keeps changing through the game. The rule is disclosed by an image of the ball in the top right corner of the screen. In the beginning the child has to catch only red or blue balls. At the higher levels of the game, the rules become more complicated. E.g. The child has to catch the ball, if it has the same color as the ball showed before it. At later stages the child has to catch a ball, if it is different color than the previous ball. The higher stages of the game involve monitoring two balls bouncing simultaneously and follow rules described before for both balls. Later on the child has to monitor three balls at the same time: red, blue and green, with the rule to catch the blue

and red, but never the green balls. 'Catch the ball' targets different cognitive functions at the same time: Sustained attention, response inhibition and cognitive flexibility. The cognitive load is increasing with the progress in the game and working memory and multiple simultaneous attention are targeted at the higher levels of the game.

Figure 9: Catch the Ball



Legend for Figure 9: Still picture of the game Catch the Ball from ACTIVATE™. The task is to follow the blue ball and click on it as soon as the color changes to red.

2. Butterflies: The aim of this game is to catch the butterflies flying across the screen and carrying cards including a number, a word or a picture on it (see Figure 10). At each stage there is a rule on which cards are the target, like e.g. containing a number or the name of a number. If a butterfly that is not a target is clicked on, it falls to the ground. The rules for the target keep changing through the game including letters of the alphabet, signs with pictures of animals, plants, furniture and things to bring when on a vacation. On higher stages the targets include different kinds of plants with an exception, like flowers. On later stages the targets include two different categories, e.g., the child first has to click on a picture of food, followed by a picture of clothing, going back and forth between the two. This game is mainly targeting the conceptualization of categories and sustained attention on all levels and targeting response inhibition and cognitive flexibility at certain levels.

Figure 10: Butterflies



Legend for Figure 10: Still picture of the game Butterflies from ACTIVATE™. The task is to click on the butterflies carrying certain cards before they fly away from the screen.

3. What Comes Next: This game targets mainly pattern recognition, cognitive flexibility and use of categories. Pictures of numbers or shapes creating a pattern are presented in the upper row with one empty space (see Figure 11). In the second row below the first pictures, numbers or shapes are presented. The task is to find the missing piece fitting best into the pattern in the upper row. The time limit for decision is shown in the upper right hand side of the screen. With a number of tasks solved, the time limit for the next questions gets shorter with three seconds being the shortest time. When a number of trials with three seconds limits are solved, the child progresses to the next level of the program. The faster the child responds, the more points can it earn.

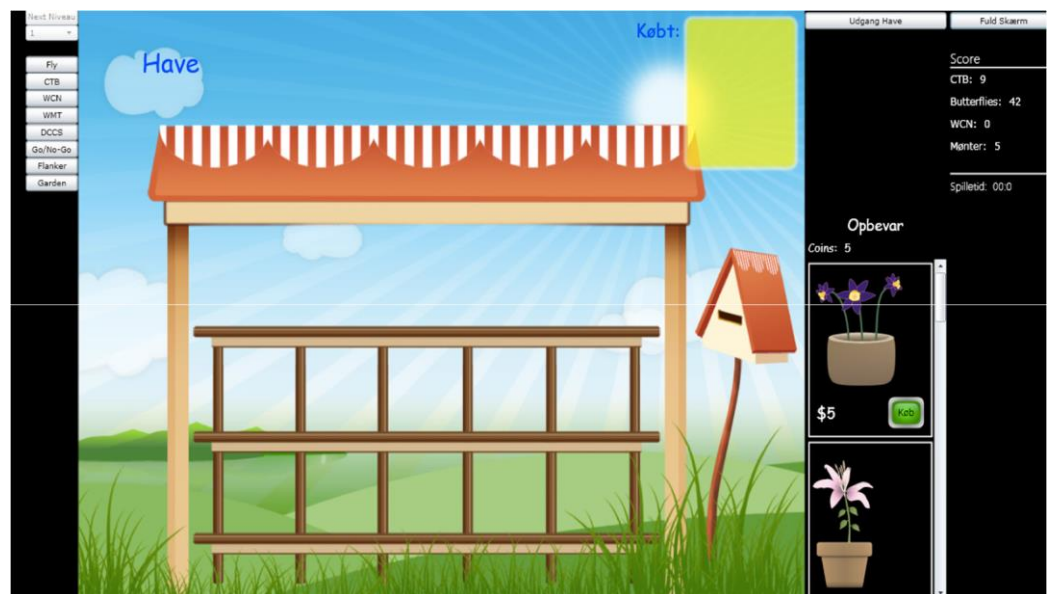
Figure 11: What Comes Next



Legend for Figure 10: Still picture of the game What comes Next from ACTIVATE™. The task is choose the figures from the second raw that fit the rule in the first row as quickly as possible.

In all three games the child is collecting points, which are converted into coins at the end of the daily session, where the child can purchase different things. The child can decide if it will buy things for a garden or to build a car, a zoo or a house. It is possible to purchase something after each session, but it is also possible to save coins to buy more expensive things later. The design of the games is intended to be interesting and rewarding for children. All participants are playing all three games, starting at the same very basic level. Progression and level of difficulty is depending on the individual performance and is dynamically adjusted during the trial, according to the abilities of each child.

Figure 12: Garden at the end of the game



Legend for Figure 12: Still picture of the Garden from ACTIVATE™. The points that have been collected during the game are converted into coins. Flowers and animals can be purchased for the garden.

The intervention with ACTIVATE™ is home-based training for 40 minutes per day, 6 days per week in 8 weeks, resulting in a cumulative training of a maximum of 32 hours. A number of parameters were registered on the online platform like every log on, time spent on task and progress. All participants in the intervention group are introduced to ACTIVATE™ at the clinic. Parents were given verbal and written instructions that the child should use a computer with an external mouse (not an iPad or a laptop with an integrated mousepad) and that the training should be performed in a quiet setting with headphones. In addition, the parents were instructed to help the child remember and engage in training and to supervise the child during training sessions, to ensure adherence. There were no restrictions on the time of the day to perform the training. We asked the parents to implement the sessions with minimal conflict with school or family schedules. Parents were offered to contact the principal investigator in case of any problems.

Control group

The control group received only TAU.

Procedures

This was a parallel, two arms, single blind, randomized and controlled trial. The eligible 70 participants were randomized 1:1 to the intervention or control group with stratification for site and medication status by the Copenhagen Trial Unit, an independent clinical intervention research unit in another city. The allocation sequence was computer-generated with a varying block size kept unknown to the investigators, and it was stratified by trial site ('Aabenraa', 'Kolding', or 'Odense') and use of medication ('yes' or 'no'). Allocation was performed by the investigator telephoning the Copenhagen Trial Unit, giving a personal PIN code as well as information about the participant (strata, participant ID number etc.), and the participant was then allocated one of the two groups.

After randomization, participants in the intervention group received an individual username and password by e-mail and used these to access the computer game at a secure online web-based platform, designed for this trial. Each log-on, progress on the games and time of playing was registered for all participants and these data were used to measure compliance in the intervention group. In the event of any technical problems, with the intervention, the parents (n=8) contacted the principal investigator by e-mail or phone, which then contacted IT-support.

Blinding

Due to the nature of the trial, it was not possible to blind the participants and their parents to group allocation. However, we employed blinding in all other possible areas. Investigators conducting the cognitive testing with CANTAB, were blind to the participants' group allocation. To reduce the risk of biasing the rating of outcomes caused by unblinding information on group allocation, we chose an objective computerized primary outcome measure on the CANTAB. The treating physicians were not directly connected to the trial and did not assess or provide information on any trial outcomes.

Outcomes

For an overview of all outcomes and assessments, please see table 1. All participating children were assessed with a series of cognitive test from the CANTAB test battery at four time points: T0=baseline; T1=after 8 weeks of intervention; T2=12 week follow up and T3= 24 week follow up after ended intervention. Each CANTAB assessment lasted between 70 and 90 minutes. While the child was assessed, parent questionnaire data were collected. If the child was unable to conduct the whole session at once, the assessment was split up. Participants were assessed at approximately the

same time of the day, at each visit and always between 8:30 a.m. and 2 p.m. to avoid time of day impacting cognitive functions. Children receiving pharmacological treatment were asked not to take their medication 24 hours prior to the cognitive testing. The parents were reminded to do so by a mobile phone text message. Timeline of assessments can be seen in Figure 13.

Primary outcome

The primary outcome was the sustained attention test from the CANTAB: 'RVP- probability of hit' (see Figure 2) assessed at the end of intervention. We choose this variable, as it was sensitive to change in our first trial. Furthermore this cognitive function is deficient in most children with ADHD our intervention ACTIVATE™ targeted sustained attention in all three games.

Secondary outcomes

The following secondary outcomes were assessed before and at the end of the intervention:

- Parent-rated ADHD symptoms assessed by ADHD-RS (parent edition) [181].
- Teacher-rated ADHD symptoms assessed by ADHD-RS (teacher edition) [181].
- Parent-rated behavior assessed by Behavior Rating Inventory of Executive Functions (BRIEF) (parent edition) [182].
- Teacher-rated behavior assessed by BRIEF (teacher-edition) [182].

We choose these measures for several reasons. They have shown good internal validity, sensitivity to change and they are widely used in both research and clinic [171, 172, 182]. Additionally the aim of cognitive training is to change cognitive functions and symptoms, why it is important to measure if the intervention has any perceived effect in the children's daily life. BRIEF has shown good internal consistency (Cronbach's alpha .80 to .98), high test-retest reliability for the clinical scales ($r=.81$ for parents and $r=.87$ for teachers) and moderate correlations between parents and teachers ratings ($r=.32$)[182]. BRIEF also shows moderate correlations with the ADHD-RS. For all outcome measures used in this trial please see Table 2.

Table 2: Outcomes and time points for assessment in the ACT trial

		Outcome type	Baseline (1 st clinic visit)	Baseline (2 nd clinic visit)	End of intervention	12 week follow up	24 week follow up	
Demographic and diagnostic variables	Age	Continuous	X					
	Sex	Dichotomous	X					
	DAWBA ¹	Continuous	X					
	K-SADS ²	Continuous	X					
	RIAS ³	Continuous	X					
	Pharmaceutical treatment at baseline	Dichotomous	X					
Primary outcome	CANTAB ⁴ -RVP ⁵ , probability of hit	Continuous		X	X	X	X	
Secondary outcomes	ADHD-RS ⁶ (parent-rated)	Continuous		X	X	X	X	
	ADHD-RS (teacher-rated)	Continuous		X	X	X	X	
	BRIEF ⁷ (parent-rated)	Continuous		X	X	X	X	
	BRIEF (teacher-rated)	Continuous		X	X	X	X	
Exploratory outcomes	CANTAB-AST ⁸	Continuous		X	X	X	X	
	CANTAB-MTS ⁹	Continuous		X	X	X	X	
	CANTAB-CRT ¹⁰	Continuous		X	X	X	X	
	CANTAB-SST ¹¹	Continuous		X	X	X	X	
	CANTAB-SWM ¹²	Continuous		X	X	X	X	
	CANTAB-SOC ¹³	Continuous		X	X	X	X	
	CANTAB-IED ¹⁴	Continuous		X	X	X	X	
	CANTAB-PAL ¹⁵	Continuous		X	X	X	X	
	BRIEF (Inhibit) (parent-rated)	Continuous		X	X	X	X	
	BRIEF (Shift) (parent-rated)	Continuous		X	X	X	X	
	BRIEF (Emotional Control) (parent-rated)	Continuous		X	X	X	X	
	BRIEF (Initiate) (parent-rated)	Continuous		X	X	X	X	
	BRIEF (Working Memory) (parent-rated)	Continuous		X	X	X	X	
	BRIEF (Plan/Organize) (parent-rated)	Continuous		X	X	X	X	
	BRIEF (Organization of Materials) (parent-rated)	Continuous		X	X	X	X	
	BRIEF (Monitor) (parent-rated)	Continuous		X	X	X	X	
	BRIEF (Inhibit) (teacher-rated)	Continuous		X	X	X	X	
	BRIEF (Shift) (teacher-rated)	Continuous		X	X	X	X	
	BRIEF (Emotional control) (teacher-rated)	Continuous		X	X	X	X	
	BRIEF (Initiate) (teacher-rated)	Continuous		X	X	X	X	
	BRIEF (Working Memory) (teacher-rated)	Continuous		X	X	X	X	
	BRIEF (Plan/Organize) (teacher-rated)	Continuous		X	X	X	X	
	BRIEF (Organization of Materials) (teacher-rated)	Continuous		X	X	X	X	
	BRIEF (Monitor) (teacher-rated)	Continuous		X	X	X	X	
	WFIRS-P ¹⁶	Continuous			X	X	X	X
	Non-serious adverse events	Dichotomous			X			
	Serious adverse events	Dichotomous			X			
	X	Baseline assessments						
	X	Assessment of primary outcome						
	X	Assessment of secondary outcomes						
X	Exploratory assessments of primary and secondary outcomes. Exploratory outcomes.							

Legend:

¹ Development and Well-being Assessment (DAWBA); ² Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS); ³ Reynolds Intellectual Assessment Scales (RIAS); ⁴Cambridge Automated Neurocognitive Test Battery (CANTAB); ⁵Rapid Visual Information Processing (RVP); ⁶Attention Attention Deficit-Hyperactivity Deficit-Rating Scale (ADHD-RS); ⁷ Behavior Rating Inventory of Executive Functions (BRIEF); ⁸ Switching Task (AST); ⁹Match to Sample (MTS); ¹⁰Choice Reaction Time (CRT); ¹¹ Stop Signal Task (SST); ¹²Spatial Working Memory (SWM); ¹³Stockings of Cambridge (SOC); ¹⁴Intra-Extra Dimensional Set Shift (IED); ¹⁵Paired Associates Learning (PAL); ¹⁶Weis's scale of disability-Parent Report (WFIRS-P).

Exploratory outcomes

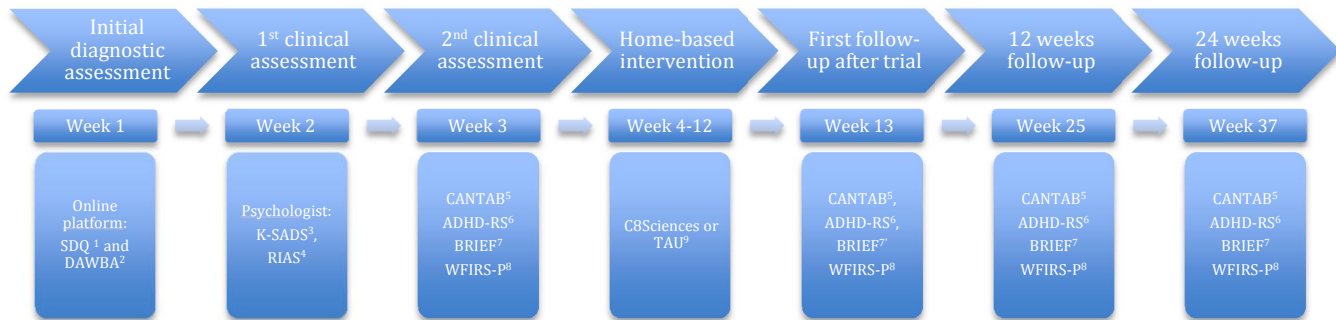
The following exploratory outcomes will be assessed at the end of the intervention:

- CANTAB Attention Switching Task (AST).
- CANTAB Match to Sample (MTS).
- CANTAB Reaction Time (RTI).
- CANTAB Stop Signal Task (SST).
- CANTAB Spatial Working Memory (SWM).
- CANTAB Stockings of Cambridge (SOC).
- CANTAB Intra-Extra Dimensional Set Shift (IED).
- CANTAB Paired Associates Learning (PAL).
- CANTAB RVP Probability of False Alarms
- CANTAB RVP Reaction Latency S.D
- BRIEF (Inhibit) (parent-rated).
- BRIEF (Shift) (parent-rated).
- BRIEF (Emotional Control) (parent-rated).
- BRIEF (Initiate) (parent-rated).
- BRIEF (Working Memory) (parent-rated).
- BRIEF (Plan/Organize) (parent-rated).
- BRIEF (Organization of Materials) (parent-rated).
- BRIEF (Monitor) (parent-rated).
- BRIEF (Inhibit) (teacher-rated).
- BRIEF (Shift) (teacher-rated).
- BRIEF (Emotional Control) (teacher-rated).
- BRIEF (Initiate) (teacher-rated).
- BRIEF (Working Memory) (teacher-rated).
- BRIEF (Plan/Organize) (teacher-rated).
- BRIEF (Organization of Materials) (teacher-rated).
- BRIEF (Monitor) (teacher-rated).
- Weis's scale of disability-Parent Report (WFIRS-P) (Weis et al., 2005).
- Non-serious adverse events.
- Serious adverse events.

Further, all outcomes were assessed again 12 and 24 weeks after the end of the intervention.

Figure 13: Timeline of the study enrolment

Timeline



Legend for Figure 13:

1) SDQ: Strength and Difficulties Questionnaire; 2) DAWBA: Development and Well-being Assessment; 3) K-SADS: Kiddie-Schedule for Affective Disorders and Schizophrenia; 4) RIAS: Reynolds Intellectual Assessment Scales; 5) CANTAB: Cambridge Automated Neurocognitive Test Battery; 6) ADHD-RS: Attention Deficit-Hyperactivity Deficit -Rating Scale; 7) BRIEF: Behavior Rating Inventory of Executive Functions; 8) WFIRS-P: Weis's scale of disability-Parent Report; 9) TAU: treatment as usual

Ethical issues

This trial was conducted in accordance with the protocol approved by the Danish Data Protection Agency (ID.nr. 2008-58-0035) and the Regional Scientific Ethical Committees for Southern Denmark (nr. S20120096). The protocol is in accordance with the latest version of the Declaration of Helsinki. No significant deviation from the protocol was implemented without prior review and approval by the regulatory authorities, unless it was necessary to eliminate an immediate hazard to the trial participants. The latter has not been the case.

Participation in the trial required written consent of both parents/legal guardians. The participants' treatment as usual was not affected, including the use of medications, by their participation in this trial, besides that patients were asked to postpone any ADHD medication for 24 hours before the CANTAB test, because medical treatment could affect efficacy measures. Trial participants received a gift certificate worth DKK 400 for participation. Transportation costs were reimbursed.

The processing of personal data was respected. There were no known risks associated with the use of computerized cognitive training. The method has been tested in many studies with patients with schizophrenia (see reviews [88, 89]) and in children with ADHD [125, 127, 129, 183]. No adverse events have been reported.

Discontinuation and withdrawal

Legal guardians could withdraw their child from the trial at any time without further explanation. Pulling a child out of the trial, did not affect his or her further treatment. Children, who were randomized, were included in the intention-to treat analyses unless they completely withdraw consent. This was not the case for any drop out.

Statistical plan and data analysis

Sample size

We choose the continuous response variable, 'CANTAB RVP probability of hit', from independent control and experimental participants allocated at a 1:1 ratio as the primary outcome. In our first trial adolescents with ADHD showed an intra-group pre-post difference on the measure, RVP probability of hit, that was normally distributed with standard deviation (SD) 0.22 points. If the true difference in the experimental and control means is 0.13 points, we have calculated that we would need to include 61 experimental participants and 61 control participants to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 90%. The type I error probability associated with this test of this null hypothesis is 5%. We aimed to include 122 participants in total.

Power

Assuming the minimal relevant difference is 0.5 SD for all the secondary outcomes and the significance level of the various tests of Hommel's procedure is within the range of $\alpha = 0.05$ and $0.05/4 = 0.0125$ and the sample size is 122, the power of the individual tests would range between 59% and 78% (Table 3). A power of 78% is judged to be reasonable, while a power of 59% is insufficient.

Table 3: Power estimations for the secondary outcomes

Outcome	Minimal relevant difference	SD ¹	Sample size	Power assuming an alpha of 1.25%	Power assuming an alpha of 5%
ADHD-RS ² (parents-assessed)	5 points	10 points	122	59%	78%
ADHD-RS (teacher-assessed)	5 points	10 points	122	59%	78%
BRIEF ³ (parents-assessed)	0.25 points	0.5 points	122	59%	78%
BRIEF (teacher-assessed)	0.25 points	0.5 points	122	59%	78%

Legend: ¹ SD: standard deviation; ² ADHD-RS: attention deficit-hyperactivity deficit disorder rating scale. Minimal relevant difference and SD calculated from a previous pilot project (Bikic et al. unpublished data); ³ BRIEF: Behavior Rating Inventory of Executive Functions. Minimal relevant difference and SD calculated from the BRIEF professional manual [182].

Multiplicity and significance

For all outcomes, we present the test statistic and the corresponding P-values for exploratory purposes. The purpose of the analysis of the secondary outcomes is to make additional claims of treatment benefits, in addition to that already established by the analysis of the primary outcome. Consequently, multiplicity adjustments are needed. Multiplicity adjustments generally require a strong control of the familywise error rate. In this regard a useful approach is the gatekeeping approach [184], which we applied in this trial.

There is one primary and four secondary outcomes. Thus the primary outcome will be the gatekeeper of the family of secondary points. The sample size has been estimated using a risk of type I error (alpha) of 0.05. The primary outcome will consequently be analyzed and interpreted according to a two-sided significance level of $P \leq 0.05$. Thus, if P of the test of the primary outcome is ≤ 0.05 , the primary outcome is assessed as statistically significant. In this case, we will use Hommel's procedure, which is uniformly more powerful than the Holm as well as the Hochberg adjustment procedures. This means that the alpha of 0.05 can be transferred to the secondary outcomes that will be tested in a pre-specified sequence at the 0.05 level of significance (see sequence in table 3). The approach requires that as soon as the P value of a test is >0.05 the null hypotheses of the remaining secondary outcomes are accepted regardless of the test statistics.

If P of the test of the primary outcome is >0.05 , the primary outcome is assessed as statistically insignificant. Consequently the trial result is insignificant, and all the null hypotheses of the four secondary outcomes will be accepted regardless of the test statistic. All exploratory outcomes and exploratory analyses of the primary and secondary outcomes will likewise be subject to statistical

tests. However, if P of the test is ≤ 0.05 the outcome will not be assessed as statistically significant due to multiplicity and the increased risk of type I error. Likewise, if $P > 0.05$, we cannot assess the outcome as statistically insignificant due to a potential lack of power. All exploratory analyses will thus be strictly hypothesis-generating.

Statistical Analyses

We performed intention to treat analysis. All variables with normally distributed residuals were analyzed with a structural equation model (SEM) using a Full Information Maximum Likelihood Estimator to address missing data. Applying this method implies that unbiased estimates of the regression parameters were obtained as long as the values are only missing at random. We used a robust variance estimator, because some outcomes had moderate violations of the normality assumption. Outcomes were treated as observed variables. Correlations between exogenous variables were estimated. Means and variances were estimated for exogenous variables with missing values. All variables were adjusted for the stratification variables “center” and “pharmaceutical treatment” at baseline. As we only recruited one patient from the center in Odense, this patient was assigned to another center (Kolding) by flipping a coin. Based on SEM we estimated beta values with 95% confidence intervals. Means and standard deviation estimates were based on a Full-Information Maximum Likelihood (FIML) estimator. All analysis were performed and analyzed according to a two-sided significance level of $p < 0.05$. Not normally distributed variables were analyzed with ordered logistic regression controlling for baseline. We performed a post hoc power calculation to address the fact, that we recruited fewer participants than anticipated. All statistical analyses were performed in STATA 13.1 [185].

Sensitivity analyses

Best-worst and worst-best sensitivity analyses of the primary outcome were performed. Here missing values in one intervention group were imputed by the minimum value found in the total material (“best case”) and missing values in the other group are imputed by the maximum value found in the total material (‘worst case’) and vice versa. The range of the estimates of the two regression parameters of the intervention indicator convey an impression of the bias one may expect if values are missing not at random.

Per-protocol analyses

For the primary and secondary outcomes we performed per-protocol analyses as exploratory analyses. Participants were included in the intervention group, if they complied with at least 20 out of the 48 scheduled computer training sessions.

Subgroup analyses

For the primary, secondary and exploratory outcomes we performed subgroup analyses according to age. We divided the participants into two age-groups of children aged 6-9 years or 10-13 years. We performed a test of interaction to assess whether the effect of the intervention is different among the younger children compared with the older children. As the randomization procedure was not stratified by age and we most likely will have reduced power for this analysis, the result is exploratory and strictly hypothesis-generating. Additionally we performed a subgroup analysis according to ADHD subtype.

Monitoring of patient compliance issues

The intervention group compliance was monitored via the computer program that records patients log on and on and which games they have played and for how long.

Results

Study 1:

Eighteen subjects were found eligible for the trial and randomized to treatment or control intervention. One patient withdrew consent after randomization, leaving nine subjects in the intervention and eight in the active placebo group.

Baseline Characteristics

Individuals allocated to the two groups were comparable on a number of characteristics at baseline. There were no significant differences in the medication status in the two groups as there were three non-medicated patients, one in control and two in the intervention group. One individual dropped out of the trial shortly after randomization (see Figure 1.). A total of 15 participants out of 18 received pharmacotherapy for ADHD (all methylphenidate) and they were asked not to change their medication status during the intervention period. Hence, we found no statistically significant group differences in the severity of ADHD symptoms, or the majority of the cognitive measures on CANTAB (see Table 4.). There were no significant differences in gender distribution or mean age across groups. However, at baseline prior to the intervention, there was a significant group difference on the attention measure RVP probability of hit ($p < 0.01$), with the placebo group performing better than the intervention group.

