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NEW APPROACH TO THE TREATMENT OF ADHD THROUGH INTERNET AND SMARTPHONES
-
FROM IMPAIRMENT TO IMPROVEMENT

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New approach to the treatment of ADHD through internet and smartphones – from impairment to improvement

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Dedicated to my late grandmother Mohtaram Moradi, my beloved Maman Bozorg, who filled each one of my childhood hours with endless love, joy and unforgettable memories.

“Never trust your fears. They don´t know your strengths.”

~ Athena Singh

ABSTRACT

Background: Attention deficit hyperactive disorder (ADHD) is a common and disabling disorder, affecting 2-4% of the adult population worldwide. Pharmacological treatment is often the only available option, however medication is not sufficient for 50-70% of the adults. Thus, it is necessary to develop and evaluate complementary treatments.
Although treatments such as cognitive and dialectic behavioral therapy (CBT and DBT) in the treatment of ADHD have been promising, they have each targeted different aspects of ADHD symptomatology, thus neither one has addressed the total variety of symptoms typically displayed in adults. Moreover, accessibility to these treatments is low.

Aims: General aims of this thesis were to develop and evaluate the efficacy of new psychological interventions for adult ADHD, addressing a variety of common impairments associated with the diagnosis, with the intention to make these interventions accessible and available through internet.

Methods: Three clinical trials were conducted. In study I, a randomized controlled trial (RCT; n=57), adults with ADHD or probable ADHD, with pronounced difficulties with inattention and organization, took part in an internet-based course on how to structure their everyday life with smartphone applications and online-tools and were compared to a wait-list control group. Study II, an uncontrolled study (n=18), evaluated the feasibility and preliminary effect of a novel treatment based on a combination of CBT and DBT. Study III, an RCT evaluating internet-based treatment for adults with ADHD (n=104), explored the efficacy of the combination treatment (ICBT) compared to an active and credible control group (internet-based applied relaxation training, IART) and to treatment as usual (TAU).

Results: The intervention in study I showed large effects on attention and organization skills for participants in the intervention group. Moreover, the improvements on hyperactivity and depression severity were also significantly better compared to the wait-list condition. The combined group treatment in study II turned out to be feasible and beneficial with large reductions of ADHD symptoms and related problems such as depression and experienced stress. Reductions in ADHD symptoms were maintained up to 6 months after treatment. In study III, ICBT and IART were shown to be equally effective with moderate effects on ADHD symptoms compared to TAU up to one year after treatment. The only significant interaction between both treatments over time was for level of general everyday functioning, favoring ICBT. Satisfaction ratings were high in the ICBT group, however some of the participants experienced the treatment as stressful or overwhelming.

Conclusions: The smartphone course, as well as the combination treatment administered in a group format, seems to be feasible and effective in improving ADHD symptoms and related problems. The internet-based combined treatment was also effective compared to treatment as usual and has the potential to increase accessibility and availability to treatment. Sustained effects were also found for the combination treatment (studies II-III) in the long term. However,

future adjustments in content need to be made to enhance the specific effects on ADHD and related symptoms.

LIST OF SCIENTIFIC PAPERS

I. Moëll B, Kollberg L, Nasri B, Lindefors N, Kaldo V. Living SMART — A randomized controlled trial of a guided online course teaching adults with ADHD or sub-clinical ADHD to use smartphones to structure their everyday life. Internet Interventions. 2015;2(1):24-31. doi:org/10.1016/j.invent.2014.11.004.

II. Nasri B, Castenfors M, Fredlund P, Ginsberg Y, Lindefors N, Kaldo V. Group Treatment for Adults With ADHD Based on a Novel Combination of Cognitive and Dialectical Behavior Interventions: A Feasibility Study. Journal of Attention Disorders. 2017: doi:1087054717690231.