Table 4: Participant characteristics at baseline

	Cognitive training group		Active placebo group		p value
	N=9		N=8		
	Mean	(SD)	Mean	(SD)	
CANTAB					
DMS % correct (all delays)	80.0	(9.4)	79.2	(17.6)	0.90
SSP span length	6.78	(1.39)	7.13	(1.25)	0.60
RVP A'	0.85	(0.66)	0.91	(0.52)	0.09
RVP probability of hit (attention)	0.50	(0.19)	0.70	(0.14)	0.01
SOC problems solved in min. moves	9.00	(2.12)	9.38	(2.13)	0.72
SWM between errors	19.88	(11.77)	23.0	(17.9)	0.68
SWM strategy	31.55	(3.97)	29.5	(4.57)	0.34
ADHD-rating scale, total score					
Parental	33.11	(12.5)	25.75	(11.89)	0.23
Adolescents	23.88	(7.97)	18.63	(10.24)	0.27
Teacher	26.57	(14.12)	24.00	(20.37)	0.79

Legend: Abbreviations: Attention-deficit/hyperactivity disorder (ADHD); standard deviation (SD); Cambridge Neuropsychological Test Automated Battery (CANTAB); Delayed Matching to Sample (DMS) is an outcome for visual memory; Rapid Visual Processing (RVP) measures attention; Spatial Span (SSP) and Spatial Working Memory (SWM) measure working memory; Intra/extra Dimensional Set Shift (IED) and Stockings of Cambridge (SOC) measure executive functions.

Feasibility of Computer Programs

Patients were asked to engage in the allocated intervention (SBT or active placebo, respectively) five times per week, for seven weeks. There were no significant differences in compliance measured by the number of completed sessions for all participants in both groups. The whole SBT group completed an overall total of 281 sessions (mean: 34.4, SD: 3.4) and the control group completed 275 sessions (mean 31.2, SD: 4.9) ($p=0.15$).

Individuals in both groups rated their perception of their respective computer programs, measured by three indexes on APQ [167]. We found no significant group differences between the two groups on any of the three subscales when measured with t-test for independent groups. APQ-subscales did not show any significant differences between the intervention and control group: APQ-Interest intervention group ($M=2.65$, $SD=1.50$), control group ($M=2.97$, $SD=1.42$), $t(14) =$

0.4378, $p = 0.0668$. APQ- Value intervention group ($M=2.91$, $SD=1.26$) and the control group ($M=3.35$, $SD=1.58$), $t(14) = 0.6236$ $p = 0.543$, APQ-Choice intervention group ($M=4.27$, $SD=1.20$) and the control group ($M=4.89$, $SD=0.95$) $t(14) = 1.110$ $p = 0.2856$. (see Table 5). Although there were no significant differences, participants playing the active placebo Tetris tended to perceive it slightly more positively than participants perceived SBT, on all measures. Both groups perceived both interventions as not very interesting and of little value to them. They experienced to have a moderate to high degree of Choice to engage in both interventions, meaning they perceived it as their own choice to play the games and they felt not forced by others (e.g. parents).

Table 5: Activity Perception Questionnaire (APQ) results

	Cognitive training group		Active placebo group		p value
	Mean	(SD)	Mean	(SD)	
Interest	2.65	(1.50)	2.97	(1.42)	0.668
Value	2.91	(1.26)	3.35	(1.58)	0.543
Choice	4.27	(1.20)	4.89	(0.95)	0.286

Legend: Abbreviations: standard deviation (SD)

Effects of Intervention on Cognition and Symptoms

The secondary aim of this trial was to compare the effect of SBT and placebo on the cognitive functions and ADHD symptoms. There were no significant between group differences on any of the cognitive outcome measures measured with ANOVA: DSM percent correct $F(1,33)=0.24$, $p=0.63$; RVPA' $F(1,33)=2.94$, $p=0.106$; RVP Probability of hit $F(1,33)=1.94$; $p=0.18$; SOC problems solved in minimum moves $F(1,33)=1.59$, $p=0.34$; SSS Span length $F(1,33)=0.93$, $p=0.349$; SWM between errors $F(1,33)=2.40$, $p=0.142$; SWM Strategy $F(1,33)=1.45$, $p=0.247$. IED stages completed was analyzed with non-parametric Wilcoxon-Mann-Whitney test $z=0.42$, $p=0.67$. There was a significant difference at baseline visual sustained attention (RVP) with the control group outperforming the intervention group.

However there were significant pre-post within-intragroup differences on some outcome measures, in both groups (see Table 6). Thus, in the SBT group, there were significant pre- to post-effects on two outcome measures of visual sustained attention RVPA' $F(1,17)=18.53$, $p=0.0026$ and

RVP Probability of hit $F(1,17)=14.63$, $p=0.0051$, indicating a better visual sustained attention after seven weeks of training with SBT with very large effect sizes (1.5 and 1.3). Similarly, the placebo Tetris group showed a significant effect in pre to post test on a measure of spatial working memory SWM Between errors $F(1,15)=6.20$, $p=0.0417$ with a large effect size (0.88).

There were no significant differences on symptoms from pre to post as measured with ANOVA for the ADHD-RS (see Table 7). After intervention ADHD-RS parent ratings in the intervention group ($M=29.4$, $SD=11.4$) were not significantly different from the control group ($M=5.7$, $SD=14.2$), $F(1,31)=0.17$, $p=0.679$. ADHD-RS teacher ratings in the intervention group ($M=28$, $SD=19.9$) were not significantly different from the control group ($M=27$, $S=22.2$), $F(1,21)=0.01$, $p=0.92$. ADHD-adolescent ratings did not differ significantly between the intervention ($M=4.27$, $SD=1.20$) and the control group ($M=4.89$, $SD=0.95$) $F(1,28)=0.00$, $F=0.976$. No adverse events were reported.

Table 6. Results on the cognitive outcome measures

Pre-post mean differences between intervention group (N=8) and active placebo group (N=9) and pre-post intra-group differences.

	Mean difference (Time 1 – Time 0)	95 % CI	Pre-post intra-group p value	Cohen’s d	Inter-group differences p value
DSM % correct (H)					
Intervention group	3.33	-7.02 – 13.68	0.48	0.24	0.63
Active placebo group	6.25	-2.62 – 15.12	0.14	0.59	
IED stages completed (H)					
Intervention group	-0.44	1.12 – 0.23	0.91	-0.5	0.52
Active placebo group	-0.13	-1.11 – 1.07	0.72	-0.1	
RVP A' (H)					
Intervention group	0.06	0.03 – 0.09	0.003*	1.5	0.11
Active placebo group	0.02	-0.03 – 0.06	0.41	0.33	
RVP prob. of hit (attention) (H)					
Intervention group	0.20	0.08 – 0.32	0.005*	1.3	0.18
Active placebo group	0.07	-0.12 – 0.25	0.41	0.32	
SOC prob. solved in min. moves (H)					
Intervention group	0.67	1.94 – 0.23	0.26	0.4	0.23
Active placebo group	0.25	-1.32 – 0.82	0.60	0.19	
SSP span length (H)					
Intervention group	0.22	-0.78 – 1.22	0.62	0.17	0.35
Active placebo group	-0.50	-1.98 – 0.98	0.80	0.28	
SWM between errors (L)					
Intervention group	1.22	-8.90 – 11.35	0.79	0.09	0.14
Active placebo group	-7.13	-13.16 – 0.36	0.04*	-0.88	
SWM strategy (L)					
Intervention group	1.00	-3.37 – 5.37	0.61	0.17	0.25
Active placebo group	-1.63	-3.72 – 0.47	0.11	-0.65	

Legend:

Abbreviations: H: a higher score is better; L: a lower score is better. Delayed Matching to Sample (DMS) is an outcome of visual memory; Attention: Rapid Visual Processing (RVP) A' is the signal detection measure of the target, regardless of response tendency (range 0.00 bad to 1.00 good). A' measures how good the subject is at detecting target sequences; Working Memory measures: Spatial Span (SSP), Spatial Working Memory (SWM), Executive functioning measures: Intra/extra Dimensional Set Shift (IED), Stockings of Cambridge (SOC).

*Significant difference.

Table 7: Mean total scores on ADHD-RS pre- and post-treatment in the intervention group and the active placebo group

	Pre-treatment					Post-treatment				
	Intervention Group		Active placebo group		Group difference	Intervention group		Active placebo group		Group difference
	Mean	(SD) ¹	Mean	(SD)	p value	Mean	(SD)	Mean	(SD)	p value
ADHD-RS²										
Parents	33.1	(12.5)	25.7	(11.8)	0.23	29.4	(11.4)	25.7	(14.2)	0.68
Adolescents	23.9	(8)	18.6	(10.2)	0.27	21.7	(8.2)	16.6	(10.3)	0.92
Teachers	26.6	(14.1)	24.0	(20.3)	0.79	28.0	(19.9)	27.0	(22.2)	0.98

Note: Attention Deficit/Hyperactivity Disorder-Rating Scale (ADHD-RS).

Study 2:

70 participants were randomized in this trial. Participants ranged in age from 6 to 13 years (M=9.95, SD=1.7) and were all Caucasian. A total of 40 (57%) participants were taking ADHD medication during the intervention with no significant differences in medication status across the two groups. Four participants dropped out of the trial before completion of the intervention. One participant in the control group did not participate in the T1 assessment, but returned to the two follow-up sessions (T2 and T3). Missing data for this second visit were estimated based on FIML. A flowchart of included participants is shown in Figure 8.

Baseline characteristics

The 70 participants allocated to the two groups were comparable on a number of measures at baseline (see Table 8). There were no statistically significant differences between the two groups, regarding age, sex, medication status, IQ or cognitive measures, parent and teacher rated ADHD symptoms, teacher rated BRIEF or parent rated functional outcome as measured by questionnaires at baseline. One exception was the parent rated BRIEF: Total score, Organize Materials, Working Memory and Metacognition Index sub-scales, where the participants in the intervention group scored significantly worse than controls at baseline.

Table 8: Diagnostic and demographic characteristics of children included at baseline

Diagnostic and demographic variables	Intervention group (n=35)	Treatment as usual group (n=35)	p-value
age, mean (SD)	9.77 (1.97)	10.14 (1.52)	0.38
female (%)	6 (17%)	5 (14%)	0.74
Medication (%) ¹	20 (57%)	20 (57%)	1.00
IQ, mean (SD)	96.20 (8.50)	95.94 (7.35)	0.89
ADHD subtype (%)			0.23
ADHD-H	3 (9%)	1 (3%)	
ADHD-I	12 (34%)	18 (53%)	
ADHD-C	20 (57%)	15 (44%)	

Note: Abbreviations: ADHD: Attention Deficit/Hyperactivity Disorder-Rating Scale; ADHD-Combined Type (ADHD-C); ADHD-I: Predominantly Inattentive Type; ADHD-H: Predominantly Hyperactive-Impulsive Type.

¹ 98% received methylphenidate

Effects on the primary cognitive outcome

Results indicate that the intervention had no effect on our primary outcome measure, the CANTAB RVP Probability of hit compared to the control group: $b=-.017$, CI (-.0907 to .0560), $z=-0.46$, $p=0.643$ (see Table 9). As we recruited fewer participants than originally anticipated, we conducted a post-hoc power calculation. It suggests that, based on our point estimates, we are dealing with an effect size of approx. 0.1-0.2 in standardized mean differences between improvements in the primary outcome for the control and intervention groups, respectively. This is a small effect size and if this estimated effect is a true effect we would require a sample of several hundred patients in order to have a statistically significant estimate. With our sample size of 70 participants, we would be able to identify even moderate treatment effects (i.e. standardized mean differences $>.68$) with a power of 80% and a 5% significance level. The small estimated effect size suggests, that the treatment cannot provide a clinically relevant improvement for patients for this measure of sustained attention. Additionally, we performed the best-worst and worst-best sensitivity analysis of primary outcome. The beta coefficient ranged from -0.07 in the worst-case scenario to 0.03 in the best-case scenario. No significant effect could be detected.

Effects on secondary outcome measures

The secondary measures were defined a priori as the total score on BRIEF as rated by parents and teachers and the total score on ADHD-RS parent and teacher version (see Table 10). Results indicate that there were no significant effects of training on BRIEF total scores for the parent version $b=-2.12$ (-5.5 to 1.26), $z=-1.23$, $p=0.22$ or teacher version: $b=3.68$ (-1.11 to 8.48), $z=1.5$, $p=0.13$. There were no significant differences for the ADHD-RS parent total score $b=-1.02$ (-6.13 to 4.09) $z=-0.39$, $p=0.69$ or ADHD-RS teacher total score $b=3.11$ (-3.63 to 9.85) $z=0.90$, $p=0.37$.

Exploratory cognitive outcome measures

All secondary and explorative variables were on continuous measurements. SEM analysis indicated a highly significant effect of the intervention on executive functions as measured at T1 by SOC problems solved in minimum moves: $b=1.22$ (.347 to 2.10), $z= 2.74$, $p=0.006$ with the intervention group outperforming the control group (and also a significant effect on this outcome at T2 and T3, see later). Three other measures were not significantly different between groups, but indicated a trend: RVP mean latency: $b= -42.63$ (-93.15 to 7.88), $z= -1.65$, $p=0.098$; SWM between errors: $b=- 5.58$ (-12.15 to .995), $z= - 1.66$, $p=0.096$ and IED EDS Errors: $b= -2.84$ (-6.52 to .834), $z= - 1.52$, $p=0.13$. In addition, SST Direction Errors on Stop and Go: $b= -5.4$ (-10.9 to .098), $z= -1.92$,

$p=0.054$ was very close to significant difference. However this difference is not a reflection of the intervention group making fewer mistakes compared to control, but is due to the control group getting worse over time. There were no significant group differences on any of the other cognitive measures (see Table 9).

Table 9: Results: Effects on the cognitive outcome measures from CANTAB

	Intervention				Treatment as usual				p-value		
	Means and standard deviations (SD)								T0-T1	T0-T2	T0-T3
	T0	T1	T3	T4	T0	T1	T3	T4			
RVP Probability of Hit (H)	0.709 (0.125)	0.702 (0.174)	0.743 (0.143)	0.777 (0.147)	0.729 (0.138)	0.728 (0.189)	0.758 (0.17)	0.743 (0.167)	0.64	0.73	0.29
RVP Mean Latency (L)	431.8 (121.7)	391.0 (105.5)	371.15 (110.9)	355.7 (85.9)	397.3 (119.7)	410.8 (152.6)	392.8 (143.4)	356.2 (115.43)	0.098	0.36	0.65
RVP Probability of false alarm (L)	0.024 (0.033)	0.014 (0.01)	0.011 (0.009)	0.03 (0.09)	0.013(0.009)	0.013 (0.012)	0.01 (0.009)	0.01 (0.018)	0.70	0.88	0.39
SWM Between errors (L)	51.5 (19.6)	41.78 (17.34)	44.49 (15.09)	43.47 (19.2)	48.86 (21.94)	47.5 (17.53)	46.43 (21.7)	43.65 (18.77)	0.096	0.80	0.91
RTI 5-choice movement time	483.7 (126.1)	497.2 (97.43)	460.26 (91.03)	464.8 (132.9)	471.1 (128.1)	469.7 (95.7)	518 (92.4)	454.6 (115.7)	0.27	0.008*	0.92
RTI Simple error score inaccurate	0.117 (0.322)	0.225 (0.489)	0.332 (0.608)	0.151 (0.477)	0.114 (0.32)	0.117 (0.322)	0.212 (0.41)	0.143 (0.35)	0.29	0.51	0.73
SOC Probl. solved min. moves (H)	7.36 (1.89)	8.08 (1.75)	8.82 (1.25)	8.80 (1.25)	6.91 (1.87)	6.72 (2.02)	7.93 (1.4)	7.79 (1.47)	0.006*	0.03*	0.017
SOC Mean Moves 4-moves (L)	5.11 (1.04)	5.18 (0.86)	5.07 (0.96)	5.12 (0.84)	5.48 (1.05)	5.39 (0.88)	5.33 (0.88)	5.3 (0.837)	0.28	0.56	0.46
AST Total Omission errors (L)	5.26 (4.32)	3.59 (4.29)	2.66 (4.15)	3.19 (3.98)	5.23 (6.8)	4.06 (5.97)	4.12 (6.76)	3.05 (6.34)	0.69	0.47	0.9
AST Total Commission errors (L)	2.35 (6.6)	1.19 (3.94)	0.447 (1.08)	0.95 (1.99)	1.43 (2.93)	1.63 (4.54)	1.63 (2.88)	2.62 (8.7)	0.49	0.01*	0.27
IED EDS Errors (L)	14.15 (11.03)	8.37 (8.9)	8.09 (9.77)	5.81 (8.2)	13.5 (10.96)	11.6 (10.67)	9.27 (9.03)	8.6 (9.59)	0.13	0.45	0.39
SST Direction Error Stop and Go (L)	9.39 (8.19)	9.34 (8.45)	8.74 (8.01)	7.4 (7.9)	10.03 (9.54)	14.66 (15.16)	12.41 (13.59)	10.75 (7)	0.054	0.19	0.08
SST SSRT last half (L)	233.9 (79.64)	276.6 (99.9)	244.49 (87.2)	200.3 (68.3)	244.1 (84.45)	250.8 (84.8)	262.1 (136.24)	223.8 (118.5)	0.093	0.87	0.39

Note: Abbreviations: H: Higher score is better; L: Lower score is better; RVP: Rapid Visual Information Processing; SWM: Spatial Working Memory; RTI: Reaction Time; SOC: Stockings of Cambridge; AST: Attention Switching Task; IED: Intra-Extra Dimensional Set Shift (IED); SST: Stop

Table 10: Effects of the intervention and treatment as usual on the behavioral measures from T0 to T1

Measures	Intervention		Treatment as usual		p
	Means and standard deviations (SD)				T0-T1
	T0	T1	T0	T1	
P- BRIEF Impulse inhibition	66.17 (9.38)	62.17 (8.52)	64.09 (10.48)	62.64 (9.31)	0,28
P- BRIEF Flexibility	69.43 (11.41)	67.19 (12.47)	64.90 (13.96)	63.43 (10.97)	0,82
P- BRIEF Emotional control	65.20 (9.40)	62.08 (11.47)	61.07 (9.29)	57.19 (10.27)	0,388
P- BRIEF AI	69.46 (9.30)	65.60 (10.51)	65.33 (8.74)	62.60 (9.29)	0,699
P- BRIEF Initiation	66.47 (8.01)	62.36 (9.77)	63.28 (8.89)	59.00 (9.76)	0,627
P- BRIEF Working Memory	74.09 (6.17)	68.6 (7.35)	69.03 (6.89)	67.26 (8.27)	0,538
P- BRIEF Plan / Organize	69.0 (8.13)	66.19 (7.8)	65.5 (6.85)	63.6 (9.27)	0.376
P- BRIEF Organize Materials	60.56 (8.82)	59.42 (8.68)	55.95 (7.89)	56.6 (11.02)	0,666
P- BRIEF Monitor	66.36 (7.79)	63.73 (8.17)	62.43 (10.45)	57.71 (11.2)	0.095
P- BRIEF Metacognitive Index	71.67 (6.38)	65.32 (8.68)	65.76 (6.57)	63.74 (9.13)	0.071
P- BRIEF Total	72.13(5.28)	67.27(7.97)	66.88 (7.22)	64.4 (9.36)	0.22
T- BRIEF Impulse inhibition	65.13 (12.28)	70.03 (12.25)	73.33 (18.67)	71.73 (19.66)	0,33
T- BRIEF Flexibility	71.57 (13.06)	77.86 (14.62)	77.31 (13.97)	73.82 (18.01)	0,213
T- BRIEF Emotional control	69.43 (14.12)	74.80 (11.94)	71.26 (16.18)	71.18 (17.33)	0,78
T- BRIEF AI	70.31 (13.73)	72.10 (12.75)	75.93 (14.09)	76.10 (19.09)	0,274
T- BRIEF Initiation	70.46 (11.61)	72.09 (11.89)	69.53 (9.57)	69.80 (11.49)	0,849
T- BRIEF Working Memory	70.67 (12.36)	72.49 (10.71)	73.03 (8.80)	73.89 (12.55)	0,532
T- BRIEF Plan / Organize	66.14 (9.59)	69.06 (8.89)	68.34 (10.08)	69.98 (10.49)	0.429
T- BRIEF Organize Materials	62.55 (11.01)	62.30 (12.65)	66.30 (20.19)	68.27 (18.83)	0,854
T- BRIEF Monitor	68.28 (12.77)	70.47 (12.79)	72.63 (12.95)	69.42 (13.56)	0.208
T- BRIEF Metacognitive Index	69.17 (9.88)	70.17 (10.86)	72.8 (11.86)	71.86 (12.70)	0.294
T- BRIEF Total	70.93 (10.11)	74.76 (10.73)	75.95 (12.44)	75.08 (15.21)	0.133
P-ADHD-I	18.35 (3.84)	15.4 (5.33)	16.42 (4.33)	15.66 (4.88)	0.43
P-ADHD-H	15.31 (5.42)	12.18 (5.76)	13.53 (6.58)	12.55 (6.54)	0.39
P-ADHD-ODD/CD	8.81 (5.30)	8.06 (5.49)	7.03 (5.46)	6.12 (5.58)	0.20
P-ADHD-total	45.56 (10.48)	34.98 (14.04)	37.28 (13.05)	35.36 (13.25)	0.70
T-ADHD-I	14.75 (5.19)	15.68 (5.39)	15.35 (6.98)	16.38 (6.51)	0.39
T-ADHD-H	11.52 (7.21)	12.48 (7.16)	12.38 (7.30)	13.09 (8.44)	0.46
T-ADHD-ODD/CD	6.59 (5.55)	7.94 (6.63)	6.61 (5.83)	7.46 (5.94)	0.49
T-ADHD-total	32.5 (12.11)	39.51 (15.22)	34.26 (16.71)	38.44 (18.59)	0.37
P-WFIRS-Total	0.96 (0.43)	0.82(0.46)	0.8(0.39)	0.73 (0.45)	0.54

Abbreviations: P: Parent rated; T: Teacher rated; BRIEF: Behavior Rating Inventory of Executive Functions [182]; ADHD-RS: Attention Deficit/Hyperactivity Disorder-Rating Scale [166]; ADHD-I: ADHD Inattention Scale; ADHD-H: ADHD Hyperactivity Scale; ADHD-ODD/CD: ADHD oppositional behavior Scale; ADHD-WFIRS: Weis's scale of disability-Parent Report [186]

Behavioral outcome measures

One of the subscales on the behavioral outcomes on parent-rated BRIEF showed a trend: Metacognition Index: $b=-3.49$ (-7.27 to .298), $z=-1.81$, $p=0.07$ favoring the intervention group. Other subscales of the BRIEF were not significantly different between groups. There were no significant differences between the intervention and the control group on the ADHD-RS subscales. All other measures were not statistically significant (see Table 10). There were no serious or non-serious adverse events reported.

Interactions with age

To explore possible interactions with age we divided participants in two groups: 6-9 years old ($n=43$) and 10-13 ($n=27$) and compared participants in the intervention group to the controls in each age group (see Table 11). For a number of measures there was a significant difference in the older group, but not in the younger group: RVP mean latency $p=0.045$, SWM between errors: $p=0.004$, SOC problems solved in minimum $p=0.009$, SST direction errors on stop and go $p=0.008$. The younger group got significantly worse on the SST SSD $p=0.000$, but not the older group.

Parent rated ADHD hyperactivity score improved for the older group, $p=0.018$, but not for the younger group. Teacher rated ADHD-total showed that the younger group significantly improved $p=0.000$ and had less ADHD hyperactivity symptoms after intervention: $p=0.000$, but not the older group.

Parent rated BRIEF Plan / Organize showed significant improvement for the older group: $p=0.036$; Metacognition Index $p=0.01$; Monitor the older group significantly got worse: $p=0.003$, but not the younger group: $b=-2.01$ (-9.91 to 5.89), $z=-0.50$, $p=0.62$. For the teacher rated BRIEF Metacognition Index: The younger group got significantly worse $p=0.01$, but not the older group

Effects at follow up: time T2 and T3

At the 12-week follow-up (T2) data on the cognitive outcome measures was available for 54 participants and at the 24-week follow up (T3) for 41 participants. Results on the follow up data for the CANTAB cognitive test indicate that the significant difference on SOC Problems solved in minimum moves was maintained over both time points: T3: $b=.724$ (.049 to 1.4), $z=2.10$, $p=0.035$ and at T4: $b=1.02$, (.182 to 1.86), $z=2.38$, $p=0.017$.

At 24-week follow up (T3), there were significant effects on two measures that did not differ significantly at T1: RTI 5-choice movement time $b=-63.47$ (-110.15 to -16.78), $z=-2.66$, $p=0.008$ and AST Total Commission errors $b= -1.36$ (-2.45 to -.277) $z=-2.46$, $p=0.014$. SST SSD 50 last half was approaching significance $b= -67.29$ (138.86 to 4.27), $b=-1.84$, $p=0.065$. Due to a large number of drop-outs (over 50% for the parents and 65% for the teachers) on the behavioral scales returned at T3 ($n= 36$ parent ratings and $n=18$ for teacher ratings) and T4 ($n= 34$ parent and $n=20$ for teacher ratings) we did not calculate results for ADHD-RS, BRIEF and WFIRS at these time points.

Table 13: Results T0-T1 for the younger (6-9 years) and older (10-13 years) age category

Measures	Older group				Younger group			
	b	CI		p	b	CI		p
CANTAB								
RVP probability of hit	0.041	-0.043	0.12	0.34	-0.069	0.17	0.036	0.19
RVP mean latency	-53.7	-106.2	-1.26	0.045*	-50.6	-159	57.7	0.3
RVP Probability of false alarm (L)	-0.0013	-0.006	0.0039	0.63	-0.0009	-0.011	0.009	0.86
SWM between errors	-10.9	-18.3	-3.49	0.004*	9.4	-84	65.2	0.8
RTI 5-choice movement time	47.5	-13.7	108	0.13	-9.4	-84	65.2	0.8
RTI Simple error score inaccurate	-0.009	-0.15	0.13	0.9	0.14	-0.22	0.5	0.44
SOC problems solved in min moves	1.59	0.4	2.79	0.009*	0.64	-0.51	1.79	0.27
SOC Mean Moves 4-moves (L)	-0.46	-1.09	0.16	0.15	0.08	-0.53	0.69	0.79
AST Total Omission errors (L)	1.58	-4.8	1.64	0.34	-0.88	-4.33	-4.15	0.97
AST Total Commission errors (L)	-0.58	-1.7	0.53	0.3	-1.75	-6.61	3.1	0.48
IED EDS Errors (L)	-2.36	-6.53	1.81	0.27	-3.3	-9	2.39	0.26
SST direction errors on stop and go	-9.76	-16.9	2.59	0.008*	2.85	-1.49	7.19	0.19
SST SSD	28	-57.9	114.9	0.52	96.7	43.3	150	0.000*
ADHD-RS								
P-ADHD-I	-1.72	-4.23	0.79	0.18	-0.26	-4.11	3.59	0.89
P-ADHD-Hyperactivity	-2.45	-4.49	-0.42	0.018*	0.9	-3.54	5.34	0.69
P-ADHD-ODD/CD	0.58	-0.89	2.05	0.44	1.62	-1.23	4.46	0.27
P-Total	-3.77	-8.97	1.42	0.15	2.02	-7.9	11.9	0.69
T-ADHD-I	0.63	-1.12	2.38	0.71	0.79	-6.79	8.37	0.84
T-ADHD-H	-0.78	-3.16	1.59	0.5	-11.2	-16.8	-5.66	0.000*
T-ADHD-ODD/CD	0.54	-3.31	3.41	0.97	-3.17	7.68	1.33	0.170
T-ADHD-total	-0.25	-7.4	6.91	0.95	-31.2	-40.1	-22.3	0.000*
BRIEF								
P- BRIEF Impulse inhibition	-2.28	-5.87	1.31	0.21	0.099	-5.85	6.05	0.97
P- BRIEF Flexibility	-4.55	-10.4	1.27	0.13	6.8	-0.74	14.3	0.07

P- BRIEF Emotional control	0.93	-4.79	6.65	0.75	1.92	-3.42	7.25	0.48
P- BRIEF AI	-2.98	-7.65	1.69	0.21	2.74	-1.42	6.9	0.2
P- BRIEF Initiation	-1.89	-7.4	3.62	0.5	5.07	-0.97	11.1	0.1
P- BRIEF Working Memory	-2.2	-7.36	2.94	0.4	-0.54	-6.09	5.01	0.89
P-Plan/organize	-4.59	-8.86	-0.31	0.036*	1.63	-4.75	8.02	0.6
P-Organize Materials	-2.69	-7.43	2.05	0.27	6.34	-1.18	13.8	0.1
P-Metacognition index	-6.79	-11.9	-1.63	0.01*	-0.49	-8.76	7.77	0.9
P-Monitor	6.55	2.26	10.8	0.003*	-2.01	-9.91	5.89	0.6
P-Total	-3.19	-7.45	1.06	0.14	-1.42	-8.96	6.12	0.7
T- BRIEF Impulse inhibition	3.61	-7.34	14.6	0.5	0.85	-2.57	4.27	0.63
T- BRIEF Flexibility	3.67	-4.12	11.5	0.36	2.92	-6.13	12	0.53
T- BRIEF Emotional control	5.13	-1.89	12.2	0.15	-4.04	-9.07	0.99	0.11
T- BRIEF AI	3.62	-5.9	13.1	0.46	0.83	-3.55	5.21	0.71
T- BRIEF Initiation	-4.69	-9.5	0.11	0.05*	8.99	2.86	15.1	0.004*
T- BRIEF Working Memory	4.43	-3.18	12	0.25	-4.27	-11.7	3.2	0.26
T-Plan/organize	1.31	-2.42	5.04	0.49	7.61	-1.61	16.8	0.11
Organize Materials	-1.1	-6.29	4.08	0.68	8.29	-0.04	16.6	0.051*
T-Monitor	6.05	-3.57	15.7	0.22	5.56	-3.03	14.1	0.2
T-Metacognition index	-0.38	-6.2	5.45	0.89	7.97	1.56	14.4	0.01*
T-Total	2.78	-2.76	8.33	0.32	4.51	-1.53	10.5	0.14
WFIRS Total	-0.09	-0.27	0.09	0.31	0.90	-0.20	0.28	0.76

Note:

*significance

Abbreviations: P: Parent rated; T: Teacher rated; H: Higher score is better; L: Lower score is better; RVP: Rapid Visual Information Processing; SWM: Spatial Working Memory; RTI: Reaction Time; SOC: Stockings of Cambridge; AST: Attention Switching Task; IED: Intra-Extra Dimensional Set Shift (IED); SST: Stop Signal Task.

BRIEF: Behavior Rating Inventory of Executive Functions [182]; ADHD-RS: Attention Deficit/Hyperactivity Disorder-Rating Scale [166]; ADHD-I: ADHD Inattention Scale; ADHD-H: ADHD Hyperactivity Scale; ADHD-ODD/CD: ADHD oppositional behavior Scale; WFIRS: Weis's scale of disability-Parent Report [186]

Compliance

There was a great variation in the number of sessions performed in the intervention group ($M=26.2$, $SD=15.89$, $min=0$, $max=48$). Compliance was low and only 66.5 % of participants performed more than 20 sessions, defined as compliers. We did a post hoc analysis on the outcome measures comparing compliers ($n=19$) and non-compliers (under 20 sessions) to controls to explore effects of more and less intense cognitive training. There were no significant differences on the most cognitive outcome measures with one exception: Compliers showed significant improvement on only one measure: SST direction errors on stop and go: $b=-7.24$, $(-12.85$ to $-1.63)$, $z=-2.53$, $p=0.01$, but no effect in non-compliers: $b=-2.74$ $(-9.39$ to $3.92)$, $z=-0.81$, $p=0.42$. Two other measures were approaching significance for compliers: RVP mean latency $b=53.92$, $(-110.43$ to $2.58)$, $z=-1.87$, $p=0.06$; AST commission errors $b=-1.41$, $(-3.02$ to $.209)$, $z=-1.71$, $p=0.088$.

For SOC problems solved in minimum moves the results were better for the non-compliers group doing under 20 sessions: $b=1.57$ $(.572$ to $2.57)$, $z=3.08$, $p=0.002$, while the compliers only approached significance: $b=.95$ $(-.11$ to $2.02)$, $z=1.76$, $p=0.079$. There was a trend for non-compliers on these measures: IED errors: $b=-3.733845$ $(-8.023063$ to $.5553737)$, $z=-1.71$, $p=0.088$ and SWM Strategy: $b=-2.32751$ $(-4.833704$ to $.178685)$, $z=-1.82$, $p=0.069$.

The functional scale WFIRS total was approaching significance in the compliers group $b=-.142$ $(-.309$ to $.024)$, $z=-1.68$, $p=0.09$, but not in the non-compliers group: $b=.178$ $(-.112$ to $.469)$, $z=1.20$, $p=0.228$.

Non-compliers had worse outcomes than controls on the parent rated ADHD-RS-CD: $b=2.13$ $(-.20$ to $4.46)$, $z=1.79$, $p=0.07$ and for teacher reported ADHD inattention symptoms $b=3.49$ $(-.329$ to $7.32)$, $z=1.79$, $p=0.07$ and hyperactivity symptoms: $b=3.11$ $(.202$ to $6.02)$, $z=2.10$, $p=0.036$.

There were some trends differences on the parent rated BRIEF subscales: BRIEF Metacognition Index for compliers: $b=-4.3$, $(-8.64$ to $.046)$, $z=-1.94$, $p=0.052$, but not for non-compliers: $b=-1.98$ $(-7.87$ to $3.92)$, $z=-0.66$, $p=0.5$. Parent rated BRIEF total was approaching significant improvement for compliers: $b=-3.39$, $(-7.21$ to $.415)$, $z=-1.75$, $p=0.08$, but not for non-compliers: $b=1.22$, $(-3.14$ to $5.58)$, $z=0.55$, $p=0.58$. Parent rated BRIEF Monitor subscale was non significant for compliers: $b=2.74$ $(-1.78$ to $7.26)$, $z=1.19$, $p=0.2$, but the non-compliers got significantly worse: $b=6.86$ $(1.70$ to $12.02)$, $z=2.61$, $p=0.009$.

Discussion

Feasibility and compliance (Paper I and III)

In our first clinical, randomized, double-blind trial comparing SBT exercises with Tetris in adolescents with ADHD, we investigated feasibility. Our results show that both interventions were feasible as home-based interventions in the age group 14 to 17 years. We also found that participants' compliance with both interventions was high with a mean of 34.4 performed sessions (SD 3.4) in the SBT group and a mean of 31.2 (SD 4.9) performed sessions in the control group. Despite the fact that the intervention was technically feasible and compliance was high, the participants rated both interventions as a little interesting and valuable. Both groups scored 'modest' on the APQ measure Choice, indicating that they did not feel that it was entirely their own choice to play and that they may have felt pressured by others to engage in the interventions. An important aspect to consider is that SBT exercises were not originally developed for adolescents, but for adults and may therefore not be age-appropriate for adolescents who perceived Tetris as a little more engaging.

We did not examine feasibility in our second trial involving children. However, compliance in the intervention group was lower than in the first trial with only 66.5% of our participants performing 20 or more sessions ($M= 26.2$, $SD=15.89$, $min=0$, $max=48$). The number of sessions performed varied much between individuals. This may indicate that the design of the games in ACTIVATE™ was not optimal or that the games may have not been sufficiently challenging, which caused the participants to lose interest in the game. ACTIVATE™ is designed to implicitly enhance the participants' motivation by incorporating rewards such as collecting coins that could be used for the virtual garden after each session. This is an important aspect, considering that children with ADHD prefer smaller, short-term rewards over larger, delayed rewards [187]. However, this incentive was not sufficiently strong to engage the children in our trial. Data from our second trial suggest that compliance was not age-dependent. One important factor that may have contributed to the difference in compliance between these two trials is the fact that the adolescents in the first trial were reminded directly with a text message every day and they may therefore have felt more obliged to play. This was not done in the second trial with children, where the messages were supposed to be sent to parents, but a number of parents did not feel that it was necessary to be reminded of the daily intervention. Another important difference is that the adolescents may have had more influence on the choice of participating in the trial, whereas it was primarily parents who decided this for their children in the second trial.

Motivation is an important aspect related to compliance in cognitive training. In the first trial, both groups had low scores on the Interest and Value dimensions in the APQ questionnaire suggesting that the adolescents felt little motivation to engage in the interventions, which may have had a negative influence on the treatment effects. In recent years, a large number of children and adolescents are engaging in very complex computer games on a daily basis. Compared with these popular games, the design of the majority of cognitive training interventions available today seems somewhat simple and naive. In the development of new cognitive training interventions, emphasis should thus be on more complex, engaging, and sophisticated designs that motivate children and adolescents. Popular computer games have already today achieved these goals.

Effects of interventions on cognition and symptoms (Paper I and III)

In our first trial (Paper I), we found no significant differences between the intervention and the active control group on cognitive and symptom measures as assessed by the CANTAB battery and the ADHD-RS, respectively. The lack of significant differences between the groups may be caused by the small sample size in this trial. Despite the randomization, we observed a significant difference on the attention measure RVP Probability of hit at baseline, favouring the Tetris group. No significant differences were seen between the groups at the end of intervention; however, the SBT group showed a significant pre-post improvement on exactly this measure with a large effect size.

Both SBT and Tetris showed positive pre-post intra-group effects on different cognitive functions. In the intervention group, significant pre-post changes were observed on the two outcomes of sustained attention (RVPA and RVP Probability of hit) with large effect sizes. In the control group, we found that Tetris had a significant positive pre-post effect on spatial working memory (SWM Between errors) with a large effect size. These results are consistent with previous findings which indicates that training of specific cognitive functions primarily has an effect on the directly targeted and trained functions as far as attention [119, 183, 188] and working memory training are concerned [128, 129, 131, 138]. The effect of Tetris on working memory found in the present study could be explained by some visual working memory load in the Tetris game. SBT targeted several cognitive functions, but not all of them on a daily basis. This may have led to low-intensity training. On the other hand, Tetris targeted the same functions for the whole intervention period.

As we found no effects of SBT and as the intervention did not seem to be appropriate for children and adolescents, we focused on a more age-appropriate intervention that targeted multiple cognitive functions simultaneously in our second trial. The aim of this trial (Paper II and

Paper III) was to investigate the effect of ACTIVATE™, a computerized intervention designed for children with ADHD, compared with treatment as usual. In contrast to SBT, where two out of six games were played for one week in a rotating manner, ACTIVATE consisted of three games that were each played every day. Our data did not allow us to confirm our primary hypothesis, namely that ACTIVATE™ would have an effect on the objective measure of sustained attention, a function that was targeted by all three games. Although we did not recruit the number of participants initially estimated, the lack of significant differences on the primary outcome measure was not due to a type II error as shown by our post hoc power analysis. We adopted a gate-keeping approach in our analysis. This implies that the lack of significant effect on our primary outcome measure would cause all other measures, regardless of their outcomes, to be considered non-significant as well. Still, we found no significant effects on the secondary outcome measures defined as the total scores on questionnaires measuring ADHD symptoms and executive functions behaviors by parents and teachers. These results indicate that the simultaneous training of a number of cognitive functions does not strengthen sustained attention or ADHD symptoms.

Significant differences between the intervention and control group were seen on one exploratory measure, accuracy in planning, in favor of the intervention group ($p=0.006$). However, the difference between the two groups corresponds to 0.30 of a standard deviation on the outcome indicating a modest effect. Furthermore, a significant difference was maintained at both the 12-week ($p=0.03$) and 24-week ($p=0.017$) follow-up. Thus, the effect was still observable 6 months post intervention. In addition, one clinical subscale of the parent-rated executive functions, BRIEF Metacognition Index, was approaching statistical significance ($p=0.09$) in favor of the intervention group. Metacognition Index summarizes five BRIEF subscales and expresses the individual's active problem solving ability. Nevertheless, exactly this measure together with the BRIEF Total score, Working memory and Organize Materials subscales were significantly different at baseline in favor of the control group. Although we have adjusted for baseline scores in our analysis, these results could indicate that the intervention group was somehow more impaired in their executive functions than the control group. These differences at baseline were not confirmed by our objective cognitive test of executive functions.

For other exploratory cognitive measures, ADHD symptoms, and parent-rated functional outcome no significant differences between groups were observed immediately after the intervention. Although there were no significant differences immediately after the intervention on measures of reaction time and impulsivity, the intervention group outperformed controls at the 12-week follow-up.

In general, transfer of effect to other cognitive or functional domains is difficult to obtain [107]. Some studies of working memory and attention training show generalization effects to untrained cognitive domains [128, 129] and a reduction of symptoms on rating scales [119, 127, 129, 143]. Several meta-analyses show that parents, who are not blind to the nature of the intervention, generally give higher effect ratings on symptom scales than blinded raters like teachers [107, 141, 143]. However, the blind status of the teachers was not surely established in these meta-analyses, which assumed that the teachers probably were blinded. For children with ADHD there is in general a weak correlation between parent and teacher ratings for inattention symptoms and only a moderate correlation for hyperactivity/impulsivity symptoms [154]. The teachers and the parents were blinded in our first trial as opposed to the second trial. Still, both trials showed no significant effects for parent or teacher ratings for either population, indicating that the cognitive training did not produce any far transfer. However, our exploratory analysis revealed a number of significant interactions with certain factors indicating that the effect of cognitive training may be dose- and age-dependent.

Age effects (Paper III)

We did not investigate the effects of age in the first trial with adolescents, as the age range was narrow and the sample size small. In our second trial, the dispersion of age was greater, and we performed exploratory analyses dividing our participants into two age categories. When comparing the intervention and control participants in each age category, we found a number of differences in the effect of intervention for the older (10-13) and the younger (6-9) group. The older group showed significant improvements in sustained attention, made fewer errors in a working memory task, improved their ability to plan, and made fewer mistakes on the Stop Signal Task, which was not the case in the younger group. These results indicate that older children gained more from cognitive interventions, which would not be in line with the neuroplasticity assumption.

The finding that the younger group performed significantly worse on the Stop Signal Task SSD ($p=0.000$), while the older group did not, is also interesting. A probable explanation for this finding may be that many younger children found this task to be very frustrating. Often children refused to perform this test at the first follow-up as they already knew the task from the baseline assessment. In many cases, children were less engaged in this task than in other outcome CANTAB tasks which were much more engaging and fun. These results should therefore be interpreted with caution as they may solely indicate that the older children were more compliant in performing this particular task.

Far transfer effects were somewhat contradictory for both age categories. The older group improved on the parent-rated ADHD-RS Hyperactivity score, while the younger group did not. Additionally, the older children improved significantly on the parent-rated BRIEF Plan/Organize and Metacognitive index subscales, indicating that they did better in developing steps and organizing as well as in active problem solving, but they got significantly worse scores on the Monitor subscale. The Monitor subscale measures the ability to assess critically one's own performance and the way one's own behavior affects others. Teacher-rated BRIEF Initiation was significantly improved for both the younger and older group, indicating a better ability to start tasks on one's own initiative.

Additionally, the younger group showed noticeable improvements on the teacher-rated ADHD-RS Total score and Hyperactivity subscale, while the older group did not. At the same time, teachers rated the younger group significantly worse than the parents on the BRIEF subscales Organize Materials and Metacognition index. This discrepancy between parent and teacher ratings for the younger group is interesting. Although differences in the parents' and the teachers' perception and behavior ratings are known, teachers usually tend to report less improvement [154]. These contradicting results may be due to the fact that the teachers only spend limited time with the children in a larger context, while the parents are more tuned in and observant of their own child. In many cognitive trials, the teachers tend to be blind to the child's allocation, while the parents usually are not blind and may be biased by the expectancy effect and their own involvement in the intervention. However, in our second trial the majority of teachers were not blind to the child's allocation status. One possible explanation for the contradicting results could be the fact that the questionnaire was not always filled out by the same teacher at all time points for each child. This variation was due to change of teachers or to the child changing class or school. Thus, the results may be an artifact of the natural interpersonal observer variation, but they may also be ascribed to the fact that some teachers might not have known the child very well at the time of rating. These results should therefore be interpreted with caution.

It seems that age may be an important factor in cognitive training, which is in line with the hypothesis of increased neuroplasticity in early childhood [108]. Our findings are not in line with two meta-analyses investigating different populations, including ADHD and cognitive training [144, 150]. These two analyses find that younger participants showed greater gains compared with controls than older participants. Peng & Miller [144] found that age is a significant moderator of effect. The effect of age may be one possible explanation, beside the obviously small sample size, for the lack of intervention effects in the first trial in adolescents aged 14 to 17. However, one trial found significant gains among adolescents and no function of age [131], while others did not [159].

Considering the exploratory nature of our results from the second trial, it is necessary to test the age hypothesis in future studies to determine if there is a real effect of ACTIVATE™ or other executive function interventions on planning ability and other cognitive functions in older children.

Comparison with findings from previous trials

Parallel to our second trial, ACTIVATE™ was tested [160] as a part of a multifaceted intervention program, the IBBS intervention. In a school-group setting, children with sub-threshold and full ADHD diagnoses were randomized to ACTIVATE™ in combination with the Good Behavior Game³ and physical training or TAU. After the intervention, there were no significant differences between the groups in terms of their ADHD symptom ratings as assessed by trained and blinded clinical assessors, teachers, or parents or in terms of their cognitive outcome measures. There are several important differences between the IBBS trial and our trial. The former was conducted in a group setting (6-10 children) at school where ACTIVATE™ was part of a broader intervention program. Opposite this, our trial was an individual, home-based, purely cognitive intervention. The training intensity and training period of computerized cognitive training were also different. Compared with our trial, cognitive training in the IBBS trial was performed for a longer period of time (15 weeks), but with fewer cognitive training sessions (3-4) per week. Additionally, also children with sub-threshold ADHD were included in the IBBS trial. Still, despite these methodological differences, our results are similar in finding no effects on the majority of cognitive outcome measures, the severity of symptoms, and executive functions behaviors. This indicates that ACTIVATE™ does not have an effect on cognition or ADHD symptoms whether it is used as an individual intervention or as a part of a multicomponent intervention. However, we did find an exploratory effect on the ability to plan, while Smith et al. [160] did not include such a measure.

Our results add to a small number of randomized trials, which have investigated the effects of broader executive function interventions focusing primarily on combined inhibition and short-memory training [137, 138]. However, these trials found an improvement on ADHD symptoms, and Johnstone et al. [138] also found significant changes in spatial working memory, ignoring distracting stimuli, and sustained attention was reported for children with AD/HD. Another two recent trials focusing on a number of cognitive functions resemble our intervention [139, 140]. Van der Oord [140] found significantly more improvement on parent-rated BRIEF total and Metacognition Index and ADHD symptoms in the intervention group than among a control population. These effects were maintained at follow-up, including additional, significant effects on teacher-rated ADHD

³ Good Behavior Game is a classroom-based strategy shown to prevent emotional and behavioral disorders 189.

Embry DD. The Good Behavior Game: a best practice candidate as a universal behavioral vaccine. *Clin Child Fam Psychol Rev*, 2002. 5(4): p. 273-97.

symptoms. Using the same intervention in a double-blind design, Dosis et al. [139] found transfer effects on visuo-spatial working memory and short-term memory, inhibitory performance, and interference, but not on cognitive flexibility, verbal working memory, complex reasoning or ADHD symptoms, BRIEF, motivational behaviors, or general problem behaviors. These two trials differed in their selection of control groups and degree of blinding, which may partly explain the differences in their results.

Control conditions

Generally, it is crucial to identify and use the right kind of control condition in cognitive training trials. Inappropriate control conditions can bias results in either direction. Using waiting list control groups makes it impossible to control for a number of factors: expectation bias, placebo effect, and non-specific factors of interactions with the clinical staff or the bare interaction with a screen. Use of the TAU control group does allow the investigator to control for the contact with the clinical staff, but not for the placebo effect, contact with the therapist, or contact with the computer screen. These are all biases that may lead to over-estimation of the effect of the investigated intervention. An optimal control condition for cognitive training would be a sham treatment that is cognitively non-challenging. This kind of control condition would also make it possible to implement a double-blind design in cognitive training and thus blind participants and parents to the child's allocation.

Still, it is not an easy task to find the right sham treatment. In cognitive training trials, it is already a challenge to engage participants in the demanding intervention for several weeks, to maintain good trial adherence, and to ensure a high motivation and prevent attrition. Some studies [129, 139] have used the actual intervention on a constantly low level as an active placebo. This is an option, but when control participants have to engage in an intervention with a very low cognitive load for several weeks, there is a risk of boredom and attrition in the control group. Additionally, the blinding could be broken, as the children and parents could probably figure out their allocation. On the other hand, if a more engaging intervention or conventional game, like Tetris, is used, this may have too large effects on cognitive functions, and a difference between groups would no longer be detected. While Tetris was perceived as even more engaging than the cognitive intervention in our first trial, Tetris may have been too active and its use may have contributed to the lack of significant differences between the groups. Tetris requires some cognitive effort and, in fact, there is accumulating evidence that Tetris has some beneficial effects on attention and visuo-spatial ability in healthy subjects [190], selective attention in older adults [191], and mental rotation measures in young, healthy adults [192]. Furthermore, skilled Tetris players outperform non-Tetris players on other mental rotation tasks, but not on other tests of spatial ability [193].

Considering these caveats with an active placebo interventions and our experience with the pre-post changes in the Tetris group in our first trial, we chose a TAU control group for our second trial. Although this kind of control condition implies a number of biases, as mentioned above, we also considered it important not to obscure any effects of ACTIVATE™ with an overactive placebo condition, especially as ACTIVATE™ had not been tested at that time. Comparison with an active intervention would have made it more difficult to interpret negative results. To include a second active control group would have required a much larger sample size than what we would have been able to recruit.

Similar issues were raised in the two other previously described studies of broader executive functions training [139, 140] which compared the same intervention to a waitlist control in one trial and a placebo condition in the second trial. Dovis et al. [139] created an appealing control condition with application of game-design elements and game principles and obtained good adherence. Both trials used the same intervention, population, and intervention period, but they obtained different results, which may be ascribed to their use of dissimilar control conditions. While the TAU control group may have inflated the results in the Van der Ord et al. [140] to some degree, the active placebo may have hidden some significant group differences in the study by Dovis et al. [139]. Hence, the active placebo control group also showed some significant pre-post changes, which indicates that there may be a cognitive effect even in low-load interventions [139]. An optimal design for disentangling the effects of an active placebo condition would be one that included both an active placebo and a passive control group. Such a design would require a substantial sample size, which is probably one of the reasons why such a study has not yet been conducted.

Dose response of training

Our intervention was somewhat similar to the intervention in the study by Dovis et al. [139] and the study by Van der Oord et al. [140] as the games in ACTIVATE™ also focus on attention, working memory, set shifting, and impulse inhibition. Contrary to us, Dovis et al. [139] found significant differences regarding working and short-term memory, inhibitory performance, and interference. However, neither Dovis et al. [139] nor Van der Oord et al. [140] used a measure of planning ability, which we found had a significant exploratory effect. An important difference between our trial and these two trials is that the study participants in Van der Oord et al.'s [140] trial completed at least 20 out of 25 sessions and the study participants in Dovis et al.'s [139] trial completed 25 sessions with only 3% not meeting compliance criteria. As we adopted an intention-

to-treat design in our analyses, we kept everyone in the intervention group regardless of the number of sessions performed. The compliance in our intervention group was low, and only 66.5% of our participants performed 20 or more sessions. We performed a post-hoc analysis in which controls were compared with compliers, defined as participants performing at least 20 sessions, and non-compliers, defined as participants performing less than 20 sessions. We found that compliers showed significant differences on only one measure of inhibition and the parent-rated BRIEF Metacognition Index subscale, while non-compliers did not. This may indicate that executive functions training may affect performance on the BRIEF Metacognition Index and inhibition when a certain training intensity is fulfilled. On the other hand, it seems that some functions like planning ability may not require intense training as both compliers and non-compliers showed significant differences as compared to controls. As our analyses were exploratory, these hypotheses need to be tested in future trials. The optimal dose of training has not been investigated in cognitive training trials for ADHD. One interesting study with normally developed children investigated the same total amount of training spread across 2, 5, 10, or 20 days [194]. All groups improved on the trained task, but only the 20-day training group showed significant far transfer. The optimal duration and intensity of training for youth with ADHD still has to be determined.

Target of training

Most cognitive training approaches are based on a number of assumptions. Tajik-Parvinchi and colleagues [195] formulated three prevalent assumptions dominating the cognitive training rationale: 1) the higher-order assumption where a particular cognitive function, e.g. working memory, is assumed to predict or influence a range of other cognitive functions. It is believed that improving this particular function will automatically generalize to other connected functions and/or symptoms. 2) The central-deficit assumption implies that a certain function is a central deficit in ADHD, often assuming that this is equal to the largest deficit. 3) The task-purity assumption assumes that a specific training task is targeting the cognitive function of interest.