III. Nasri B, Cassel M, Claesson J, Larsson M, Hirvikoski T, Ginsberg Y, Lindefors N, Kaldo V. Internet delivered Cognitive Behavioral Therapy for Adults with ADHD - A Randomized Controlled Trial. *Submitted manuscript.*

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LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
ANOVA	Analysis of variance
ASD	Autism spectrum disorder
ASRS v1.1	Adult ADHD Self Report Scale version 1.1
BDI	Beck's depression inventory
CBT	Cognitive behavior therapy
CGI - I	Clinical global impression – Improvement scale
CSS	Current symptom scale
CSQ	Client satisfaction questionnaire
DBT	Dialectic behavior therapy
DSM	Diagnostic and statistical manual of mental disorders
HADS-D	Hospital anxiety and depression scale – (depression)
IART	Internet-based applied relaxation training
ICBT	Internet-based cognitive behavioral therapy
iCBT-G	Internet-based cognitive behavior therapy- group format
iCBT-S	Internet-based cognitive behavior therapy- self-help format
IT	Internet
MADRS-S	Montgomery Åsberg depression rating scale – self rated
Post	Measuring point at treatment end
Pre	Measuring point at treatment start
PSS	Perceived stress scale
RCT	Randomized controlled trial
SDS	Sheehan's disability scale
TAU	Treatment as usual
TCS	Treatment credibility scale

1 INTRODUCTION

"I am in the mood to dissolve the sky." ~ Virginia Wolf

1.1 ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS

ADHD is characterized as one of the most common, pervasive, and impairing psychological disorders among children [1] and is one of the most thoroughly researched disorders in the field of medicine [2], affecting many aspects of functioning and development. The core symptoms of ADHD; inability to sustain attention, impulsivity, and hyperactive behavior; can significantly hinder success in social, academic, and home environments [3].

The prevalence rate of ADHD ranges from approximately 3% to 9% of youth worldwide [4,5]. Longitudinal data shows that 50%- 70% of children with ADHD continue to have symptoms as adolescents and adults [6,7]. The decline in ADHD prevalence may be due to the finding that ADHD symptoms, especially hyperactivity, decline as a function of age [8].

Despite the decrease in hyperactivity [6], adolescents and adults with ADHD continue to have impairing symptoms of inattention, hyperactivity, and impulsivity [9] and experience the same domains of functional impairment as children with ADHD [10]. Academic [11], social [12] and family [13] domains are frequently impaired in adolescents with ADHD.

The diagnostic criteria for ADHD have been modified in the Diagnostic and Statistical Manual of Mental Disorders (5th ed; DSM-5 [14]) to better reflect the changing nature of the diagnosis throughout a lifespan [3]. However, essentially the same symptoms as in DSM-IV [15] are retained in DSM-5 with some revisions. In order for individuals 17 and above to receive a formal diagnosis of ADHD according to the DSM-5, five or more symptoms of inattention and/or five or more symptoms of impulsivity/hyperactivity must be displayed before the age of 12 (six for individuals younger than 17 in each area respectively), without the requirement of creating impairment by age 12. In DSM-5, symptoms of inattention and/or impulsivity/hyperactivity must be evident in more than one context but do not have to cause functional impairment in multiple contexts. To be diagnosed, the symptoms have to interfere with, or significantly reduce the quality of, academic, social, or occupational functioning. Additionally, the severity level must be specified by the clinicians as either Mild, Moderate, or Severe.

Three ADHD subtypes are used to categorize (adult) individuals:
* Combined Presentation - for individuals who display at least 5 inattentive and 5 hyperactive-impulsive symptoms in combination, while still meeting all the other diagnostic criteria.

* Predominantly Inattentive Presentation - when sufficient inattentive but insufficient hyperactive-impulsive symptoms are present.

* Predominantly Hyperactive-Impulsive Presentation - when sufficient hyperactive-impulsive symptoms but insufficient inattentive symptoms are displayed.

In adults, the cognitive and behavioral deficits include insufficient listening skills, being forgetful and easily distracted, difficulties in maintaining attention in paperwork, reading, finishing or initiating complex tasks at meetings, sitting through longer meetings, low frustration tolerance and making careless mistakes [16].