The first two assumptions have found no support in the literature as the central cognitive deficit in ADHD has not been identified; and there is evidence for heterogenic, multiple cognitive dysfunctions in individuals with ADHD [44, 45]. To date, no ADHD-specific cognitive profile has been detected; and individuals with ADHD differ in terms of the degree and range of their specific cognitive dysfunctions. Considering this cognitive heterogeneity, it would make sense to provide individualized cognitive training for individuals with ADHD. A general problem in cognitive training for ADHD is that no single study has so far been able to tailor interventions to the individual cognitive deficits of the trial participants or has taken the baseline cognitive deficits into account

when choosing the intervention or performing the randomization. True also for both of our trials is that common practice includes participants with ADHD without considering individual cognitive dysfunctions at baseline. Despite evidence for the presence of heterogenic cognitive dysfunctions and symptom profiles [44, 45, 68], individuals with ADHD are still assumed to have equal needs and to benefit equally from the intervention. A child with ADHD with attention and impulse inhibition deficits and normal-range working memory may benefit little from working memory training and may show no far transfer towards attention or impulsivity. In fact, the connection between specific cognitive deficits, their hierarchical order and interaction, and the potential of generalization to other cognitive dysfunctions and symptoms have not yet been empirically proven [195].

The third assumption, task-purity [195], has been the subject of ongoing debate for a number of years. It has been questioned to which extent cognitive training interventions in general target the intended cognitive functions, especially in case of working memory training. Although many interventions claim to train working memory, researchers have suggested that the majority of working memory programs do, in fact, train short-term memory instead [107, 117] because they mostly focus on simple span tasks training, which targets short-term memory. Tajik-Parvinchi et al. [195] found that trials using simple span task, like Cogmed, did not show far transfer effects, while trials using complex span task did. This indicates that simple span tasks may not aim at the right target.

In our trials, we targeted multiple cognitive functions simultaneously with the intention to embrace the diversity of cognitive deficits presented in individuals with ADHD. This approach did not yield the expected results. This may be so for a number of reasons related to task-purity issues, or may be so because we did not target the right functions, did so with too low intensity, because the intervention was not sufficiently engaging and motivating, or because the majority of participants were not particularly deficient on the targeted functions. Considering the heterogeneity of ADHD on the cognitive, neural, and symptomatic level, it would be important to investigate the effects of cognitive training at a subgroup level in search for specific groups that may benefit from certain kinds of cognitive interventions. Also the issue of different ADHD subtypes should be considered in future trials. In an examination of ADHD subtype in our second trial (paper III), we found that compared with controls, the gains of intervention were largest for the inattentive subtype (ADHD-I), showing significant differences in working memory, planning ability, and impulse inhibition; and on the parent-rated BRIEF Metacognition Index. Inversely, compared with controls, the combined subtype showed significant improvements only on the planning ability. Research indicates that the combined and the inattentive subtype may differ at the neurological level [196] and may thus need different interventions. Unfortunately, most trials to date did not have large

enough sample sizes to allow these explorations. In future studies, the approach should be driven by the specific needs at the individual level, i.e. an individualized cognitive training approach should be adopted in which the participants' baseline cognitive profile is taken into account.

Methodological issues: Strengths and limitations

Trial 1. (Paper I):

We conducted a randomized, controlled double-blind trial with no pro-profit bias. Several limitations should be taken into account when interpreting the results. Our sample size was small and, most importantly, the control intervention (Tetris) showed some beneficial effects on cognitive measures indicating that it was not useful as an active placebo condition. We did not control for the time trial participants spent on electronically devices and computer games in their free time outside the intervention. SBT exercises might not be the best choice for adolescents with ADHD as they were originally designed for adults. Hence, based on our trial design and the data obtained, we cannot conclude for sure that training with SBT would not have had beneficial effects on cognition or symptoms in adolescents with ADHD in a different setting.

Trial 2 (Paper II and III): Our second trial has a number of strengths: The drop-out rate during the intervention was small. We performed intention-to-treat analysis, using full information maximum likelihood estimator to account for missing data. Additionally, we ensured adequacy of generation of allocation sequence, allocation concealment, and blinding wherever possible. Our outcome measures were a priori defined as primary, secondary, and exploratory outcome measures in our published trial protocol [197] and there is no for-profit bias. However, our trial does have some limitations: Due to our TAU design, we were not able to blind the participants, their parents, or teachers to group allocation. Although we included objective outcome measures, our secondary outcome measures consisted of questionnaires rated by parents and teachers who were not blinded to group allocation. Additionally, we were not able to recruit the number of participants we originally anticipated, which reduces our power to detect significant differences. At our two follow-up time points, many participants did not return the questionnaires, why we choose not to analyze these survey data. Our exploratory analyses regarding age effects, ADHD subtype, and compliance, were performed on a relatively small number of participants. The teacher ratings were not always provided by the same teacher, which can induce natural variability in scores and may explain some of the unusual results we found. Furthermore, we did not control for the time participants spent on computer games in daily life. We were not able to conduct all the analyses we had planned (Paper II). In our protocol, we stated that with the intention to improve efficiency, all auxiliary variables present among the outcomes would be added to the model. However, we have not done this. Because of the nature of our data, no outcomes could be added as auxiliary variables. This implied

that usually all outcomes were missing if data on a single outcome were not obtained. In some cases, we could have used auxiliary variables. Still, we avoided doing so because we considered it irrelevant due to the overweight of negative findings. Additionally, because we recruited fewer participants than anticipated, we prioritized to keep a reasonable ratio between model parameters and observations. We did not perform sequential analysis to assess the results of significance testing, taking the sparse data into consideration. We were not able to conduct blinded statistical analysis.

In both of our trials, we found some significant differences between groups at baseline favoring the control group for an attention measure in the first trial and for a number of subscales including the total score on the parent-rated BRIEF questionnaire. These significant differences may suggest that the randomization did not work as intended. On the other hand, in general, the significant differences in our trials both before and after intervention may be due to chance considering the large number of outcome variables tested.

Conclusions and future directions

We conducted two different trials with two different populations, children and adolescents, to address the questions whether cognitive training targeting multiple cognitive functions can help children and adolescents with ADHD to improve cognition, symptoms, and functional outcome. The results of both trials indicate that cognitive training is associated with no gains for the broader ADHD population as far as cognition and severity of ADHD symptoms are concerned. In the first trial, we found no effects of broader cognitive training on any cognitive or symptom measures for adolescents with ADHD. However, these results may have been biased by our choice of active control group. In our second trial, ACTIVATE™ did not show any effect on any of our primary or secondary outcomes for children with ADHD, indicating no effects on sustained attention, symptoms of ADHD, and executive functions in an intention-to-treat analysis. However, we found that there may be beneficial effects on the ability to plan. We also found some interesting effects at the subgroup level regarding the age of participants, ADHD subtypes, and the number of training sessions completed. Our results indicate that certain subgroups of patients with ADHD, like older individuals and the ADHD inattentive subtype, may benefit more from cognitive training than others. Also other factors, like intensity of training and compliance, may be important when considering the effect of cognitive training.

It would be important to design intervention programmes that intrinsically motivate and engage participants in future trials. New cognitive training interventions should have a more

complex design with possibilities for tailored individualized training taking individual cognitive deficits and needs into account. In addition, the fact that many young people today spend a considerable amount of time playing computer games may have a cognitive effect in itself and should be controlled for in future studies. Our findings also suggest that it may be relevant to explore the possible beneficial effects of popular computer games, like Tetris, on cognition, many of which are freely available on the Internet. A crucial task for the future of this field of research is to identify active control interventions that do not have direct, beneficial effects on the outcome measure while being engaging and fun at the same time.

The evidence from our and previous studies does not indicate that cognitive training should be recommended as a clinical intervention for ADHD. However, before finally dismissing cognitive training as a possible treatment option, in future studies it would be important to investigate the effects of individualized, motivating approaches on specific cognitive functions and symptoms, especially in older children with ADHD. Considering that ADHD is a very heterogeneous disorder with great inter-individual variation, future studies with larger samples should investigate effects at subgroup levels.

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Papers I-III

Research Article

A Double-Blind Randomized Pilot Trial Comparing Computerised Cognitive Exercises to Tetris in Adolescents with Attention-Deficit/Hyperactivity Disorder

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Cognitive Training in Adolescents with ADHD

Abstract

Background: To examine the feasibility and efficacy of computerized cognitive exercises from Scientific Brain Training (SBT), compared to the computer game Tetris as an active placebo, in a pilot study of adolescents with Attention-deficit/hyperactivity disorder (ADHD).

Method: Eighteen adolescents with ADHD were randomized to treatment or control intervention for seven weeks. Outcome measures were cognitive test, symptom and motivation questionnaires.

Results: SBT and Tetris were feasible as home-based interventions and participants' compliance was high, but participants perceived both interventions as not very interesting or helpful. There were no significant group differences on cognitive and ADHD-symptom measures after intervention. Pre-post intra-group measurement showed that the SBT had a significant beneficial effect on sustained attention, while the active placebo had significant beneficial effects on working memory, both with large effect sizes.

Conclusion: Although we found no significant differences between groups on any measure there were significant intragroup changes for each group.

Trial registration:

Retrospectively registered at clinicaltrials.gov: NCT02728011, date of registry March 24, 2016

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Keywords: ADHD, cognitive training, working memory training, adolescents, CANTAB, Tetris.

Background

Attention Deficit/ Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity and impulsivity symptoms with an estimated prevalence of approximately 5% [1-3]. ADHD has been shown to be associated with severe reductions of academic performance and psychosocial functioning [4, 5] and increased school drop out rates [5]. Affected individuals are more susceptible to develop other psychiatric disorders, substance abuse, criminality, adverse health events and premature death [6-14].

The etiology of ADHD is still unknown, but a complex interplay between multiple genes and environmental risk factors seems to be the most likely explanation [15]. Imaging studies have found evidence for a global brain volumetric reduction of approximately 10% in subjects with ADHD [16-18] and a mean delay of cortical maturation of three to five years when compared to typically developing controls [18]. Besides the evidence of both structural and organizational differences in the brain of children with ADHD compared to controls, there is also a significant impairment in a range of cognitive functions, mostly in spatial working memory, impulse inhibition and vigilance [19, 20]. Cognitive dysfunctions are strongly related to the ability to cope in daily life, typically denoted as functional outcome [21, 22] and are not very well targeted by pharmacotherapy, the first choice treatment for ADHD. Pharmacotherapy only partially alleviate cognitive dysfunctions [23] and seem to have little or no effect on specific executive functions, while beneficial effects are only evident on cognitive tasks without executive components [24, 25]. In addition twenty to thirty percent of patients do not respond to pharmacotherapy, some

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have adverse effects [26-28] and the long-term effects are both understudied and relatively unknown [29-32]. Therefore exploration of non-pharmacological treatments in randomized controlled trials is necessary.

Cognitive training, most often a computer-based intervention that consists of different game-like programs designed to ameliorate cognitive functions, has been under investigation for the past decade as a treatment for ADHD. Cognitive training is theoretically rooted in neuroplasticity and in the assumption that training can result in formation and/or reorganization of neurological functions. A number of trials have examined cognitive training programs, targeting different aspects of cognition. The vast majority of trials have focused solely on training working or short-term memory [33-35]. Fewer trials have focused on attention alone [36-39] or mixed executive functions [40, 41]. To date, several meta-analysis have been conducted on the existing cognitive training trials [34, 42-45], and the overall conclusion from those is that working / short term memory has near-transfer effects, meaning that working memory training does improve the functions, that are directly targeted in training, in this case short-term and working memory in moderate effect sizes, but these effects do not generalize to other untrained cognitive functions, which is referred to as far transfer [42, 43, 45]. For verbal working memory, these near-transfer effects were not sustained at follow-up, whereas for visuo-spatial working memory, limited evidence suggested that such effects might be maintained [44]. On the other hand training attention and mixed executive functions do not show significant near transfer effects [45].

There are significant far transfer effects of cognitive training to ADHD symptoms and ratings of executive functions only when reported by raters most proximal to the treatment setting (who are most likely not blinded) but not when rated

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by probably blinded raters [42]. Cortese and colleagues (2015) concluded that there were no effects of working memory training specifically on ADHD symptoms. In contrast, interventions targeting multiple neuropsychological deficits had large effects on ADHD symptoms rated by probably not blinded raters (Standardized Mean Difference (SMD)=0.79) [42].

Some effects of cognitive training were also found on the neural level. Functional magnet resonance-imaging (fMRI) studies have found response inhibition tasks to increase activity in orbitofrontal, superior frontal, middle temporal and inferior frontal cortex and a selective attention task increased activity in cerebellum, the latter correlated with improvement on measures of attention after only ten days of combined attention and executive functions training [46]. The same kind of training was also found to increase focal volumetric gray matter in bilateral middle frontal cortex and right inferior-posterior cerebellum [47].

Most previous studies examining effects of cognitive training have focused on children, and there is a lack of studies on adolescents with ADHD [41, 48]. Adolescents with ADHD may be particularly important targets for new treatments, as they often discontinue pharmacological treatment with few alternative treatment options available. The primary aim of this trial was to examine the feasibility of a series of tasks from the computer program Scientific Brain Training (SBT) compared to the computer game Tetris in adolescents with ADHD. Feasibility was defined as the perceived interest and self-reported value of the training, as well as the participants adherence to the program. The secondary aim was to evaluate the effect of SBT on cognition and ADHD-symptoms as compared to an active control group.

Method

Setting and Sample

Participants were recruited from the child and adolescent psychiatric departments in the Region of Southern Denmark, in September 2010 and the trial was conducted from October to December 2010. Participants who fulfilled the following criteria were included: 1) a clinical diagnosis of hyperkinetic disorder (F90.0, corresponding to ADHD combined type) [49]; 2) age between 14-17 years; 3) IQ > 80. The exclusion criteria were: 1) pharmacological treatment other than methylphenidate, dexamphetamine and/or atomoxetine; 2) comorbid conduct disorder, autism spectrum disorders or major depression; 3) history of head trauma or verified neurological disease; 4) motor or perceptual disabilities which prevented the use of a computer; 5) medical illness that required treatment; and 6) no access to a computer and internet at home.

In Denmark clinical assessments within child and adolescent psychiatry are performed using ICD-10 criteria [49]. Only adolescents with the most narrow definition of Hyperkinetic Disorder (F90.0), which is a valid proxy for ADHD combined type were included into the study [50, 51]. We identified 135 adolescents with ADHD at the clinic. Screening of case records for exclusion criteria of these individuals identified 91 fulfilling exclusion criteria. Parents of the remaining 44 eligible for inclusion received information about the study and eighteen provided written informed consent. Participants were a mean age of 15.6 years (Standard deviation (SD)=0.99) and were all Caucasian. The sample consisted of 76.5 % boys. All participants had a clinically estimated IQ with Wechsler Intelligence Scale for Children (WISC)-IV [52] higher than or equal to 80. See Figure 1. for the flowchart

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of participant inclusion. CONSORT Extension for Non-Pharmacologic Treatment Checklist can be reviewed in the Appendix.

(Insert Figure 1 about here)

Measures

A psychologist blinded to the randomization status tested all participants with Cambridge Neuropsychological Test Automated Battery (CANTAB) [53] before randomization and within one week after seven weeks of training. Parents, participants and teachers completed the Attention Deficit/Hyperactivity Disorder-Rating Scale (ADHD-RS) [54] before randomization and again after seven weeks of training. Participants also filled out the Activity Perception Questionnaire (APQ) after the intervention [55]. APQ measures motivation and the perceived meaningfulness and value of the intervention and was used to determine the feasibility of the treatment at the end of the intervention. Participants were recruited from the same center, but they did not go to the same school district. We asked parents to take the questionnaires to the teachers, to fill them out and bring them back to the next appointment.

Cognitive functions were assessed with the following tests from CANTAB: The Motor Screening Task (MOT) screens for visual, movement and comprehension difficulties.

The Big/Little Circle (BLC) test assesses comprehension, learning and reversal.

Attention tests:

Rapid Visual Information Processing (RVP)(A' and probability of hit) is a test of sustained attention (similar to the Continuous Performance Task). Match to Sample Visual Search (MTS) (percent correct) is a matching test, with a speed/accuracy

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trade-off. It is a simultaneous visual search task with response latency dissociated from movement time. Efficient performance on this task requires the ability to search among the targets and ignore the similar distractor patterns. Visual memory: DMS Delayed Matching to Sample (DMS) assesses forced choice recognition memory for novel not verbalized patterns, and tests both simultaneous and short-term visual memory. Executive functions: Spatial Span (SSP) (Span Length) assesses working memory capacity, and is a visuo-spatial analogue of the Digit Span test. Spatial Working Memory (SWM) (between errors and strategy) is a test of the ability to retain spatial information and to manipulate remembered items in working memory. Stockings of Cambridge (SOC) (problems solved in minimum moves) is a spatial planning test. The time used to complete the pattern and the number of moves required are taken as measures of the user's planning ability. Intra-Extra Dimensional Set Shift (IED) (stages completed) is a test of rule acquisition and reversal. It features visual discrimination, attentional set formation maintenance, shifting and flexibility of attention. This test is a computerized analogue of the Wisconsin Card Sorting test. Two artificial dimensions are used in the test: Color-filled shapes and white lines.

The following rating scales were used: 1) Feasibility was measured by the Activity Perception Questionnaire (APQ) that measures different dimensions in a computer-related activity [55]: a) Interest (did you like the training, was it interesting); b) Value (was it useful to do the training) and c) Choice (was it your own choice to play). APQ consists of 25 questions that are rated on a Likert scale from 1 to 7 (1 corresponds to "not true at all", 4 corresponds to "somewhat true" and 7 corresponds to "very true"). 2) ADHD-Rating Scale (RS) is a 26-item symptom rating scale, comprising nine items on inattentiveness, nine items on hyperactivity/impulsive behavior and eight questions on oppositional behavior [56].

Intervention

SBT Exercises.

The intervention group used a selection of beta-exercises from Scientific Brain Training (SBT)-program [57], which is a commercially available program for adults. Out of nine cognitive exercises available at that time, we selected six. The remaining three were excluded, as they were not considered appropriate for this age group. The following SBT exercises were used: Entangled Figures, Shapes and Colors, Under Pressure, Displaced Characters, Heraldry and Objects Where are You? The games had different difficulty levels and adjusted automatically to the user's performance. Promotion to the next level depended on 90 % accuracy three times in a row at one level. If the accuracy was under 60 % twice in a row, the user was automatically returned to the previous level. Participants played two games each week in a rotating manner independently of participants' performance each week.

Following exercises were used: 1) Entangled figures: This exercise trains visual and spatial skills and working memory. Characteristics of an object have to be identified and memorized and then the details are transformed into a whole by visualizing them. 2) Shapes and Colors: The goal is to memorize several figures of various shapes and colors and then recognize them among slightly different ones. This exercise demands attention to detail and the use of discrimination and differentiation for shapes and tests visual short-term memory and building strategies. 3) Under Pressure: Three types of stimuli (a red circle, a black cross, and a letter) appear one after another at different spots, anywhere on the screen. The aim is to determine quickly whether the red circle appears above or below the black cross. This task trains sustained attention and vigilance. 4) Displaced Characters: The task is to attentively observe figures in one list, and select in a second list those figures that are

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not in the first list. At the beginning of the task, both lists are on the same screen (direct comparison). At later stages, they are on separate screens. This task focuses on a process of distinguishing visual shapes and differences, as well as similarities amongst the characters. 5) Heraldry: The task is to memorize a coat of arms with all the elements that make up the heraldry, thus paying attention to shapes, colors, and patterns to distinguish between the various details. The user then has to recreate the coat of arms with its components. This exercise focuses on visual and spatial memory and perception and aims to improve visual attention and concentration skills. 6) Objects, Where are You?: The task is to memorize the location of several pictures on a grid, and then recall them in the same spot. This exercise trains visual and spatial memory and perception as the user has to create associations between two types of information, an image and its location. It requires a strategy to make a comprehensive association in order to memorize objects, maintaining attention to detail and a focus on the visual and spatial information.

Control intervention: Tetris.

The control group played a common version of the game Tetris. Tetriminos are game pieces composed of four-square blocks. Tetriminos fell down randomly into the playing field, which is a rectangular vertical shaft. The aim is to manipulate the function of these Tetriminos by moving each one sideways and rotating by 90-degree units. The aim is to create a horizontal line of ten blocks without gaps. When such a line is created, it disappears, and any block above the deleted line falls down. When a certain number of lines is cleared, the game enters a new level. At each subsequent level the Tetriminos fall faster, and the game ends when the stack of Tetriminos reaches the top of the playing field and no new Tetriminos are able to enter. The game

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was not adaptive in terms of the fact that participants had to start on the lowest level each day.

Procedures

This was a randomized, double-blinded trial. Prior to randomization, the parents, participant and a teacher completed the ADHD-RS questionnaire and all participants were tested with CANTAB. The 18 participants were then randomized to either active intervention with SBT exercises or Tetris. A clinician, unrelated to the trial and blinded to baseline data and participant ID, performed the randomization by selecting the numbers assigned to each participant from an envelope. Participants and parents were blind to group allocation. They were informed that one of the two treatments was expected to be more effective than the other. Both groups were introduced to their assigned computer game at the clinic. All participants received an individual username and password and used these to access the computer game to which they were allocated to, at a secure online web-based platform, designed for this trial. They were asked to play at home for half an hour a day, five days a week for seven weeks. Compliance was measured as each login was registered for both groups. The amount of time of playing and progress on games was only registered for the SBT group. The SBT homepage automatically closed down the program after 30 min of playing. The control group played Tetris and participants and their parents used a timer to control for time. All participants and their parents received a daily reminder by a text message on a cell phone. The principal investigator called the parents and participants once a week to discuss compliance or any possible problems.

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Statistical Analyses

The intervention and placebo groups were compared before and after treatment using t-test and repeated measures analysis of variance (ANOVA) when the outcomes of interest were normally distributed, and non-parametric Wilcoxon-Mann-Whitney test otherwise. APQ scores were tested using two-sample t test with equal variances. Intra group correlations were measured using one way ANOVA when the outcome of interest was normally distributed and the non-parametric version was used when the outcome of interest was not normally distributed (Friedman test). The participant who dropped out of the trial was excluded from the statistical analysis. The level of significance was set at $\alpha > 0.05$ in all analyses. All analyses were carried out using statistical program Stata version 11.

Results

Eighteen subjects were found eligible for the trial and randomized to treatment or control intervention. One patient withdrew consent after randomization, leaving nine subjects in the intervention and eight in the active placebo group.

Baseline Characteristics

Individuals allocated to the two groups were comparable on a number of characteristics at baseline. There were no significant differences in the medication status in the two groups as there were three non-medicated patients, one in control and two in the intervention group. One individual dropped out of the trial shortly after randomization (see Figure 1.). A total of 15 participants out of 18 received pharmacotherapy for ADHD (all methylphenidate) and they were asked not to change their medication status during the intervention period. Hence, we found no

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statistically significant group differences in the severity of ADHD symptoms, or the majority of the cognitive measures on CANTAB (see Table 1.). There were no significant differences in gender distribution or mean age across groups. However, at baseline prior to the intervention, there was a significant group difference on the attention measure RVP probability of hit ($p < 0.01$), with the placebo group performing better than the intervention group.

(Table 1. about here)

Feasibility of Computer Programs

Patients were asked to engage in the allocated intervention (SBT or active placebo, respectively) five times per week, for seven weeks. There were no significant differences in compliance measured by the number of completed sessions for all participants in both groups. The whole SBT group completed an overall total of 281 sessions (mean: 34.4, SD: 3.4) and the control group completed 275 sessions (mean 31.2, SD: 4.9) ($p=0.15$).

Individuals in both groups rated their perception of their respective computer programs, measured by three indexes on APQ [55]. We found no significant group differences between the two groups on any of the three subscales when measured with t-test for independent groups. APQ- subscales did not show any significant differences between the intervention and control group: APQ-Interest intervention group ($M=2.65$, $SD=1.50$), control group ($M=2.97$, $SD=1.42$), $t(14) = 0.4378$, $p = 0.0668$. APQ- Value intervention group ($M=2.91$, $SD=1.26$) and the control group ($M=3.35$, $SD=1.58$), $t(14) = 0.6236$ $p = 0.543$, APQ-Choice intervention group ($M=4.27$, $SD=1.20$) and the control group ($M=4.89$, $SD=0.95$) t

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(14) = 1.110 $p = 0.2856$. (see Table 2). Although there were no significant differences, participants playing the active placebo Tetris tended to perceive it slightly more positively than participants perceived SBT, on all measures. Both groups perceived both interventions as not very interesting and of little value to them. They experienced to have a moderate to high degree of Choice to engage in both interventions, meaning they perceived it as their own choice to play the games and they felt not forced by others (e.g. parents).

(Table 2. about here)

Effects of Intervention on Cognition and Symptoms

The secondary aim of this trial was to compare the effect of SBT and placebo on the cognitive functions and ADHD symptoms. There were no significant between group differences on any of the cognitive outcome measures measured with ANOVA: DSM percent correct $F(1,33)=0.24$, $p=0.63$; RVPA' $F(1,33)=2.94$, $p=0.106$; RVP Probability of hit $F(1,33)=1.94$; $p=0.18$; SOC problems solved in minimum moves $F(1,33)=1.59$, $p=0.34$; SSS Span length $F(1,33)=0.93$, $p=0.349$; SWM between errors $F(1,33)=2.40$, $p=0.142$; SWM Strategy $F(1,33)=1.45$, $p=0.247$. IED stages completed was analyzed with non-parametric Wilcoxon-Mann-Whitney test $z=0.42$, $p=0.67$. There was a significant difference at baseline visual sustained attention (RVP) with the control group outperforming the intervention group.

However there were significant pre-post within-intragroup differences on some outcome measures, in both groups (see Table 3). Thus, in the SBT group, there were significant pre- to post-effects on two outcome measures of visual sustained attention RVPA' $F(1,17)=18.53$, $p=0.0026$ and RVP Probability of hit

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$F(1,17)=14.63$, $p=0.0051$, indicating a better visual sustained attention after seven weeks of training with SBT with very large effect sizes (1.5 and 1.3). Similarly, the placebo Tetris group showed a significant effect in pre to post test on a measure of spatial working memory SWM Between errors $F(1,15)=6.20$, $p=0.0417$ with a large effect size (0.88).

(Table 3 about here)

There were no significant differences on symptoms from pre to post as measured with ANOVA for the ADHD-RS (see Table 4). After intervention ADHD-parents intervention group ($M=29.4$, $SD=11.4$) was not significantly different from the control group ($M=5.7$, $SD=14.2$), $F(1,31)=0.17$, $p=0.679$. ADHD-teachers intervention group ($M=28$, $SD=19.9$) was not significantly different from the control group ($M=27$, $S=22.2$), $F(1,21)=0.01$, $p=0.92$. ADHD-adolescent intervention group ($M=4.27$, $SD=1.20$) and the control group ($M=4.89$, $SD=0.95$) did not differ significantly $F(1,28)=0.00$, $F=0.976$. No adverse events were reported.

(Table 4 about here)

Discussion

This clinical, randomized, double blind trial was the first trial comparing SBT exercises with Tetris in adolescents with ADHD and it showed that both interventions were feasible to be used as home based interventions in this age group. The trial also found that participants' compliance regarding both interventions was high. Despite the technical feasibility and high compliance, the participants rated

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both interventions as of little interest and of little value to them. Our selection of SBT exercises tended to be perceived slightly less interesting than the popular computer game Tetris by the participants, but there were no significant differences. The results indicate that both interventions are feasible, but not very interesting for adolescents with ADHD. Both groups scored modest on the APQ measure Choice, indicating that they may have felt pressured by the parents to engage in the interventions. The design of the SBT games does not seem to be age-appropriate for this target group. Tetris seemed to be more engaging than the SBT games for adolescents. Motivation is important for sustaining the focus of adolescents with ADHD on cognitive training and the fact that both groups had low scores on Interest and Value in the APQ might suggest that the adolescents felt little motivation to engage in the interventions, which may have had negative influences on treatment effects.

Effects on cognition and symptoms

We found no significant differences between groups using SBT exercises and Tetris on cognitive and symptom measures as assessed by CANTAB and ADHD-RS, respectively. However, the absence of significant differences between groups may be due to the small sample size of the trial. Despite the randomization, there was a significant difference on the attention measure RVP Probability of hit at baseline, favouring the Tetris group. The SBT exercises group showed a significant intra group improvement on exactly this measure from baseline to post assessment with a large effect size, but with no significant difference between the two groups.

Both SBT and Tetris showed positive pre-post intra group effects on different cognitive functions. SBT showed a significant pre-post intra-group

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beneficial effect on two outcomes of sustained attention (RVPA' and RVP Probability of hit) with large effect sizes. Tetris had a significant positive pre-post intra-group effect on spatial working memory (SWM Between errors) with a large effect size. These results are consistent with previous findings indicating that training of specific cognitive functions primarily has effects on these specifically trained functions regarding attention [36, 38, 39] and working memory training [33, 40, 41, 58]. However, generalisation to other cognitive or functional domains seem much more difficult to obtain [45]. Some studies of working memory and attention training have shown generalization effects to untrained cognitive domains [33, 58] and a reduction of symptoms on rating scales [38, 58, 59]. Two meta-analyses have shown that there is generally a greater effect on symptom scales when rated by parents, who are not blind to the nature of the intervention compared to ratings by blinded raters [45, 60]. However for children with ADHD there is in general a weak correlation between parent and teacher ratings for inattention symptoms and a moderate correlation for hyperactivity/impulsivity symptoms [61].

Our results also demonstrated the obvious. In cognitive training trials in general, it is crucial to identify and use the right kind of control condition. At the same time it is difficult to find the right sham treatment. In order not to produce an effect, a sham treatment has to be cognitively non-challenging. This kind of intervention might not be interesting and engaging for the participants for a period of several weeks and cause attrition in the control group. If a more engaging intervention, like Tetris is used, it might have a too large impact on cognitive functions and a difference between groups can no longer be detected. Tetris may be too active of an intervention and may not be useful as a control activity. In fact, there is accumulating evidence that Tetris has some beneficial effects on attention and

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visuo-spatial ability in healthy subjects [62], selective attention in older adults [63] and mental rotation measures in young, healthy adults [64]. Tetris requires some cognitive effort, as the participants must stack falling objects efficiently using mental rotation and planning. There is also evidence suggesting that skilled Tetris players outperform non-Tetris players on other mental rotation tasks, but not on other test of spatial ability, suggesting that they are faster in their response because they use the same mental rotation procedures [65]. Alternatively, using a treatment-as-usual control group can be an option. However, this will not control for the placebo effect, contact with the therapist or contact with the computer screen, biases, which may lead to over-estimating the effect of an active intervention.

The beneficial effect of Tetris on working memory, that we found, could be explained by some working memory load in the Tetris game. SBT did not target one specific cognitive measure, but several cognitive functions. Therefore the training load on each individual cognitive function may have been too small. Considering the great cognitive heterogeneity in individuals with ADHD, it would make sense to provide an individualized cognitive training. To date, no ADHD-specific cognitive profile has been detected and individuals with ADHD differ in the degree and range of their specific cognitive dysfunctions. Most cognitive programs are not tailored individually to the cognitive deficits of each person. Furthermore, it is uncertain in which extent cognitive training interventions in general actually target the intended cognitive functions. For instance, although many interventions claim that they train working memory, researchers have suggested that some of these programs in fact train short-term memory instead [66].

The results of this trial should be interpreted in light of some limitations. First, the sample size was small, the control intervention (Tetris) did not act as a

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placebo as intended but seem to actually have beneficial effects on cognitive measures. SBT was originally designed for adults and seem not be suitable and interesting for adolescents. Hence, based on our data and study design we cannot conclude that training with SBT has no beneficial effects on cognition or symptoms in adolescents with ADHD.

Future trials in this age group should be focussed on designing and using an intervention program that motivates adolescents and find alternative control interventions that don't have direct beneficial effects on cognition. New cognitive training programs should be developed to offer a more complex and engaging design and with possibilities for individualized training. Today, many adolescents engage in very complex computer games on a daily basis and compared to these games many cognitive training programs available today may seem somewhat primitive in their design. In addition, the fact that many young people today spend a considerable amount of time playing computer games might have a cognitive effect and should be controlled for. Our findings suggest that it may be relevant to explore the possible beneficial effects on cognition of popular computer games like Tetris, many of which are freely available on the Internet.

Conclusion:

This pilot trial comparing SBT exercises with Tetris in adolescents with ADHD showed that both interventions were feasible to be used as home based interventions, but were not very interesting and engaging for this age group. Although we found no significant differences between groups on any measure there were significant intragroup changes for each group indicating beneficial effects on specific aspects of cognition. It is important to acknowledge the need of designing more interesting and

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engaging cognitive training interventions for adolescents to be able to draw conclusion about their effect. Additionally this trial is highlighting the possible beneficial cognitive effects of mainstream computer games.

Declaration

Ethical Approval and Consent to participate

The trial was conducted in accordance with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (2010-41-4970) and the Regional Scientific Ethical Committee for Southern Denmark (S-20100075). All participants and their guardians provided written consent before participation in the trial.

Consent to Publish

Written informed consent was obtained from the participants and their guardians for participation in the trial and publication of data. The consent form is held by the authors and is available for review by the Editor-in-Chief. However because of the small population data on gender and age have been removed from Table 1. to ensure that individuals could not be identified.

Availability of supporting data

Original data is available upon request. Data will be stored in Rigsarkivet [67], a Danish national data storage agency and can be accessed there.

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Competing interests:

Torben Østergaard Christensen holds the license for the Danish version of Scientific Brain Training (SBT) subsequently revised and now referred to as Happy Neuron Pro. The other authors have no conflicts of interest.

List of abbreviations

ADHD: Attention-deficit/hyperactivity disorder

ADHD-RS: Attention Deficit / Hyperactivity Disorder-Rating Scale

APQ: Activity Perception Questionnaire

BLC: The Big/Little Circle

CANTAB: Cambridge Neuropsychological Test Automated Battery

fMRI: Functional magnet resonance-imaging

IED: Intra-Extra Dimensional Set Shift

MOT: Motor Screening Task

MTS: Match to Sample Visual Search

RVP: Rapid Visual Information Processing

SBT: Scientific Brain Training

SMD: Standardized Mean Difference

SOC: Stockings of Cambridge

SSP: Spatial Span

SWM: Spatial Working Memory

WISC: Wechsler Intelligence Scale for Children

DMS Delayed Matching to Sample (DMS)

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Authors' contributions

AB: Conception and design of the trial, literature search, collection and assembly of data, data analyses, manuscript writing and final approval of the manuscript. SD: Conception and design of the trial, literature search, data analyses, critical revision and final approval of the manuscript. JFL: Conception and design of the trial, critical revision and final approval of the manuscript. NB: Conception and design of the trial, planning statistical analyses, critical revision and final approval of the manuscript. TØC: Conception and design of the trial, critical revision and final approval of the manuscript. All authors read and approved the final manuscript.

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Table 1.

Title: Participant characteristics at baseline

Description: Specification of participants characteristics and their scores on outcome measures at baseline

	Cognitive training group		Active placebo group		p value
	N=9		N=8		
	Mean	(SD)	Mean	(SD)	
CANTAB					
DMS % correct (all delays)	80.0	(9.4)	79.2	(17.6)	0.90
SSP span length	6.78	(1.39)	7.13	(1.25)	0.60
RVP A'	0.85	(0.66)	0.91	(0.52)	0.09
RVP probability of hit (attention)	0.50	(0.19)	0.70	(0.14)	0.01
SOC problems solved in min. moves	9.00	(2.12)	9.38	(2.13)	0.72
SWM between errors	19.88	(11.77)	23.0	(17.9)	0.68
SWM strategy	31.55	(3.97)	29.5	(4.57)	0.34
ADHD-rating scale, total score					
Parental	33.11	(12.5)	25.75	(11.89)	0.23
Adolescents	23.88	(7.97)	18.63	(10.24)	0.27
Teacher	26.57	(14.12)	24.00	(20.37)	0.79

Legend: Abbreviations: Attention-deficit/hyperactivity disorder (ADHD); standard deviation (SD); Cambridge Neuropsychological Test Automated Battery (CANTAB); Delayed Matching to Sample (DMS) is an outcome for visual memory; Rapid Visual Processing (RVP) measures attention; Spatial Span (SSP) and Spatial Working Memory (SWM) measure working memory; Intra/extra Dimensional Set Shift (IED) and Stockings of Cambridge (SOC) measure executive functions.

Table 2.

Title: Activity Perception Questionnaire (APQ) results

Description: APQ results for both groups after the intervention was completed

	Cognitive training group		Active placebo group		p value
	N=9		N=7		
	Mean	(SD)	Mean	(SD)	
Interest	2.65	(1.50)	2.97	(1.42)	0.668
Value	2.91	(1.26)	3.35	(1.58)	0.543
Choice	4.27	(1.20)	4.89	(0.95)	0.286

Legend: Abbreviations: standard deviation (SD)

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Table 3.

Title: Results on the cognitive outcome measures

Description: Pre-post mean differences between intervention group (N=8) and active placebo group (N=9) and pre-post intra-group differences.

	Mean difference (Time 1 – Time 0)	95 % CI	Pre-post intra- group p value	Cohen's d	Inter-group differences p value
DSM % correct (H)					
Intervention group	3.33	-7.02 – 13.68	0.48	0.24	0.63
Active placebo group	6.25	-2.62 – 15.12	0.14	0.59	
IED stages completed (H)					
Intervention group	- 0.44	1.12 – 0.23	0.91	-0.5	0.52
Active placebo group	-0.13	-1.11 – 1.07	0.72	-0.1	
RVP A' (H)					
Intervention group	0.06	0.03 – 0.09	0.003*	1.5	0.11
Active placebo group	0.02	- 0.03 – 0.06	0.41	0.33	
RVP prob. of hit (attention) (H)					
Intervention group	0.20	0.08 – 0.32	0.005*	1.3	0.18
Active placebo group	0.07	- 0.12 – 0.25	0.41	0.32	
SOC prob. solved in min. moves (H)					
Intervention group	0.67	1.94 – 0.23	0.26	0.4	0.23
Active placebo group	0.25	- 1.32 – 0.82	0.60	0.19	
SSP span length (H)					
Intervention group	0.22	- 0.78 – 1.22	0.62	0.17	0.35
Active placebo group	- 0.50	-1.98 – 0.98	0.80	0.28	
SWM between errors (L)					
Intervention group	1.22	- 8.90 – 11.35	0.79	0.09	0.14
Active placebo group	- 7.13	-13.16 – 0.36	0.04*	-0.88	
SWM strategy (L)					
Intervention group	1.00	-3.37 – 5.37	0.61	0.17	0.25
Active placebo group	- 1.63	-3.72 – 0.47	0.11	-0.65	

Cognitive Training in Adolescents with ADHD

Legend:

Abbreviations: H: a higher score is better; L: a lower score is better. Delayed Matching to Sample (DMS) is an outcome of visual memory; Attention: Rapid Visual Processing (RVP) A' is the signal detection measure of the target, regardless of response tendency (range 0.00 bad to 1.00 good). A' measures how good the subject is at detecting target sequences; Working Memory measures: Spatial Span (SSP), Spatial Working Memory (SWM), Executive functioning measures: Intra/extra Dimensional Set Shift (IED), Stockings of Cambridge (SOC).

*Significant difference.

Cognitive Training in Adolescents with ADHD

Table 4

Title: Mean total scores on ADHD-RS pre- and post-treatment in the intervention group and the active placebo group

Description: Specification of ADHD-RS outcomes at each time point in the trial.

	Pre-treatment					Post-treatment				
	Intervention Group		Active placebo group		Group difference	Intervention group		Active placebo group		Group difference
	Mean	(SD) ¹	Mean	(SD)	p value	Mean	(SD)	Mean	(SD)	p value
ADHD-RS²										
Parents	33.1	(12.5)	25.7	(11.8)	0.23	29.4	(11.4)	25.7	(14.2)	0.68
Adolescents	23.9	(8)	18.6	(10.2)	0.27	21.7	(8.2)	16.6	(10.3)	0.92
Teachers	26.6	(14.1)	24.0	(20.3)	0.79	28.0	(19.9)	27.0	(22.2)	0.98

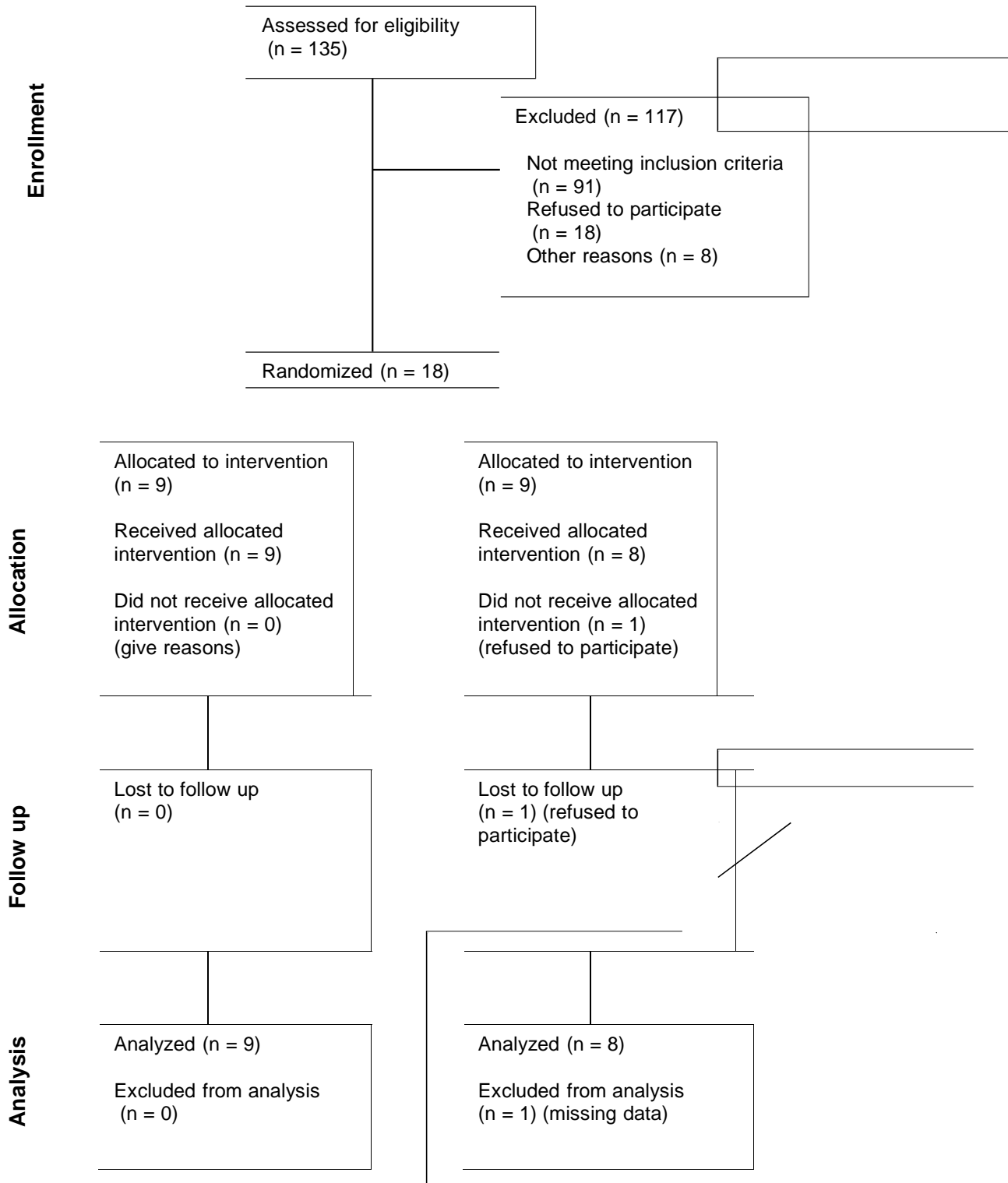
Note: Attention Deficit/Hyperactivity Disorder-Rating Scale (ADHD-RS).

Legend:

¹ SD: standard deviation

² ADHD-RS: attention deficit-hyperactivity deficit disorder rating scale. Minimal relevant difference and SD calculated from a previous pilot project.

Figure 1.
Flow-chart of enrollment



Legend for Figure1:

This chart shows the flow and number of adolescents with ADHD eligible, excluded, randomized, lost to follow-up and analyzed in this study.

Cognitive computer training in children with attention deficit hyperactivity disorder (ADHD) versus no intervention: study protocol for a randomized controlled trial



Aida Bikic^{1,2,3*}, James F. Leckman³, Jane Lindschou⁴, Torben Ø. Christensen⁵ and Søren Dalsgaard⁶

Abstract

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder characterized by symptoms of inattention and impulsivity and/or hyperactivity and a range of cognitive dysfunctions. Pharmacological treatment may be beneficial; however, many affected individuals continue to have difficulties with cognitive functions despite medical treatment, and up to 30 % do not respond to pharmacological treatment. Inadequate medical compliance and the long-term effects of treatment make it necessary to explore nonpharmacological and supplementary treatments for ADHD. Treatment of cognitive dysfunctions may prove particularly important because of the impact of these dysfunctions on the ability to cope with everyday life. Lately, several trials have shown promising results for cognitive computer training, often referred to as cognitive training, which focuses on particular parts of cognition, mostly on the working memory or attention but with poor generalization of training on other cognitive functions and functional outcome. Children with ADHD have a variety of cognitive dysfunctions, and it is important that cognitive training target multiple cognitive functions.

Methods/Design: This multicenter randomized clinical superiority trial aims to investigate the effect of “ACTIVATE™,” a computer program designed to improve a range of cognitive skills and ADHD symptoms. A total of 122 children with ADHD, aged 6 to 13 years, will be randomized to an intervention or a control group. The intervention group will be asked to use ACTIVATE™ at home 40 minutes per day, 6 days per week for 8 weeks. Both intervention and control group will receive treatment as usual. Outcome measures will assess cognitive functions, symptoms, and behavioral and functional measures before and after the 8 weeks of training and in a 12- and 24-week follow-up.

Discussion: Results of this trial will provide useful information on the effectiveness of computer training focusing on several cognitive functions. Cognitive training has the potential to reduce cognitive dysfunctions and to become a new treatment option, which can promote a more normal neural development in young children with ADHD and thus reduce cognitive dysfunctions and symptoms. This could help children with ADHD to perform better in everyday life and school.

Trial registration: ClinicalTrials.gov: NCT01752530, date of registration: 10 December 2012

Keywords: ADHD, Cognitive training, Cognitive remediation, Cognition, Computer training, Nonpharmacological treatment

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Background

ADHD is one of the most prevalent psychiatric disorders in child and adolescent psychiatry, affecting approximately 5 % of school-aged children and adolescents [1–3]. ADHD is associated with poor academic performance, poor social functioning [4, 5], increased risk of drug abuse [6, 7], psychotic disorders [8, 9] and criminality [10, 11], as well as increased mortality [12]. The etiology of ADHD is still unknown, but there is evidence for a complex interaction between multiple genes and environmental factors [13]. Empirical studies have shown structural and functional abnormalities in the brain of individuals with ADHD [14, 15]. Additionally, the brain in children with ADHD is characterized by a cortical maturation delay in terms of the reaching the peak cortical thickness [16].

A wide range of cognitive functions is affected in ADHD, yet a specific ADHD cognitive profile has not been identified [17]. The cognitive impairments are very heterogenic in severity and the affected areas. Spatial working memory, impulse inhibition and vigilance are found to be the most impaired functions according to two large meta-analyses of observational studies comparing cognitive functions in patients with ADHD with healthy participants [18, 19]. Functions like inhibitory control, selective and sustained attention, attention switching and processing speed are also significantly impaired [16, 20–22]. These features are associated with the executive control system [23–26] and are often manifest in early childhood and persistent over time [11, 27]. Executive dysfunctions are often seen in individuals with ADHD. Children with ADHD display significant impairment in executive functions compared to typically developing controls as a group, but only 50 % of the patients exhibit executive dysfunctions at the individual level [28].

Although there is some evidence supporting the beneficial effects of stimulant medication for ADHD [29], the treatment is not a cure as the symptoms return immediately after treatment discontinuation. Furthermore, 20 % to 30 % of individuals with ADHD do not show a positive response to stimulant medications, and long-term effects are variable [30–32].

Cognitive training

Cognitive training is rooted in cognitive rehabilitation, based on the concept that direct training can result in a reorganization of neural functions. Among other effects, neuroplasticity allows the central nervous system to learn new skills, remember information and reorganize neural networks in response to external stimulation [33]. The basic mechanisms involved are neurogenesis, programmed cell death and activity-dependent synaptic plasticity [33]. Childhood is a period of changes in the brain's anatomical structure and synaptic connections. A child's

brain is more susceptible to the environmental impact than the adult's brain due to increased plasticity [33]. Thus, injuries and some neurological diseases are overcome by children faster and easier than by adults. Several studies indicate that the peak of brain plasticity is reached within the first 7 years of life [34], although the potential is likely to be lifelong. For example, a functional magnetic resonance imaging (fMRI) open trial of young healthy adults found that training working memory resulted in an increased brain activity in the dorsolateral, prefrontal, and parietal association cortex, indicating plasticity of the neural system [35]. These cortical areas are overlapping the prefrontal regions, which are likely implicated in the pathology of ADHD [36, 37]. Despite the hypothesis that children under the age of 7 have better neuroplasticity and therefore may benefit more from cognitive training as compared to older children, we have not identified any studies investigating the effect of cognitive training in different age groups.

Cognitive training is typically delivered in a computerized format and is aimed at training cognitive functions that are deficient in a patient population by using a special kind of computer games. A rapidly growing number of randomized trials support the hypothesis that cognitive dysfunctions can be trained in children with ADHD [38–41]. Most ADHD trials with children have focused solely on working memory training and findings have been somewhat inconsistent [42–44]. Overall, working memory training shows effects on verbal and spatial working memory [45], and these effects are generalized to improved sustained attention up to 6 months follow-up [42]. Some few studies have shown improvements in academic abilities, but there is no consensus yet as several newer studies had negative results [46–48]. Working memory, combined with response inhibition training, has shown significant improvements on symptoms, spatial working memory, ability to ignore distracting stimuli and sustained attention as rated by a significant other [41]. Training of executive functions improved parent-rated executive functions and ADHD behavior when compared to waiting-list condition [49].

Fewer trials have focused on the attention training in children with ADHD that results in a significant improvement in trained and untrained attention and vigilance [39, 50–52], a measure of school performance and a significant reduction in parent and teacher observation of inattention [39, 40, 53]. In addition, the effects on inhibition and working memory have been found [52], and significant changes in inattentiveness, behavior and executive functions measured by parent ratings on Behavior Rating Inventory of Executive Functions (BRIEF) [54].

Structural and functional correlates of cognitive training have been shown in several small studies. Enhanced activity in neural structures closely related to ADHD

pathology [55] and increase of focal volumetric gray area in bilateral middle frontal cortex and right inferior-posterior cerebellum after attention and executive functions training [56]. Cognitive training has also been shown to induce neurochemical changes at the synapse in dopamine function after training [57].

In conclusion, randomized trials and observational studies suggest that cognitive training of children with ADHD has some beneficial effects. However, the empirical evidence in this field is still insufficient as most trials have a high risk of systematic errors (bias) mainly due to lack of blinding, incomplete outcome data, and selective outcome reporting. Further, most trials have small sample sizes, which result in an increased risk of imprecision. As children with ADHD have impairments in many different cognitive functions, there is a need for randomized trials to examine effects of broader cognitive training, rather than focusing on only one or two domains, for instance, working memory, response inhibition or sustained attention. It is important to validate and extend existing knowledge on the effects of cognitive training for patients with ADHD.