The core ADHD symptoms of inattention, hyperactivity and impulsivity also contribute to the impairments in executive functioning, inhibitory control, working memory, and motivation. These neuropsychological deficits act as barriers for adults with ADHD in acquiring and implementing compensatory skills. This dysfunction in adaptive behaviors like organization and planning can lead to maintenance of the symptoms.

After years of chronic underachievement and multiple failure experiences, adults with ADHD develop maladaptive negative cognitions and beliefs that negatively affect motivation and increase avoidance behavior and mood disturbance [17].

1.2 ETIOLOGY

The genetic background of ADHD is complex and the exact etiology is still unknown [18]. Family, adoption and twin studies support the role of ADHD as a highly heritable disorder [18] where heritability estimates as high as 90% [19] with direct polygenetic and environmental influence [20]. Neuroimaging studies show maturation delay in cortical thickness in children with ADHD, most prominent in prefrontal regions. These regions are important for control of cognitive processes like motor planning and attention [21,22]. Furthermore, the cerebellum, caudate, and prefrontal cortex have emerged as the essential areas displaying deficits in ADHD [18]. These regions are interconnected by a network or neurons, which are sensitive to the neurochemical environment. Additionally, they are sustained by neurotransmitters such as dopamine and norepinephrine, showing great importance in the regulation of attention, emotions, thoughts, behavior, and actions. Helpful pharmacotreatment in ADHD aims to restore the fine balance of the neurotransmitters in the prefrontal cortex [18]. Moreover, the role of environmental factors as mediators or moderators of genetic have been explored in recent studies with inconsistent results [23].

1.3 COMORBIDITY AND RELATED PROBLEMS

Comorbidity is common and up to 80% of the adults also fulfil the diagnostic criteria for depression, anxiety disorders, sleep disorders, and personality disorders [24,25]. Other comorbid conditions are bipolar disorder, autism spectrum disorder (ASD) and eating disorders, although in a smaller number of cases [26]. In adolescence and adult life, ADHD is shown to also have a negative impact on risky behaviors such as motor vehicle operation, substance abuse and sexual risk taking [27-29.]

Emotional regulation deficits are also implicated in ADHD [30,31] and brief recurrent depressive or dysphoric states or feelings of emptiness are all common in ADHD. When reviewing the literature, some authors finds the comorbidity between ADHD and borderline personality disorder of particular interest [32,33]. Deficits in affect regulation, impulse control, substance abuse, low self-esteem and disturbed interpersonal relationship are similar problems between ADHD and borderline personality disorder. Mechanisms of affect regulation, however, differ quite dramatically in the two conditions. Unlike participants with borderline personality disorder who tend to show a "freezing behavior" or a "dissociative state" in emotionally stressful situations, participants with ADHD often try to regulate their labile emotional balance by excessive sports, sexual behavior, or sometimes impulsive aggressive behavior ("fight or flight"). Due to difficulties in impulse control and emotional instability, these participants are prone to interpersonal conflicts [34].

In sum, adults with ADHD remain symptomatic and have the same and additional functional impairments and psychiatric comorbidities as children with ADHD. Despite the fact that adults with ADHD seek assessment and treatment in increasing numbers, there have been far fewer research studies that have focused on treating adults compared to studies on children with the disorder [35].

1.4 TREATMENT

1.4.1 Pharmacological treatment

The majority of adults diagnosed with ADHD are offered pharmacological treatments as the major treatment option and few participants are given psychological treatment following completion of neuropsychiatric assessment and diagnosis [25]. Unfortunately, pharmacological treatment is not effective for about 20- 50% of the adults due to insufficient/lack of response and side effects [36,37].