Hence, to overcome some of these limitations, the present trial will use ACTIVATE™ a cognitive computerized program that aims to improve eight different cognitive functions. We will include a sample of children and adolescents with ADHD, and in addition to considering the ratings of clinical symptoms by parents and teachers, we will measure the outcome with an objective, valid and reliable cognitive test battery. The trial is, to our knowledge, the first to examine the effect of cognitive training on the outcome of Cambridge Automated Neurocognitive Test Battery (CANTAB) in children with ADHD.

Methods/Design

Objectives

The primary objective is to investigate whether computer training with the games embedded in ACTIVATE™ (<http://denmarkstudy2.c8sciences.com/?language=da>) has a positive effect on specific cognitive functions. The secondary objectives are to investigate whether there is an effect on ADHD symptoms and functional outcome. Exploratory objectives are to investigate the effects at 12 and 24 weeks after training and to investigate whether younger children benefit more from training than older children.

Trial sites

Participants are included in three sites in southern Denmark: the Child Psychiatric Departments of Aabenraa (including Augustenborg), Kolding and Odense.

The three sites are part of the same organization, Region of Southern Denmark, and are under the same leadership. All children and adolescent mental health hospitals in

Denmark are state-owned, and everyone is eligible to get treatment. Referral from the treating physician or school psychologists is required. No children who are being treated by private practicing child and adolescent psychiatrists will be included in the study. One site (Odense) is part of a university hospital, and the two other sites are part of regional hospitals. Eventual differences between sites will be assessed using data on demographics.

Enrollment of children into the trial is done consecutively throughout the calendar year. The vast majority of children will be enrolled during school year. A few participants will be enrolled during school vacations, but as the intervention is home-based, this will likely not affect the adherence.

Assessments of eligibility

All children who are newly referred with ADHD symptoms to one of the Child Psychiatric Departments or currently in treatment with ADHD-medication will be invited to participate in the trial and will be offered an individual information session, after which their custodian can give their informed consent. The diagnostic assessment is done in a two-step model: In Step 1 parents, a teacher and children over 11 years of age complete an online questionnaire, including the Strength and Difficulties Questionnaire (SDQ) [58, 59] in conjunction with the psychiatric diagnostic interview Development and Well-being Assessment (DAWBA). The DAWBA is a valid hybrid between a structured and a semi-structured interview for the diagnosis of child and adolescent psychiatric disorders according to both the ICD-10 and DSM-IV [60, 61]. DAWBA's sensitivity is 92 % in a clinical sample and its specificity is 89 % for all psychiatric diagnoses in a community sample [60]. Parents and teachers answer structured and open-ended questions regarding diagnostic symptoms using the online DAWBA-platform. A child and adolescent psychiatrist rates this information clinically. Children fulfilling diagnostic criteria for ADHD based on this rating of DAWBA proceed to Step 2, which includes a confirmatory clinical interview with parents at the hospital, using the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS, ADHD section) [62]. K-SADS is a semi-structured clinical interview of parents and children and is the most widely used psychometric instrument for the diagnostic investigation of children in clinical research. All children with confirmed ADHD are assessed with Reynolds Intellectual Assessment Scales (RIAS) [63] to ensure that all participants have an IQ above 80. Finally, children are included in the trial if they comply with the following inclusion and exclusion criteria.

Inclusion criteria

Children are included if the following inclusion criteria are fulfilled: ADHD diagnosis after DAWBA interview [60] and verification with clinical interview K-SADS, ADHD section parent interview [62]; age between 6 and

13 years, both inclusive; the patient has access to a computer and the internet; and informed consent.

Exclusion criteria

Patients fulfilling any of the following exclusion criteria will not be included: comorbid conduct disorder, autism spectrum disorder, depression or schizophrenia; head injury or verified neurological disease; intelligence quotient (IQ) < 80; motor or perceptual handicaps that prevent computer use; medical condition that requires primary treatment, and no informed consent from custodian (Fig. 1).

Interventions

Both the intervention group and the control group will receive treatment as usual (TAU). TAU consists of clinical assessment and treatment. Clinical assessment includes intelligence tests, cognitive testing, school observations and parent and teacher questionnaires. TAU may involve psycho-education, parent

training, advising the parents and school, and for some children, medication. Parallel to the trial, the participating children will undergo a regular assessment and treatment procedure at the clinic. It is the treating specialist, who is independent of the trial and blind to the child's randomization status, who will consider possible medical treatment, independent of the child's participation in the trial. Children in medical treatment are asked not to change their medication dose during the 8 weeks of intervention.

Intervention group

In addition to TAU, the intervention group will use the computer program ACTIVATE™ (<http://denmarkstudy2.c8sciences.com/?language=da>). ACTIVATE™ includes an engaging computer program aimed to train multiple cognitive functions simultaneously: sustained attention, working memory, speed of information processing, response inhibition, cognitive flexibility, category formation, pattern recognition and multiple simultaneous

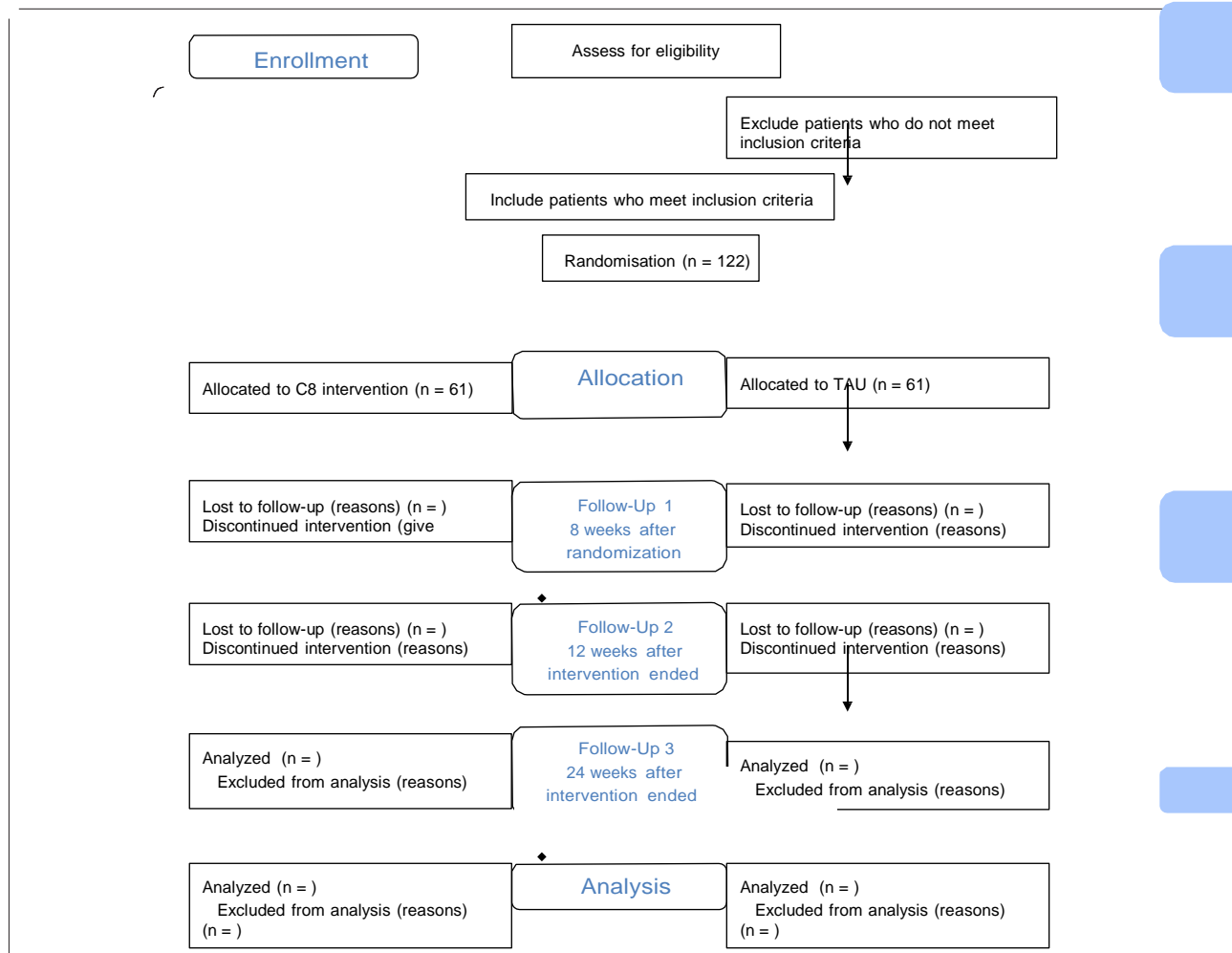


Fig. 1 CONSORT 2010 Flow Diagram. Flow diagram of participant enrollment and randomization in the trial

attention. **ACTIVATE™** consists of three different games: “Catch the ball,” “Butterflies,” and “What comes next.” These are described below.

1. **Catch the ball:** In this game, there is a ball moving across the computer screen. The child has to use the computer mouse to chase the ball with the arrow on the screen. Every time the ball turns red, the child should put the arrow on the ball, click the mouse, and thus, catch the ball. Every time a child catches a ball, the computer makes a nice sound, and the child gets points. If the child waits too long to click or clicks outside of the ball, s/he will miss the ball, and the computer will make a different sound. The child has to watch the ball all the time and get as many points as possible. When many balls have been caught, the speed will increase. If the child misses some balls, then they will begin to move more slowly, and it will be easier to catch them. The target - red balls or blue balls - will keep changing. The rule is disclosed by looking at the ball on the top of the screen. In the beginning, the child has to catch only the red or blue balls. As the child progresses to higher levels of the game, the rules will begin to change: Initially, the child has to catch a ball when it is the same color as the previous one. Later, the child has to catch a ball if it is a different color than the previous one. Then, two balls bounce across the screen at the same time and have to be watched simultaneously, as all of the rules described before now apply to both balls. Later, three balls - red, blue and green - are introduced, and the child has to catch the blue and red, but never the green balls. “Catch the ball” engages different cognitive functions at the same time: sustained attention, response inhibition and cognitive flexibility. The load on these cognitive functions is increasing during the game and working memory and multiple simultaneous attention are trained at the higher levels of the game.
2. **Butterflies:** In this game, there are butterflies flying across the screen. Each one carries a sign with a number, a word or a picture on it. The child uses the computer mouse to click on all the signs that have a number or the name of a number. Sometimes the number is spelled out in letters like “t” “w” “o” for 2. These are the targets to look for and click on before the butterfly carries them all the way across the screen. If a child clicks on the wrong butterfly, it falls to the ground. As the child progresses to higher levels, the rules keep changing. The child has to look for signs with letters of the alphabet, animals, plants, furniture and things to take on a vacation. Later, the targets are different kinds of plants with an exception, such as flowers. As the game progresses, the targets change to two different categories, for example, the child has first to click on a picture of food, after that on a picture of clothing, and to continue to go back and forth between the two. This game is mainly engaging the conceptualization of categories and sustained attention on all levels. Some levels also make demands on response inhibition and cognitive flexibility.
3. **What comes next:** This game trains mainly pattern recognition and, on some higher levels, cognitive flexibility and the use of categories. The child sees some pictures, numbers or shapes in a row that make a pattern or sequence. There is an empty space in the top row. There are some other pictures, numbers or shapes in another set of boxes in a second row below the first. The task is to click on the thing in the second row that goes best in the empty space in the first row, and fits with the pattern on the first row. On the upper right-hand side of the screen, the time allowed to make a choice is displayed. When a child gets questions right, the time remaining to answer the next questions is shortened. Three seconds is the shortest time given to provide an answer. The child graduates and moves on to new levels of the program when enough questions have been answered correctly with only 3 seconds for each question. When a child has worked hard on a level for a long enough time, the computer will move to the next level even if the child was not able to answer the questions within the 3 seconds. The faster the child works, the more points s/he can earn.

In all three games, the child is earning points, which are converted into coins. At the end of all three games, the child comes to a “garden” where s/he can purchase different things. The child can decide to buy things for the garden, such as plants and animals, or a car, a zoo or a house. The child can buy things after each game or can save coins to buy more expensive things later. The games are designed in a manner to be interesting and rewarding for children. All participants are doing the same kind of exercises. All participants start at the same very basic level. Progression and the level of difficulty in the games depend on the child’s performance. Hence, the level of difficulty is therefore dynamically adjusted during the trial, according to the abilities of each child or cognitive phenotype.

Training with **ACTIVATE™** is home-based for 40 minutes per day, 6 days per week, for 8 weeks, resulting in a cumulative training of a maximum of 32 hours.

ACTIVATE™ records each time the participant logs on and is measuring compliance, time on task and progress. All participants randomized to the intervention group are introduced to the program at the clinic. In case of any problems with the program, the participants can contact the principal investigator. C8 is also providing IT support. Parents are given verbal and written instructions that the child should use a computer with an external mouse (not an iPad or a laptop with an integrated mousepad), that training should be performed in a quiet setting, and that using headphones is mandatory. In addition, the parent are instructed to help the child remember and engage in training and to supervise the child during training sessions, to ensure adherence. We are in touch with parents, and they can contact us any time. Parents are given the instruction to supervise the child and make sure they are doing the training. There were no restrictions on the time of the day the training should be performed. However, we inform parents that most children usually like to do the exercises in the late afternoon or early evening and that parents should ensure that sessions do not conflict with school or family schedules.

Control group

The control group will only receive treatment as usual.

Randomization

Randomization is performed centrally by the Copenhagen Trial Unit. Participants are randomized 1:1 to the intervention group or control group. The allocation sequence is computer-generated with a varying block size kept unknown to the investigators, and it is stratified by trial site (“Aabenraa,” “Kolding,” or “Odense”) and use of medication (“yes” or “no”). Allocation is performed by the investigator telephoning the Copenhagen Trial Unit, giving a personal PIN code as well as information about the participant (strata, participant ID number etc.), and the participant is then allocated to an intervention group.

To examine whether the randomization sufficiently reduced the risk of systematic group differences between children in the intervention and the control arm, we will compare the distribution of history of scholar retention events, and pharmacological treatment (dose and type of medication) in the child, mean parental age, socioeconomic status and level of education, and the number of people living at home.

Blinding

Due to the nature of the trial, it is not possible to blind the participants and their parents. However, we will employ blinding in all other possible areas. Investigators

conducting the cognitive testing with CANTAB will be blind to the participants’ group allocation. The statistical analyses will be performed blinded with the two intervention groups coded as, for example, X and Y. The analyses will be presented blinded to the Steering Committee, who will draw two conclusions: one assuming that X is the intervention group and Y is the control group, and one assuming the opposite. After this, the blind will be broken.

To reduce the risk of biasing the rating of outcomes caused by unblinding information on group allocation, we chose an objective computerized primary outcome measure on the CANTAB. Still, the clinicians performing the CANTAB are blinded to group allocation. The treating physicians are not directly connected to the trial and do not assess or provide information on any trial outcomes. Due to regulations by the ethics committee, we were not allowed to inform the treating physician about included children to avoid that influencing the treatment in the outpatient clinic. Hence, as these clinicians were responsible for the treatment as usual (TAU) in both groups, they were also blinded to the group allocation of the child to ensure that this did not affect the TAU.

Outcomes

For an overview of all outcomes and assessments, please see Table 1.

Each CANTAB assessment lasts between 70 and 90 minutes. We aim to collect all cognitive assessments between 8:30 am and 2:00 pm to avoid a time of the day that would have an impact on the cognitive performance. While the child is being assessed, the parent questionnaire data are collected. If the child is unable to complete the assessment in one session, the assessment can be split up.

Primary outcome

CANTAB is a nonverbal computerized cognitive test battery with solid psychometric properties [64–66] (Cambridge Cognition Limited, 2011). The primary outcome is the sustained attention test from the CANTAB: “Rapid Visual Information Processing (RVP) probability of hit,” assessed at the end of the intervention.

Secondary outcomes

The following secondary outcomes will be assessed at the end of the intervention:

1. Parent-rated ADHD symptoms assessed by ADHD-Rating Scale (ADHD-RS) (parent edition) [67].
2. Teacher-rated ADHD symptoms assessed by ADHD-RS (teacher edition) [67].

Table 1 Outcomes and time points for assessment in the trial. Specification of all outcome measures at each time point in the trial

	Outcome type	Baseline (First clinic visit)	Baseline (Second clinic visit)	End of intervention	12 week follow up	24 week follow up	
Demographic and diagnostic variables	Age	Continuous	X				
	Sex	Dichotomous	X				
	DAWBA ^a	Continuous	X				
	K-SADS ^b	Continuous	X				
	RIAS ^c	Continuous	X				
	Pharmaceutical treatment at baseline	Dichotomous	X				
Primary outcome	CANTAB ^d -RVP ^e , probability of hit	Continuous					
Secondary outcomes	ADHD-RS ^f (parent-rated)	Continuous		X			
	ADHD-RS (teacher-rated)	Continuous		X			
	BRIEF ^g (parent-rated)	Continuous		X			
	BRIEF (teacher-rated)	Continuous		X			
Exploratory outcomes	CANTAB-AST ^h	Continuous		X			
	CANTAB-MTS ⁱ	Continuous		X			
	CANTAB-CRT ^j	Continuous		X			
	CANTAB-SST ^k	Continuous		X			
	CANTAB-SWM ^l	Continuous		X			
	CANTAB-SOC ^m	Continuous		X			
	CANTAB-IED ⁿ	Continuous		X			
	CANTAB-PAL ^o	Continuous		X			
	BRIEF (Inhibit) (parent-rated)	Continuous		X			
	BRIEF (Shift) (parent-rated)	Continuous		X			
	BRIEF (Emotional control) (parent-rated)	Continuous		X			
	BRIEF (Initiate) (parent-rated)	Continuous		X			
	BRIEF (Working memory) (parent-rated)	Continuous		X			
	BRIEF (Plan/Organize) (parent-rated)	Continuous		X			
	BRIEF (Organization of materials) (parent-rated)	Continuous		X			
	BRIEF (Monitor) (parent-rated)	Continuous		X			
	BRIEF (Inhibit) (teacher-rated)	Continuous		X			
	BRIEF (Shift) (teacher-rated)	Continuous		X			
	BRIEF (Emotional control) (teacher-rated)	Continuous		X			
	BRIEF (Initiate) (teacher-rated)	Continuous		X			
	BRIEF (Working memory) (teacher-rated)	Continuous		X			
	BRIEF (Plan/Organize) (teacher-rated)	Continuous		X			
	BRIEF (Organization of materials) (teacher-rated)	Continuous		X			
	BRIEF (Monitor) (teacher-rated)	Continuous		X			
	WFIRS-P ^p	Continuous		X			
	Non-serious adverse events	Dichotomous					
	Serious adverse events	Dichotomous					
	X	Baseline assessments					
		Assessment of primary outcome					
		Assessment of secondary outcomes					
	Exploratory assessments of primary and secondary outcomes.						
	Exploratory outcomes.						

Legend:

^aDevelopment and Well-being Assessment (DAWBA); ^bKiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS); ^cReynolds Intellectual Assessment Scales (RIAS); ^dCambridge Automated Neurocognitive Test Battery (CANTAB); ^eRapid Visual Information Processing (RVP); ^fAttention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS); ^gBehavior Rating Inventory of Executive Functions (BRIEF); ^hSwitching Task (AST); ⁱMatch to Sample (MTS); ^jChoice Reaction Time (CRT); ^kStop Signal Task (SST); ^lSpatial Working Memory (SWM); ^mStockings of Cambridge (SOC); ⁿIntra-Extra Dimensional Set Shift (IED); ^oPaired Associates Learning (PAL); ^pWeis's scale of disability-Parent Report (WFIRS-P)

Each CANTAB assessment lasts between 70 and 90 minutes and is collected between 8:30 am and 2:00 pm. While the child is assessed, questionnaire data from the parents are collected. If the child is unable to complete the assessment in one session, the assessment can be split up

3. Parent-rated behavior assessed by Behavior Rating Inventory of Executive Functions (BRIEF) (parent edition) [68].
4. Teacher-rated behavior assessed by BRIEF (teacher-edition) [68].

Exploratory outcomes

The following exploratory outcomes will be assessed at the end of the intervention:

1. CANTAB Attention Switching Task (AST).
2. CANTAB Match to Sample (MTS).
3. CANTAB Choice Reaction Time (CRT).
4. CANTAB Stop Signal Task (SST).
5. CANTAB Spatial Working Memory (SWM).
6. CANTAB Stockings of Cambridge (SOC).
7. CANTAB Intra-Extra Dimensional Set Shift (IED).
8. CANTAB Paired Associates Learning (PAL).
9. CANTAB RVP Probability of False Alarms.
10. CANTAB RVP Reaction Latency S.D.
11. BRIEF (Inhibit) (parent-rated).
12. BRIEF (Shift) (parent-rated).
13. BRIEF (Emotional Control) (parent-rated).
14. BRIEF (Initiate) (parent-rated).
15. BRIEF (Working Memory) (parent-rated).
16. BRIEF (Plan/Organize) (parent-rated).
17. BRIEF (Organization of Materials) (parent-rated).
18. BRIEF (Monitor) (parent-rated).
19. BRIEF (Inhibit) (teacher-rated).
20. BRIEF (Shift) (teacher-rated).
21. BRIEF (Emotional Control) (teacher-rated).
22. BRIEF (Initiate) (teacher-rated).
23. BRIEF (Working Memory) (teacher-rated).
24. BRIEF (Plan/Organize) (teacher-rated).
25. BRIEF (Organization of Materials) (teacher-rated).
26. BRIEF (Monitor) (teacher-rated).
27. Weis's scale of disability-Parent Report (WFIRS-P) (Weis et al., 2005).
28. Non-serious adverse events.
29. Serious adverse events.

Further, all outcomes will be assessed again 12 and 24 weeks after the end of the intervention (Fig. 2).

Ethical issues

This trial is being conducted in accordance with the protocol approved by the Danish Data Protection Agency (ID.nr. 2008-58-0035) and the Regional Scientific Ethical Committees for Southern Denmark (nr. S20120096). The protocol is in accordance with the latest version of the Declaration of Helsinki. No significant deviation from the protocol will be implemented without prior review and approval by the regulatory authorities unless it may be necessary to eliminate an immediate hazard to the trial participants. In this case, the deviation will be reported to the regulatory authorities as quickly as possible.

A child can participate in the trial if the written consent of both parents is obtained. The patients' treatment as usual will not be affected, including the use of medications, by their participation in this trial. When testing with CANTAB, patients will be asked to postpone any ADHD medication for 24 hours before testing, when medical treatment can affect efficacy measures. Trial participants will receive a gift certificate worth DKK 400 for participation. Transportation costs will be reimbursed.

The processing of personal data will be respected. There are no known risks associated with the use of computerized cognitive training. The method has been tested in many studies with patients with schizophrenia (see reviews [69, 70]) and in children with ADHD [38–40, 53]. No adverse events have been reported.

Discontinuation and withdrawal

Although parents may have agreed to participate, they can always withdraw their child from the trial without

further explanation. Pulling a child out of the trial, will not affect his or her further treatment. Patients can choose to stop at any time in the trial. Patients who were randomized will be included in the intention-to treat analyses unless they completely withdraw consent. In this case, all data regarding this participant will be deleted.

Statistical plan and data analysis

Sample size

We are planning a trial of a continuous response variable, "CANTAB RVP probability of hit," from an independent control, and experimental participants will be allocated at a 1:1 ratio. In a pilot project (Bikic et al., unpublished data), adolescents with ADHD played a set of games from Scientific Brain Management for 7 weeks. Here, the "CANTAB RVP probability of hit" was normally distributed, with a standard deviation (SD) of 0.22 points. If the true difference in the experimental and control mean is 0.13 points, we will need to include 61 experimental participants and 61 control participants to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 90 %. The type I error probability associated with this test of this null hypothesis is 5 %. We will thus include 122 participants in total.

Power

Assuming the minimal relevant difference is 0.5 SD for all the secondary outcomes and the significance level of the various tests of Hommel's procedure is within the range of $\alpha = 0.05$ and $0.05/4 = 0.0125$ and the sample size is 122, the power of the individual tests will range between 59 % and 78 % (Table 2). A power of 78 % is judged to be reasonable, whereas a power of 59 % is insufficient.

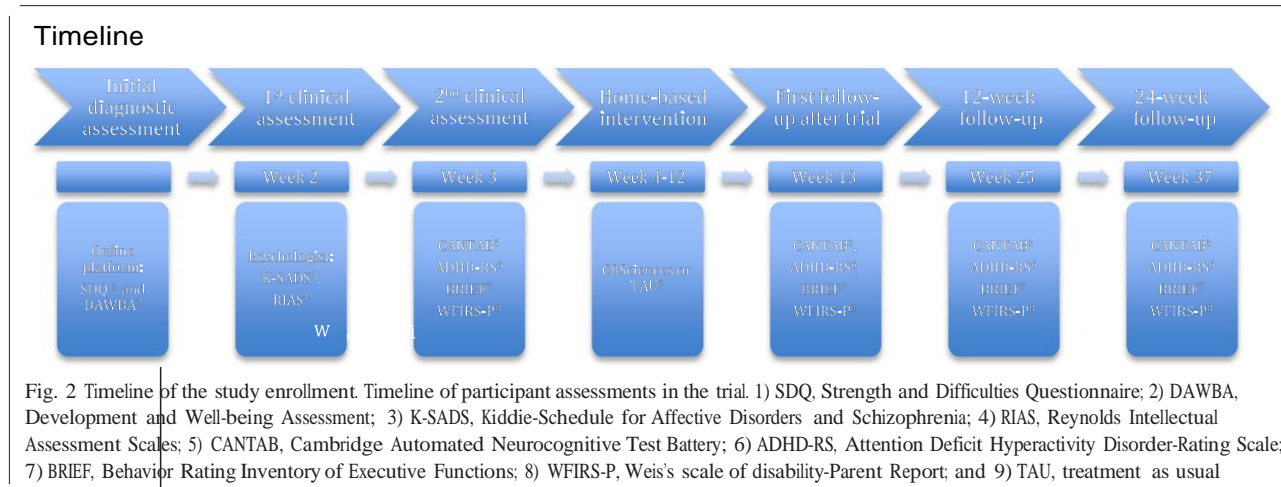


Table 2 Power estimations for the secondary outcome measures ADHD-RS and BRIEF

Outcome	Minimal relevant difference	SD ^a	Sample size	Power assuming an alpha of 1.25 %	Power assuming an alpha of 5 %
ADHD-RS ^b (parents-assessed)	5 points	10 points	122	59 %	78 %
ADHD-RS (teacher-assessed)	5 points	10 points	122	59 %	78 %
BRIEF ^c (parents-assessed)	0.25 points	0.5 points	122	59 %	78 %
BRIEF (teacher-assessed)	0.25 points	0.5 points	122	59 %	78 %

Legend:

^aSD, standard deviation

^bADHD-RS, attention deficit hyperactivity disorder rating scale. Minimal relevant difference and SD calculated from a previous pilot project (Bikic et al. unpublished data)

^cBRIEF, Behavior Rating Inventory of Executive Functions. Minimal relevant difference and SD calculated from the BRIEF professional manual [68]

Multiplicity and significance

For all outcomes, we will present the test statistic and the corresponding P values for exploratory purposes.

The purpose of the analysis of the secondary outcomes is to make additional claims of treatment benefits in addition to those already established by the analysis of the primary outcome. Consequently, multiplicity adjustments are needed. Multiplicity adjustments generally require a strong control of the familywise error rate. With regard to this, a useful approach is the gatekeeping approach [71], which we will apply in this trial.

There is one primary and four secondary outcomes. Thus, the primary outcome will be the gatekeeper of the family of secondary outcomes. The sample size has been estimated using a risk of type I error (alpha) of 0.05. The primary outcome will consequently be analyzed and interpreted according to a two-sided significance level of $P \leq 0.05$. Thus, if P of the test of the primary outcome is ≤ 0.05 , the primary outcome is assessed as statistically significant. In this case, we will use Hommel’s procedure, which is uniformly more powerful than the Holm as well as the Hochberg adjustment procedures. This means that the alpha of 0.05 can be transferred to the secondary outcomes that will be tested in a pre-specified sequence at the 0.05 level of significance (see sequence in Table 2). The approach requires that as soon as the P value of a test is > 0.05 , the null hypotheses of the remaining secondary outcomes are accepted regardless of the test statistics.

If P of the test of the primary outcome is > 0.05 , the primary outcome is assessed as statistically insignificant. Consequently, the trial result is insignificant, and all the null hypotheses of the four secondary outcomes will be accepted regardless of the test statistic.

All exploratory outcomes and exploratory analyses of the primary and secondary outcomes will likewise be subject to statistical tests. However, if P of the test is ≤ 0.05 , the outcome will not be assessed as statistically significant due to multiplicity and the increased risk of a type I error. Likewise, if $P > 0.05$, we cannot assess the outcome as statistically insignificant due to

a potential lack of power. All exploratory analyses will thus be strictly hypothesis generating.

Analytical model

For the analysis of the continuous outcomes, structural equation models (for example, “proc calis” in SAS 9.3) including the direct maximum likelihood method (full information likelihood) will be used (see section on missing values). If the assumptions of a regression analysis are not fulfilled, a non-parametric test will be used (van Elteren’s test with stratification by one variable “center”). For dichotomous outcomes, we will use logistic regression to compare the results in the two groups.

Adjustments

All analyses will be adjusted for the stratification variables (“center” and “pharmaceutical treatment at baseline”), and the outcome variable value will be assessed at baseline.

Missing values

In the analysis of the continuous variables, structural equation models (for example, “proc calis” in SAS 9.3) that include the direct maximum likelihood method (full information likelihood) will be used. Applying this method implies that unbiased estimates of the regression parameters will be obtained as long as the values are only missing at random. To improve the efficiency, all auxiliary variables present among the outcomes will be added to the model. An auxiliary variable is defined as a variable not in the analytical model but correlated (defined as $|r| > 0.40$) with one or more variables that 1) have missing values, and 2) are included in the analytical model. Thus, the auxiliary variables included may vary from one regression equation to the next one.

Sensitivity analyses

Best-worst and worst-best sensitivity analyses of the primary outcome will be done. Here, missing values in one intervention group are imputed by the minimum value

found in the total material (“best case”), and missing values in the other group are imputed by the maximum value found in the total material (“worst case”) and vice versa. The range of the estimates of the two regression parameters of the intervention indicator will convey an impression of the bias one may expect if values are missing not at random.

Per-protocol analyses

For the primary and secondary outcomes, we will use exploratory analyses to perform per-protocol analyses. Participants will be included in the intervention group, if they have complied with at least 20 out of the 48 scheduled computer training sessions. Participants will be included in the control group if they have not attended any computer training sessions.

Subgroup analyses

For the primary and secondary outcomes, we will perform subgroup analyses according to age. We will divide the participants into two age groups of children aged 6 to 9 years or 10 to 13 years. We will perform a test of interaction to assess whether the effect of the intervention is different among the younger children compared with the older children. If P of the test of interaction is ≤ 0.05 , we will present separate estimates for the two subgroups. As the randomization procedure was not stratified by age and we most likely will have reduced power for this analysis, the result is exploratory and strictly hypothesis generating.

Sequential analysis

As the recruitment in the trial until present has been slower than anticipated, we may face a scenario where we have to end recruitment before the sample size of 122 participants has been met. In this case, we plan to perform sequential analysis to assess the results of significance testing, taking sparse data and into consideration [72]. We will for the primary outcome, CANTAB-RVP, use a minimal clinically relevant difference of 0.13 and a variance of 0.0484 (corresponding to a SD of 0.22). For the secondary outcomes, we will use minimally relevant differences of 5 points and a variance of 100 (corresponding to a SD of 10 points) for both ADHD-RS assessments and a minimal clinical relevance of 0.25 points and variance of 0.25 (corresponding to a SD of 0.5 points) for both BRIEF assessments. For all outcomes, we will use a type I error of 5 %, and a type II error of 10 %. We will use the trial sequential analysis program for these analyses (<http://ctu.dk/tsa/>) [73–76].

Discussion of clinical relevance

If the trial results indicate that this intervention reduces specific cognitive deficits in children with ADHD

without causing any adverse reactions effects, our interpretation will be that the intervention can be an important part of a treatment plan as cognitive dysfunctions are very common in children with ADHD. Furthermore, if we find improvement in the BRIEF measures and ADHD-RS, this would suggest that the effects of the intervention could be generalized to behavior in an everyday setting.

Monitoring of patient compliance issues

The intervention group compliance will be monitored via the computer program that records patients log on, which games they have played, and for how long.

Financial support

Aida Bikic is the initiator of the trial and the investigator psychologist, research coordinator and PhD student. Participants are being randomized in the Child and Adolescent Psychiatric setting of Augustenborg and Aabenraa, Odense and Kolding. The trial has received grants from Region of Southern Denmark Psychiatry Research, The Region of Southern Denmark's PhD pool, Child and Adolescent Psychiatric Department Aabenraa, TrygFonden (J.nr. 7-12-1137) and the University of Southern Denmark. C8 Sciences allowed us to use the ACTIVATE™ program at no charge in this trial. None of the funders has any role in the development of the trial design, trial conduct or trial reporting.

Discussion

This trial is a multicenter, randomized clinical superiority trial investigating the effect of a home-based 8-week intervention for children with ADHD, using a computerized cognitive training program, ACTIVATE™. ACTIVATE™ was designed to enhance a broad range of cognitive functions. The trial has several strengths: it is conducted with adequate generation of allocation sequence; adequate allocation concealment; adequate blinding wherever possible; adequate reporting of all relevant outcomes; adequate handling of incomplete outcome data; and has no for-profit bias [77–80]. The trial results will offer new and valuable contributions to the field of cognitive training in children with ADHD.

The trial also has some limitations. Due to the nature of the trial, it is not possible to blind the participants, their parents, or their teachers. A “sham” intervention for the control group was considered. However, in order to introduce an active control intervention that would function as a true placebo, we needed to be sure that this intervention had no beneficial or harmful effects, which is difficult to document. Furthermore, a placebo-training program would be somewhat boring in order to have no training effect. This would potentially cause

problems with low adherence in the control group and reveal group allocation. We consequently chose a “treatment as usual” control group, thereby accepting the risk of bias regarding the blinding that this entails.

We included both drug-naïve children and children receiving pharmaceutical therapy in the trial. As the randomization procedure is stratified for this variable, it is not expected to influence the trial results. Furthermore, all children are required to be free of medication 24 hours before cognitive testing in order to influence the results as little as possible. All patients are required to perform cognitive assessments at four time points without medication. This may present a potential threat of bias in terms that patients, who are not able to function without medication for 24 hours prior to the testing, could choose not to participate in the study. In this case, some of the more severe cases with ADHD might not be represented in the study sample. Overall, inclusion of children regardless of pharmaceutical treatment status is expected to increase the external validity of the trial results.

We do not consider dropout of medical treatment during the trial a threatening issue. In Denmark, ADHD assessments, diagnostic procedures and initiation of ADHD-medications is restricted to specialists of child and adolescent psychiatry, and general practitioners are not allowed to initiate this treatment [81, 82]. This result in a lower prevalence of children and adolescents treated with ADHD-medications (prevalence in 2010 was only 1.5 % [83], compared to most other European countries and certainly to most parts of the USA, and probably to a less negative public attitude toward medication. Adherence to medication in Denmark is likely higher than in many other countries. The study protocol requires medicated children to stay on medication during the intervention period. Parents are encouraged to continue the children’s medication, if they are on it at time of inclusion.

Trial status

The first participant was included and randomized in March 2013. Recruitment is currently ongoing.

Abbreviations

ADHD: Attention Deficit Hyperactivity Disorder; ADHD-RS: Attention Deficit Hyperactivity-Rating Scale; AST: Attention switching task; BRIEF: Behavior Rating Inventory of Executive Functions; CANTAB: Cambridge Automated Neurocognitive Test Battery; CRT: Choice reaction time; DAWBA: Development and Well-being Assessment; IED: Intra-Extra Dimensional Set Shift; K-SADS: Kiddie-Schedule for Affective Disorders and Schizophrenia; MTS: Match to sample; PAL: Paired associates learning; RIAS: Reynolds Intellectual Assessment Scales; RVP: Rapid visual information processing; SWM: Spatial working memory; SOC: Stockings of Cambridge; SST: Stop Signal Task; SDQ: Strength and Difficulties Questionnaire; TAU: Treatment as usual; WFIRS-P: Weis’s scale of disability-Parent Report.

Competing interests

James Leckman has received support from the NIH (salary and research funding), Tourette Syndrome Association (research funding), Grifols, LLC (research funding), and Klingenstein Third Generation Foundation (medical student fellowship program). He receives book royalties from John Wiley and Sons, McGraw Hill, and Oxford University Press. There are no competing interests.

Authors’ contributions

AB contributed with the conception and design of the trial, literature search, collection and assembly of data, data analyses, manuscript writing and final approval of the manuscript. SD contributed with the conception and design of the trial, literature search, data analyses, critical revision and final approval of the manuscript. JFL contributed with the conception and design of the trial, critical revision and final approval of the manuscript. JL contributed with the conception and design of the trial, planning statistical analyses, critical revision and final approval of the manuscript. TØC contributed with the conception and design of the trial, critical revision and final approval of the manuscript. All authors read and approved the final manuscript.

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Cognitive computer training versus treatment as usual in children with Attention Deficit-Hyperactivity Deficit Disorder (ADHD): Results from a randomized, controlled trial.

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Abstract

Objective: Multicenter randomized clinical superiority single blind trial investigated the effect of a computer training program targeting multiple cognitive skills.

Method: 70 children with ADHD, aged 6-13, were randomized to intervention or control group. The intervention group used ACTIVATE™ for 8 weeks and both groups received treatment as usual (TAU) and were assessed in regard to cognitive functions, symptoms, behavioral and functional outcome measures after 8, 12 and 24 weeks.

Results: There was no significant effect on the primary outcome, sustained attention. The intervention had a significant and sustained effect on planning ability ($p=0.006$). In an exploratory analysis, older children (age 10-13) showed significant gains on several cognitive and behavioral measures, but not older children (6-9).

Conclusion: There were no significant effects of the intervention for the primary or secondary outcome measures, but for the ability to plan ($p<0.006$). Older children benefited more from the intervention than younger children.

Trial registration: ClinicalTrials.gov: NCT01752530, date of registration: December 10, 2012

Keywords: ADHD, cognitive training, cognitive remediation, cognition, computer training, non-pharmacological treatment

Introduction

Attention Deficit Hyperactivity Deficit Disorder is one of the most prevalent psychiatric conditions in childhood with an estimated prevalence around 5%. Children with ADHD also display significant impairments in a number of cognitive functions compared to typically developing controls (Nigg, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). However, there is no specific cognitive profile for individuals with ADHD as their cognitive deficits are heterogenic in the type and severity of dysfunction with great variation at the individual level (Willcutt et al., 2005). Sustained attention and executive functions (EF) are the most affected areas (Nigg, 2005; Willcutt et al., 2005), although only half of the children with ADHD have an actual executive function deficit (Lambek et al., 2011).

Pharmacological treatment is very effective for the core symptoms of ADHD (Storebo et al., 2015), but the impact on cognition, particularly executive functions, is limited (Coghill, Rhodes, & Matthews, 2007; Pietrzak, Mollica, Maruff, & Snyder, 2006; Rhodes, Coghill, & Matthews, 2006) which makes it important to investigate other treatments.

For more than a decade research has focused on cognitive training as a possible new treatment approach for ADHD (Klingberg et al., 2005; Klingberg, Forssberg, & Westerberg, 2002). Cognitive training is theoretically based on the concept of neuroplasticity, which implies that the brain can be changed by new experience. The brains of individuals with ADHD show both structural (Valera, Faraone, Murray, & Seidman, 2007) and functional (Ashtari et al., 2005; Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011) anomalies, and the target of cognitive training is to strengthen deficient networks and areas by external stimulation in hope that these effects will decrease symptoms and improve functional

outcomes. The search for a new intervention has resulted in a range of different approaches to cognitive training being driven by different theoretical frameworks. For instance, studies on working memory training have lead the field (Gray et al., 2012; Klingberg et al., 2005; Klingberg et al., 2002), followed by attention and broader executive functions training (Dovis, Van der Oord, Wiers, & Prins, 2015; Johnstone et al., 2012; Semrud-Clikeman et al., 1999; Shalev, Tsal, & Mevorach, 2007). The focus of the most cognitive training approaches has been to achieve improvement both on the directly trained functions like attention or working memory measured by tests dissimilar to the intervention (near transfer) and, more importantly, to other untrained cognitive functions and symptoms (far transfer).

The field of cognitive training has grown so much over the past years that several meta-analysis and systematic reviews have been conducted on the subject (Cortese et al., 2015; Melby-Lervag & Hulme, 2013; Rapport, Orban, Kofler, & Friedman, 2013; Shinaver, Entwistle, & Soderqvist, 2014; Shipstead, Redick, & Engle, 2012; Sonuga-Barke et al., 2013). Despite different inclusion criteria across the meta-analysis and different understandings and definitions of what cognitive training approaches target, there is a consistent evidence of moderate near-transfer effects on working / short term memory (Cortese et al., 2015; Melby-Lervag & Hulme, 2013; Rapport et al., 2013), while there are no significant far-transfer effects on inhibition, attention ratings or academic performance (Cortese et al., 2015; Melby-Lervag & Hulme, 2013; Rapport et al., 2013).

Studies of attention or executive function training have found no significant near transfer effects on the trained functions (Rapport et al., 2013).

In general, there are large discrepancies in teachers' and parents' ratings of a child's behavior, where parents often report a greater severity of symptoms

(Narad et al., 2015). This discrepancy is also reflected across cognitive training trials that often use parent and teacher ratings as outcome measures for symptoms and executive functions. The meta-analyses show significant effects of cognitive training on ADHD total and inattention symptoms and executive function, with moderate effect sizes on parental ratings and somewhat smaller effects on teacher ratings (Cortese et al., 2015; Sonuga-Barke et al., 2013). Working memory training was found not to generalize to severity of ADHD symptoms, while interventions targeting multiple cognitive functions were shown to have large effects, when rated by parents (Cortese et al., 2015), which makes it interesting to explore effects of cognitive training targeting broader cognitive functions.

In the current randomized controlled trial in children with ADHD we tested a new intervention, ACTIVATE™, that targets a wide range of cognitive functions: sustained attention, response inhibition, cognitive flexibility, working memory, pattern recognition and category formation and use and its effects on cognition, symptoms and functional outcome.

Method

Setting and Sample

Participants were recruited at the Child and Adolescent Psychiatric Departments Aabenraa (including Augustenborg), Kolding and Odense from January 2013 to October 2015. A detailed protocol for this trial has been published previously (Bikic, Leckman, Lindschou, Christensen, & Dalsgaard, 2015). A total of 164 families provided informed consent and were invited to participate in the diagnostic interview, Development and Well-being Assessment (DAWBA) via an online platform (Goodman, Ford, Richards, Gatward, & Meltzer, 2000). The DSM-IV

criteria for ADHD, conduct disorder, autism spectrum disorder, depression and schizophrenia were assessed for this trial. DAWBA was filled out by the parent (s), child if older than 11 years and in the majority of cases also a teacher. If parents failed to complete the DAWBA online within 10 days of invitation, they were contacted and reminded to do so by the principal investigator. Of 164 invited families 122 participated in the DAWBA interview, which was then rated by one of two medical doctors (residents at child and adolescent psychiatry), trained as clinical DAWBA-raters. To ensure a high inter-rater reliability, the first 10 interviews rated by each of the raters were also rated blindly by a child psychiatrist (S. Dalsgaard), who had extensive clinical experience and was trained as a clinical DAWBA-rater by the developer of the instrument, professor Robert Goodman. Overall, the inter-rater-reliability test showed a high composite agreement percentage of 87.5% (95% CI 60.4-97.8%) and an overall Cohen's Kappa of 0.75. According to Landis & Koch (1977) a value of 0.61-0.80 corresponds to a substantial agreement. Inconsistencies between ratings in these initial interviews were discussed and a consensus about diagnoses was reached.

Participants meeting full or sub-threshold criteria for an ADHD diagnosis in DAWBA (n=86) were invited to a clinical interview by one of three trained psychologists, to confirm the ADHD diagnosis, using the ADHD section of the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman et al., 1997). To ensure inter-rater reliability for the K-SADS, the first 10 cases of each of the three psychologists were videotaped and also rated by an experienced K-SADS rater (N. Bilenberg or A. Bikic). After the parent(s) completed the K-SADS interview, the intellectual level of participants was tested by a trained psychologist, using the Reynolds Intellectual Assessment Scales (RIAS) (Reynolds, 2003).

Inclusion criteria for participation in the trial were: Fulfilling DSM-IV criteria for ADHD (in DAWBA interview, and verified with K-SADS); age between 6-13 years; access to a computer and internet connection and informed consent obtained. Furthermore, the following exclusion criteria were applied: Diagnosis of comorbid conduct disorder, autism spectrum disorders, depression or schizophrenia; medical history of head injury or a verified neurological disorder; intelligence quotient (IQ) <80; motor or perceptual handicaps which would interfere with computer use; medical condition requiring primary treatment; and no informed consent from custody. Finally, 78 participants were considered eligible for the trial. Eight families decided not to participate for various reasons (lack of time, change of mind, starting medication treatment, and/or family difficulties) hence 70 participants were included in the study. Participants were asked not to change their medication status during the intervention period. However two participants (one in each group) started medication during the intervention. They were, like all other participants required not to take medication 24 hours prior to the cognitive test.

Cognitive Outcome Measures

All participants were tested with following tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (De Luca et al., 2003): The Motor Screening Task (MOT) screening for visual, movement and comprehension difficulties.

Attention tests: Attention Switching Task (AST) (Total Omission and Commission Errors) is a test of the participant's ability to switch attention and to ignore task-

irrelevant information. Rapid Visual Information Processing (RVP)(Probability of Hit and Mean Latency) is a test of sustained attention. Executive functions: Spatial Working Memory (SWM)(Between Errors) is a test of ability to retain and manipulate spatial information. Stockings of Cambridge (SOC) (Problem solved in minimum moves) is a spatial planning test. Intra-Extra Dimensional Set Shift (IED)(EDS Errors) is a test of rule acquisition, reversal, attentional set formation maintenance, shifting and flexibility of attention. Stop Signal Task (SST) (Direction Errors Stop and Go and SSRT last half) is task measuring response inhibition. Reaction time: Reaction time (RTI)(5-choice movement time and simple error score inaccurate) provides motor and mental response speeds and movement time.

Behavioral Outcome Measures

The following questionnaires were used: 1) ADHD-Rating Scale-IV (ADHD-RS) is a symptom rating scale (DuPaul, Power, Anastopoulos, & Reid, 1998). The Danish version of the ADHD-RS-IV is a translation of the 26-item version, comprising nine items on inattentiveness, nine items on hyperactivity/ impulsive behavior and eight questions on oppositional behavior (Barkley, Edwards, & Robin, 1999). 2) BRIEF is a 86-item rating scale for parents and teacher assessing executive function behaviors in the school and home environments (Gioia, Isquith, Guy, & Kenworthy, 2000). BRIEF consist of eight clinical scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor) and two validity scales (Inconsistency and Negativity). The clinical scales form two broader Indexes (Behavioral Regulation and Metacognition) and an overall score, the Global Executive Composite. 3) WFIRS-P is 50-item questionnaire where parents are asked to rate their child's functional impairment over the past month (Gajria et al., 2015).

There are six domain scores (Family, Learning and School, Life Skills, Child's Self-Concept, Social Activities and Risky Activities).

Interventions

Both the intervention and control group received treatment as usual (TAU) described in detail in our protocol (Bikic et al., 2015). Besides TAU, the intervention group was encouraged to use the computer program ACTIVATE™

(<http://denmarkstudy2.c8sciences.com/?language=da>) six times a week for eight

weeks. We used the first version of ACTIVATE™ consisting of three exercises:

Catch the Ball, Butterflies and What Comes Next. These games are targeting a broad range of cognitive functions with focus on sustained attention, response inhibition, cognitive flexibility and control, speed of information processing, multiple simultaneous attention, working memory, category formation and pattern recognition.

For a detailed description please see Bikic et al. (2015).

Procedures

This was a parallel, two arms, single blind, randomized and controlled trial. Prior to randomization, the parents and a teacher completed the ADHD-RS and BRIEF questionnaires. In addition, the parents completed the WFIRS-P questionnaire. All participating children were assessed with a series of cognitive tests from the CANTAB test battery at four time points: T0=baseline; T1=after 8 weeks of intervention; T2=12 week follow up and T3= 24 week follow up after ended intervention. Participants were assessed at approximately the same time of the day at each visit and always between 8:30AM and 2PM to avoid time of day impacting cognitive functions. Children receiving pharmacological treatment were asked not to

take their medication 24 hours prior to the cognitive testing. The parents were reminded to do so by a text message via mobile phone. The eligible 70 participants were then randomized 1:1 with stratification for site and medication status. The Copenhagen Trial Unit, an independent clinical intervention research unit in another city, performed the randomization, described in detail in Bikic et al. (2015) The investigators performing the cognitive test with CANTAB were blind to the child's allocation at each assessment. After randomization, participants in the intervention group received an individual username and password by e-mail and used these to access the computer game at a secure online web-based platform, designed for this trial. Each log-on, progress on the games and time of playing was registered for all participants and these data were used to measure compliance in the intervention group. In the event of any technical problems, with the intervention, the parents (n=8) contacted the principal investigator by e-mail or phone, who then contacted IT-support.

Ethics

The trial was conducted in accordance with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (ID.nr. 2008-58-0035) and the Regional Scientific Ethical Committee for Southern Denmark (nr. S20120096). The trial was registered at ClinicalTrials.gov (NCT01752530) and the trial protocol has been published (Bikic et al., 2015).

Statistical Analyses

We performed intention to treat analysis. All variables with normally distributed residuals were analyzed with a structural equation model (SEM) using a

Full Information Maximum Likelihood Estimator to address missing data. We used a robust variance estimator, because some outcomes had moderate violations of the normality assumption. Outcomes were treated as observed variables. Correlations between exogenous variables were estimated. Means and variances were estimated for exogenous variables with missing values. All variables were adjusted for the stratification variables “center” and “pharmaceutical treatment” at baseline. As we only recruited one patient from the center in Odense, this patient was assigned to another center (Kolding) by flipping a coin. Based on SEM we estimated beta values with 95% confidence intervals. Means and standard deviation estimates were based on a Full-Information Maximum Likelihood (FIML) estimator. All analysis were performed and analyzed according to a two-sided significance level of $p < 0.05$.

We performed a post hoc power calculation to address the fact, that we recruited fewer participants than anticipated. Additionally, we performed a best-worst and worst-best sensitivity analysis of primary outcome substituting missing values with the minimum and maximum observed values. All statistical analyses were performed in STATA 13.1 (StataCorp, 2013). The primary outcome in this trial has been defined a priori as the continuous response variable, ‘CANTAB RVP probability of hit’. Secondary outcomes have been defined as the total scores for the ADHD-RS and BRIEF for the parent and teacher version respectively.

Results

70 participants were randomized in this trial. Participants ranged in age from 6 to 13 years ($M=9.95$, $SD=1.7$) and were all Caucasian. A total of 40 (57%) participants used ADHD medication during the intervention, with no significant differences in medication status between the two groups. Four participants dropped

out of the trial before completion of the intervention. One participant in the control group did not participate in the T1 assessment, but returned to the two follow-up sessions (T2 and T3). Missing data for this second visit were estimated based on FIML. A flowchart of included participants is shown in Figure 1.

(Please insert Figure 1 about here)

Baseline Characteristics

The 70 participants allocated to the two groups were comparable on a number of measures at baseline (see Table 1). There were no statistically significant differences between the two groups, regarding age, sex, medication status, IQ or cognitive measures, parent and teacher rated ADHD symptoms, teacher rated BRIEF or parent rated functional outcome as measured by questionnaires at baseline. One exception was the parent rated BRIEF: Total score, Organize Materials, Working Memory and Metacognition Index sub-scales, where the participants in the intervention group scored significantly higher than controls at baseline.

(Please insert Table 1 about here)

Effects on the Primary Cognitive Outcome

Results indicate that the intervention had no effect on our primary outcome measure, the CANTAB RVP Probability of hit compared to the control group: $b = -.017$, CI (-.0907 to .0560), $z = -0.46$, $p = 0.643$ (see Table 2). Although we recruited fewer participants than originally anticipated, with our sample size of 70 participants, we would be able to identify even moderate treatment effects (i.e. standardized mean differences $>.68$) with a power of 80% and a 5% significance level.. Additionally, we performed the best-worst and worst-best sensitivity analysis of primary outcome. The beta coefficient ranged from -0.07 in the worst-case

scenario to 0.03 in the best-case scenario. No significant effect could be detected.

(Please insert Table 2 about here)

Effects on Secondary Outcome Measures

The secondary measures were defined a priori as the total score on BRIEF as rated by parents and teachers and the total score on ADHD-RS parent and teacher version (see Table 3). Results indicate that there were no significant effects of training on BRIEF total scores for the parent version $b=-2.12$ (-5.5 to 1.26), $z=-1.23$, $p=0.22$ or teacher version: $b=3.68$ (-1.11 to 8.48), $z=1.5$, $p=0.13$. There were no significant differences for the ADHD-RS parent total score $b=-1.02$ (-6.13 to 4.09) $z=-0.39$, $p=0.69$ or ADHD-RS teacher total score $b=3.11$ (-3.63 to 9.85) $z=0.90$, $p=0.37$.

Effects on exploratory measures

Cognitive outcome measures.

All secondary and explorative variables were on continuous measurements. SEM analysis indicated a highly significant effect of the intervention on executive functions as measured at T1, by the variable SOC problems solved in minimum moves: $b=1.22$ (.347 to 2.10), $z= 2.74$, $p=0.006$ with the intervention group outperforming the control group (and also a significant effect on this outcome at T2 and T3, see later). However The difference between the two groups on the accuracy in planning corresponds to 0.30 of a standard deviation on the outcome indicating a modest effect. Four other measures were not significantly different between groups, but indicated a trend: RVP mean latency ($p=0.098$); SWM between errors ($p=0.096$); IED EDS Errors ($p=0.13$) and SST Direction Errors on Stop and Go ($p=0.054$).

However the difference on the latter is not is due to the control group getting worse

over time. There were no significant group differences on any of the other cognitive measures (see Table 3.).

(Please insert Table 3 about here)

Behavioral outcome measures.

The subscale Metacognition Index on parent-rated BRIEF showed a trend in favor of the intervention group ($p=0.07$). Other subscales of the BRIEF were not significantly different between groups. There were no significant differences between the intervention and the control group on the ADHD-RS subscales or any other measures (see Table 3.). There were no serious or non-serious adverse events reported.

Interactions with age.

To explore possible interactions with age we divided participants in two groups: 6-9 years old ($n=43$) and 10-13 ($n=27$) and compared participants in the intervention group to the controls in each age group (see Table S1 in the supplemental material). For a number of CANTAB measures there was a significant difference in the older group, but not in the younger group: RVP mean latency ($p=0.045$), SWM between errors ($p=0.004$), SOC problems solved in minimum ($p=0.009$), and SST direction errors on stop and go ($p=0.008$).

In addition, parent rated ADHD hyperactivity score improved for the older group, ($p=0.018$), but not for the younger group. Teacher rated ADHD-total scores and hyperactivity scores were significantly improved in the younger group ($p<0.000$), but not the older group.

Several parent rated BRIEF subscales showed significant improvement for the older group: Plan/Organize ($p=0.036$) and Metacognition Index ($p=0.01$). On the Monitor subscale the older group got significantly worse ($p=0.003$), but not the older group. For the teacher rated BRIEF Metacognition Index: The younger group got significantly worse ($p=0.01$), but not the older group.

Effects at follow up: time T2 and T3.

At the 12-week follow-up (T2) data on the cognitive outcome measures was available for 54 participants and at the 24-week follow up (T3) for 41 participants. Results on the follow up data for the CANTAB cognitive test indicate that the significant difference on SOC Problems solved in minimum moves was maintained over both time points, at T2 ($p=0.035$) and at T3 ($p=0.017$).

At the 24-week follow up (T3), there were significant effects on two measures that did not differ significantly at T1: RTI 5-choice movement time ($p=0.008$) and AST Total Commission errors ($p=0.014$) and SST SSD 50 last half approached significance ($p=0.065$). Due to a large number of drop-outs (over 50% for the parents and 65% for the teachers) on the behavioral scales returned at T3 ($n= 36$ parent ratings and $n=18$ for teacher ratings) and T4 ($n= 34$ parent and $n=20$ for teacher ratings) we did not calculate results for ADHD-RS, BRIEF and WFIRS at these time points.

Compliance.

There was a great variation in the number of sessions performed in the intervention group ($M= 26.2$, $SD=15.89$, $min=0$, $max=48$). Compliance was low and

only 66.5 % of participants performed more than 20 sessions, defined as compliers. We did a post hoc analysis on the outcome measures comparing compliers (n=19) and non-compliers (n=51) to controls to explore effects of more and less intense cognitive training. There were no significant differences on the most cognitive outcome measures with one exception: Compliers showed significant improvement on only one measure: SST direction errors on stop and go ($p=0.01$), but no effect in non-compliers ($p=0.42$). Parent rated BRIEF (f BR 9) Monitor subscale was non significant for compliers ($p=0.2$), but the non-compliers got significantly worse ($p=0.009$). No other group differences between compliers and non-compliers were found (see Table S2 in the supplemental material).

Discussion

The aim of this trial was to investigate the effect of ACTIVATE™, a computerized intervention targeting multiple cognitive functions, compared to treatment as usual. Our primary hypothesis, that this intervention would have an effect on an objective measure of sustained attention, could not be confirmed. Although we recruited fewer participants than initially anticipated, the absent effect on the primary outcome measure was not due to a Type II error, as shown by our post hoc power analysis. We have adopted a gate keeping approach stating that if there was no significant effect on our primary outcome measure, all other measures would not be considered significant either, regardless of their outcomes. Still, we found no significant effect on the secondary outcome measures, defined as the total scores on the BRIEF and ADHD –RS questionnaires for parents and teachers, indicating that there was no effect of ACTIVATE™ on parents and teacher reported symptoms.

Significant differences between the intervention and control group were seen on some exploratory measures. ACTIVATE™ had an effect on the accuracy in planning (SOC). There was a highly significant difference between groups ($p=0.006$) after intervention, indicating that the ability to plan was improved in the intervention group as compared to the control group with a modest effect. Furthermore the significant difference was maintained at both the 12-week ($p=0.03$) and 24-week ($p=0.017$) follow-up, thus the effect was still observable 6 months post intervention. However this change had a modest effect at best. In addition, one subscale of the parent rated executive functions, BRIEF Metacognition Index, was approaching statistical significance in favor of the intervention group. Metacognition Index is the sum of five BRIEF subscales and reflects the individual's ability to initiate activity, generate and organize problem-solving ideas, to sustain working memory, to monitor success and failure in problem solving, and to organize materials and environment. However BRIEF Total score and the Metacognition Index, Working memory and Organize Materials subscales were significantly different at baseline in favor of the control group. Although we have adjusted for baseline scores in our analysis, these results can indicate, that the intervention group was somehow more impaired in their executive functions or had parents with more negative attitudes towards the children. Other exploratory cognitive measures showed no significant differences between groups immediately after intervention. There were no near or far transfer effects on parent or teacher rating scales for ADHD or the parent rated functional scale after the intervention.

In our analyses of age we found a number of differences in the gains of intervention between the older (10-13) and the younger (6-9) group. The older group showed significant improvements on sustained attentional function, made

fewer errors in the working memory task, improved ability to plan and made fewer mistakes on the stop signal task, while the younger group did not. Actually the younger group got significantly worse on the stop signal task, but not the older group. This can probably be explained with that the children found the stop signal task to be very frustrating and often did not wish to conduct the test, especially at the first follow-up, where they already knew the task. The results might indicate, that the older children might have been more compliant in this task.

The older group also improved on the parent rated ADHD-RS Hyperactivity score. Additionally, the older children obtained significant differences on the parent rated BRIEF Plan/Organize and Metacognitive index subscales on but they got significantly worse on Monitor subscale. Teacher-rated BRIEF Initiation was significant for both the younger and older group. On the other hand the younger group showed some improvements on the teacher rated ADHD-RS Total score and Hyperactivity subscale, but not the older group. At the same time younger group got worse on teacher rated Organize Materials and Metacognition index. Together, these results indicate some possible effects of ACTIVATE™. It seems that age might be an important factor when using cognitive training, which is not in accordance with the hypothesis that the potential for neural changes is larger in early childhood, because of increased neuroplasticity (Johnston et al., 2009). However, as our results are exploratory, it would be necessary to test this hypothesis as a primary outcome in future studies to determine if there is a real effect of the intervention on planning ability.

ACTIVATE™ has been tested previously (Smith et al., 2016) in a different setting, where it was incorporated as a part of a multifaceted intervention program, the Integrated Brain, Body, and Social (IBBS) intervention. In a

randomized, controlled trial children with ADHD or subthreshold ADHD used ACTIVATE™ in a group setting at school, in combination with the Good Behavior Game and physical training and controls received TAU. Results showed no significant differences on any measure. Despite the methodological differences, our results are similar in finding no effect on the majority of cognitive outcome measures, severity of symptoms and executive functions behaviors indicating that ACTIVATE™ is not useful for children with ADHD as an individual or part of a multifaceted intervention. However, we found an exploratory effect on the ability to plan, while Smith et al. (2016) did not include such a measure.

Our results add to a small number of randomized trials, which have investigated the effects of broader executive functions interventions focusing on combined inhibition and short memory training (Johnstone et al., 2012; Johnstone, Roodenrys, Phillips, Watt, & Mantz, 2010), and two trials additionally including set-shifting (Dovis et al., 2015; van der Oord, Ponsioen, Geurts, Ten Brink, & Prins, 2014). The two latter trials are most similar to our intervention. However Van der Oord (2014) found significantly improved parent-rated BRIEF total and Metacognition Index and ADHD symptoms. These effects were maintained at follow-up and showed additionally significant effects on teacher rated ADHD symptoms. Using the same intervention in a double blind design, Dovis et al. (2015) found transfer effects on visuospatial working memory and short term memory, inhibitory performance and interference, but not on any other cognitive measure, ADHD symptoms, BRIEF, motivational behaviors or general problem behaviors. These two trials differed in their selection of control groups and degree of blinding. Van der Oord used a wait list control, while Dovis et al (2015) had two control groups, a partially active intervention group and a placebo group.

The optimal control group in cognitive training trials would be an active placebo group performing a control intervention that has no impact on cognition. An active placebo group does not only control for the contact with the therapist and the computer, but also allows to blind participants and their parents ensuring a double blind design. However the challenge is to identify an active placebo-training program that has no effects without any impact on cognitive functions and we therefore chose not to use it and use TAU instead. Some studies, especially those using Cogmed, have used the actual intervention on a consistently low level in a non-adaptive fashion as an active control. However, in cognitive intervention trials it is challenging enough to engage the participants in the demanding intervention for several weeks, maintain good adherence to the trial, a high motivation and prevent them from dropping out. If control participants have to engage in an intervention with very low cognitive load for several weeks, this could be perceived as boring and cause attrition. Additionally, the blinding could be broken, because participants and parents probably could figure out which group they are in. In a previous trial (Bikic et al., submitted) we have used the game Tetris as a control condition. In that trial we found no differences between the groups at the end of the intervention, but there were several different pre-post effects for both the intervention and Tetris group, individually. Importantly, Dosis et al. (2015) used a new control condition with good adherence, by the application of game-design elements and game principles in a non-game context: a gamification of the intervention. However, in that trial the active control group also showed some significant pre-post changes, indicating that there might be a cognitive effect even in low load interventions, which could have obscured group differences (Dosis et al., 2015) and could explain the

differing results between the Dovis et al. (2015) and the Van der Oord et al. (2014) trials.

Our intervention was somewhat similar to the intervention in the Dovis et al. (2015), and the Van der Oord et al. (2014) as the games in ACTIVATE™ also focus on attention, working memory, set shifting and impulse inhibition. Our results are similar to Van der Oord et al. (2014), finding an effect on the parent rated BRIEF Metacognition Index, although our result was only approaching significance. Dovis et al. (2015) found effects on working memory and short-term memory, inhibitory performance and interference, which we did not find. However, neither Dovis et al. (2015) nor Van der Oord et al. (2014) used a measure of planning ability, which we found a significant effect on. A difference to our trial is that in the Van der Oord et als. (2014) study participants completed at least 20 out of 25 sessions and in the Dovis et al. (2015) study participants completed 25 sessions with only 3% failing to meet compliance criteria. As we adopted an intent-to-treat design in our analyses, we kept everyone in the intervention group regardless of the number of sessions performed. The compliance in the intervention group was low and only 66.5% of our participants performed 20 or more sessions. A post hoc analysis comparing compliers performing at least 20 sessions to controls showed that they significantly outperformed non-compliers on only one measure of inhibition and on the parent rated BRIEF Metacognition Index subscale as compared to controls. Again this may indicate that executive functions training could have an effect on BRIEF Metacognition Index and inhibition if a certain intensity of training is fulfilled. On the other hand it seems that some functions might not require intense training, like for the planning ability measure, which showed significant differences for the whole sample. As our analyses were exploratory, these hypotheses need to be tested in future trials.

An examination of ADHD subtype showed that the gains of intervention were largest for the inattentive subtype (ADHD-I) compared with controls, showing significant differences in working memory, planning ability and impulse inhibition and on the parent rated BRIEF Metacognition Index, while the combined subtype only showed significant improvements on the planning ability, compared to controls. Research indicates that the combined and the inattentive subtype might be different on neurological level (Diamond, 2005) and thus might need different interventions.

A general problem across all cognitive training studies is that so far not a single study has tailored the interventions to the existing cognitive deficits of the trial participants. The common practice has been to include participants with ADHD regardless of the individual cognitive deficits at baseline. Individuals with ADHD are thus assumed to have identical needs and expected to benefit from the intervention equally, despite evidence that individuals with ADHD exhibit heterogenic cognitive profiles and symptoms (Lambek et al., 2011; Nigg, 2005; Willcutt et al., 2005). If an individual with ADHD exhibits problems with attention, but has normal working memory, it would make little sense to train working memory and expect this to generalize to attention. Indeed, the connection between specific cognitive deficits, their hierarchical order and interaction and the generalization to other cognitive dysfunctions and symptoms have not yet been empirically proven. Most cognitive training approaches focus on the assumption that the largest cognitive deficits presented in individuals with ADHD somehow might be the most central ones for the disorder. However, the central cognitive deficit in ADHD has still not been identified and it is still questioned if this kind of core cognitive deficit exists for the whole

ADHD population (Nigg, 2005). Considering the heterogeneity of the disorder on the cognitive, neural and symptom level, it would be important to look at the effects of cognitive training on a subgroup level and identify specific groups that might benefit from certain kinds of cognitive interventions. Unfortunately most trials to date did not have large enough sample sizes to allow these explorations. The approaches of the future should be driven by the specific needs of individual cognitive profiles.

Our trial has several strengths. The number of drop outs during the intervention was small. We performed intent to treat analysis, using FIML to account for missing data. Additionally, we performed adequate generation of allocation sequence, adequate allocation concealment and adequate blinding wherever possible. We tested a priori defined primary, secondary and exploratory outcome measures as they were published in our trial protocol (Bikic et al., 2015) and there is no for-profit bias. However, our trial does have some limitations: We were not able to blind the participants and their parents or teachers to group allocation. Although we included objective outcome measures, our secondary outcome measures were based on questionnaires rated by parents and teachers, who were not blind to group allocation, which can induce possible placebo effects. Additionally, we were not able to recruit the number of participants we originally anticipated, reducing our power to detect significant differences. At the two follow up time points the drop out was substantial for the returned questionnaires and we were not able to analyze survey data for these time points. Our exploratory analyses were performed on a relatively small number of participants. The teacher ratings were not always provided by the same teacher, which can induce a natural variability in scores and might explain some of the unusual results we found.

To conclude, ACTIVATE™ did not show an effect on any of our primary or secondary outcomes. We found that it may have beneficial effects of the ability to plan and before dismissing it as a possible treatment, it would be important to investigate the age effects on specific cognitive functions in future studies.

We also found some interesting effects on the subgroup level regarding age of the participants, ADHD subtypes and the number of training sessions completed.

Considering that ADHD is a very heterogenic disorder at the individual level, future studies with larger samples should investigate effects on subgroup levels.

Conflict of Interest

None.

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Table 1. Diagnostic and Demographic Characteristics of Children at Baseline

Diagnostic and demographic Variables	Intervention group (n=35)	Treatment as usual group (n=35)	p-value
age, mean (SD)	9.77 (1.97)	10.14 (1.52)	0.38
female (%)	6 (17%)	5 (14%)	0.74
Medication (%) ¹	20 (57%)	20 (57%)	1.00
IQ, mean (SD)	96.20 (8.50)	95.94 (7.35)	0.89
ADHD subtype (%)			0.23
ADHD-H	3 (9%)	1 (3%)	
ADHD-I	12 (34%)	18 (53%)	
ADHD-C	20 (57%)	15 (44%)	

Abbreviations: ADHD: Attention Deficit/Hyperactivity Disorder-Rating Scale; ADHD-Combined Type (ADHD-C); ADHD-I: Predominantly Inattentive Type; ADHD-H: Predominantly Hyperactive-Impulsive Type.

¹ 98% received methylphenidate

Table 2. Results: Effects on the cognitive outcome measures from CANTAB

	Intervention				Treatment as usual				p-value		
	Means and standard deviations (SD)								T0-T1	T0-T2	T0-T3
	T0	T1	T3	T4	T0	T1	T3	T4			
RVP Probability of Hit (H)	0.709 (0.125)	0.702 (0.174)	0.743 (0.143)	0.777 (0.147)	0.729 (0.138)	0.728 (0.189)	0.758 (0.17)	0.743 (0.167)	0.64	0.73	0.29
RVP Mean Latency (L)	431.8 (121.7)	391.0 (105.5)	371.15 (110.9)	355.7 (85.9)	397.3 (119.7)	410.8 (152.6)	392.8 (143.4)	356.2 (115.43)	0.098	0.36	0.65
RVP Probability of false alarm (L)	0.024 (0.033)	0.014 (0.01)	0.011 (0.009)	0.03 (0.09)	0.013(0.009)	0.013 (0.012)	0.01 (0.009)	0.01 (0.018)	0.70	0.88	0.39
SWM Between errors (L)	51.5 (19.6)	41.78 (17.34)	44.49 (15.09)	43.47 (19.2)	48.86 (21.94)	47.5 (17.53)	46.43 (21.7)	43.65 (18.77)	0.096	0.80	0.91
RTI 5-choice movement time	483.7 (126.1)	497.2 (97.43)	460.26 (91.03)	464.8 (132.9)	471.1 (128.1)	469.7 (95.7)	518 (92.4)	454.6 (115.7)	0.27	0.008*	0.92
RTI Simple error score inaccurate	0.117 (0.322)	0.225 (0.489)	0.332 (0.608)	0.151 (0.477)	0.114 (0.32)	0.117 (0.322)	0.212 (0.41)	0.143 (0.35)	0.29	0.51	0.73
SOC Probl. solved min. moves (H)	7.36 (1.89)	8.08 (1.75)	8.82 (1.25)	8.80 (1.25)	6.91 (1.87)	6.72 (2.02)	7.93 (1.4)	7.79 (1.47)	0.006*	0.03*	0.017
SOC Mean Moves 4-moves (L)	5.11 (1.04)	5.18 (0.86)	5.07 (0.96)	5.12 (0.84)	5.48 (1.05)	5.39 (0.88)	5.33 (0.88)	5.3 (0.837)	0.28	0.56	0.46
AST Total Omission errors (L)	5.26 (4.38)	3.6 (5.01)	2.85 (4.16)	3.2 (4.8)	5.23 (6.9)	4.06 (6.07)	4.07 (6.9)	3 (6.49)	0.88	0.57	0.39
AST Total Commission errors (L)	2.35 (6.6)	1.19 (3.94)	0.447 (1.08)	0.95 (1.99)	1.43 (2.93)	1.63 (4.54)	1.63 (2.88)	2.62 (8.7)	0.49	0.01*	0.27
IED EDS Errors (L)	14.15 (11.03)	8.37 (8.9)	8.09 (9.77)	5.81 (8.2)	13.5 (10.96)	11.6 (10.67)	9.27 (9.03)	8.6 (9.59)	0.13	0.45	0.39
SST Direction Error Stop and Go (L)	9.39 (8.19)	9.34 (8.45)	8.74 (8.01)	7.4 (7.9)	10.03 (9.54)	14.66 (15.16)	12.41 (13.59)	10.75 (7)	0.054	0.19	0.08
SST SSRT last half (L)	233.9 (79.64)	276.6 (99.9)	244.49 (87.2)	200.3 (68.3)	244.1 (84.45)	250.8 (84.8)	262.1 (136.24)	223.8 (118.5)	0.093	0.87	0.39

Abbreviations: H: Higher score is better; L: Lower score is better; RVP: Rapid Visual Information Processing; SWM: Spatial Working Memory; RTI: Reaction Time; SOC: Stockings of Cambridge; AST: Attention Switching Task; IED: Intra-Extra Dimensional Set Shift (IED); SST:

Table 3

Effects of the intervention and treatment as usual on the behavioral measures from T0 to T1					
Measures	Intervention		Treatment as usual		p
	Means and standard deviations (SD)				T0-T1
	T0	T1	T0	T1	
P- BRIEF Impulse inhibition	66.17 (9.38)	62.17 (8.52)	64.09 (10.48)	62.64 (9.31)	0,28
P- BRIEF Flexibility	69.43 (11.41)	67.19 (12.47)	64.90 (13.96)	63.43 (10.97)	0,82
P- BRIEF Emotional control	65.20 (9.40)	62.08 (11.47)	61.07 (9.29)	57.19 (10.27)	0,388
P- BRIEF AI	69.46 (9.30)	65.60 (10.51)	65.33 (8.74)	62.60 (9.29)	0,699
P- BRIEF Initiation	66.47 (8.01)	62.36 (9.77)	63.28 (8.89)	59.00 (9.76)	0,627
P- BRIEF Working Memory	74.09 (6.17)	68.6 (7.35)	69.03 (6.89)	67.26 (8.27)	0,538
P- BRIEF Plan / Organize	69.0 (8.13)	66.19 (7.8)	65.5 (6.85)	63.6 (9.27)	0.376
P- BRIEF Organize Materials	60.56 (8.82)	59.42 (8.68)	55.95 (7.89)	56.6 (11.02)	0,666
P- BRIEF Monitor	66.36 (7.79)	63.73 (8.17)	62.43 (10.45)	57.71 (11.2)	0.095
P- BRIEF Metacognitive Index	71.67 (6.38)	65.32 (8.68)	65.76 (6.57)	63.74 (9.13)	0.071
P- BRIEF Total	72.13(5.28)	67.27(7.97)	66.88 (7.22)	64.4 (9.36)	0.22
T- BRIEF Impulse inhibition	65.13 (12.28)	70.03 (12.25)	73.33 (18.67)	71.73 (19.66)	0,33
T- BRIEF Flexibility	71.57 (13.06)	77.86 (14.62)	77.31 (13.97)	73.82 (18.01)	0,213
T- BRIEF Emotional control	69.43 (14.12)	74.80 (11.94)	71.26 (16.18)	71.18 (17.33)	0,78
T- BRIEF AI	70.31 (13.73)	77.10 (12.75)	75.93 (14.09)	76.10 (19.09)	0,274
T- BRIEF Initiation	70.46 (11.61)	72.09 (11.89)	69.53 (9.57)	69.80 (11.49)	0,849
T- BRIEF Working Memory	70.67 (12.36)	72.49 (10.71)	73.03 (8.80)	73.89 (12.55)	0,532
T- BRIEF Plan / Organize	66.14 (9.59)	69.06 (8.89)	68.34 (10.08)	69.98 (10.49)	0.429
T- BRIEF Organize Materials	62.55 (11.01)	62.30 (12.65)	66.30 (20.19)	68.27 (18.83)	0,854
T- BRIEF Monitor	68.28 (12.77)	70.47 (12.79)	72.63 (12.95)	69.42 (13.56)	0.208
T- BRIEF Metacognitive Index	69.17 (9.88)	70.17 (10.86)	72.8 (11.86)	71.86 (12.70)	0.294
T- BRIEF Total	70.93 (10.11)	74.76 (10.73)	75.95 (12.44)	75.08 (15.21)	0.133
P-ADHD-I	18.35 (3.84)	15.4 (5.33)	16.42 (4.33)	15.66 (4.88)	0.43
P-ADHD-H	15.31 (5.42)	12.18 (5.76)	13.53 (6.58)	12.55 (6.54)	0.39
P-ADHD-ODD/CD	8.81 (5.30)	8.06 (5.49)	7.03 (5.46)	6.12 (5.58)	0.20
P-ADHD-total	45.56 (10.48)	34.98 (14.04)	37.28 (13.05)	35.36 (13.25)	0.70
T-ADHD-I	14.75 (5.19)	15.68 (5.39)	15.35 (6.98)	16.38 (6.51)	0.39
T-ADHD-H	11.52 (7.21)	12.48 (7.16)	12.38 (7.30)	13.09 (8.44)	0.46
T-ADHD-ODD/CD	6.59 (5.55)	7.94 (6.63)	6.61 (5.83)	7.46 (5.94)	0.49
T-ADHD-total	32.5 (12.11)	39.51 (15.22)	34.26 (16.71)	38.44 (18.59)	0.37
P-WFIRS-Total	0.96 (0.43)	0.82(0.46)	0.8(0.39)	0.73 (0.45)	0.54

Abbreviations: P: Parent rated; T: Teacher rated; BRIEF: Behavior Rating Inventory of Executive Functions (Gioia et al., 2000); ADHD-RS: Attention Deficit/Hyperactivity Disorder-Rating Scale (DuPaul et al., 1998)); ADHD-I: ADHD Inattention Scale; ADHD-H: ADHD Hyperactivity Scale; ADHD-ODD/CD: ADHD oppositional behavior Scale; ADHD-WFIRS: Weis's scale of disability-Parent Report (Gajria et al., 2015)

Figure 1.

CONSORT 2010 Flow Diagram