The 25 %–50 % of adults treated with medication who show improvement in core symptoms may still have residual symptoms in life domains such as education, work, life skills (e.g. driving), and relationships [17,38]. Even though medication may help improve the basic symptoms of ADHD, this does not necessarily lead to overall functional improvement. The need for

complementary interventions such as psychological treatments for ADHD and its possible comorbid disorders should be emphasized [39-42]. Thus, there is a clear need for effective treatments for adolescents with ADHD. When left untreated, costs for the individual and society are high.

1.4.2 Psychological interventions

Research regarding psychological interventions for adults with ADHD shows emerging evidence for cognitive behavior therapy (CBT) as a promising treatment approach [17,43-49]. Dialectical behavior therapy (DBT), modified according the special needs of participants with ADHD, has also shown moderate to large effect sizes in the treatment of adult ADHD [34,50]. A recent meta-analysis comparing psychosocial interventions and medication for adolescents with ADHD showed that behavior therapy produced the greatest effects on impairment and that medication produced the greatest effects on symptoms [51].
Moreover, one study has shown that CBT produces greater improvements in ADHD symptoms when combined with pharmacotherapy, rather than CBT alone [52], findings in line with another, multimodal and multicentre study [53] showing better outcomes for psychological interventions when combined with methylphenidate over a 1-year period, as compared with placebo. Thus, CBT seems to be most effective as part of a multimodal treatment package. However, more randomized controlled trials are needed to evaluate if effects found in treatment studies derive from specific treatment mechanisms or from non-specific mechanisms such as patient expectations and therapist credibility [54]. Moreover, evaluation of long-term outcomes in the treatment of ADHD is limited [17].

CBT for adults with ADHD includes behavioral interventions targeting the learning and practice of compensatory skills (requiring consistency and repetition), together with cognitive interventions for dealing with negative thoughts and resulting negative emotions which contribute to avoidance and procrastination [43]. According to Safren's cognitive behavioral model, neuropsychological deficits contribute to functional impairments over time, resulting in a history of underachievement and failures by hindering the individual from acquiring and using compensatory strategies [48]. The compensatory strategies provided in the CBT programs usually include cognitive interventions such as cognitive restructuring, prioritization, organization, time management, dealing with procrastination, psychoeducation, problem solving, anger management, stress management, money management, relationship management, self-instruction, and mindfulness [43].

The emotional strategies (mainly used in DBT) include emotional regulation, impulse control/ self-control/self-regulation, self-motivation, emotional management, self-esteem, and self-respect [34]. These strategies may be used alone or in combination in any CBT program for adults with ADHD [17].

There are several reasons why CBT and DBT interventions may work for adults with ADHD. While some of them develop some effective ways of coping with the symptoms, most of the adults are unable to cope effectively with their deficits and are therefore unable to meet the demands of life. Moreover, they may be more motivated to seek treatment and be receptive to skill based treatments such as CBT due to their increased awareness of the deficits in their functioning [49,55].

Furthermore, the main focus in CBT is on building skills to compensate for deficits in executive functioning and working memory [48]. In DBT, change-oriented skills are used together with acceptance-oriented skills [50]. A recently published study [56], blending individual sessions of DBT/CBT with group sessions, has shown promising effects for adults who respond only partially or not at all to drug therapy. However, the study was uncontrolled with a small sample size. Moreover, the content of the intervention is somewhat unclear in the article with only two CBT inspired sessions included in the intervention, and the conclusion is that the scope of CBT was rather limited when compared with Safren's manual [57].

Safren's manual, together with Hesslinger's, are the two most widely accepted and used treatment manuals for ADHD in Swedish psychiatric healthcare today. However, accessibility to these treatments is very limited due to a scarcity of therapist resources. Furthermore, due to the variety and complexity of adult ADHD, clinicians often choose to combine preferred techniques from both these manuals without knowing if this strategy leads to desired outcomes in therapy. In conclusion, there is a need to scientifically evaluate the effects of a treatment manual that combines techniques from both of these therapeutic treatments. A combination manual could offer adults with ADHD a treatment that addresses the variety and complexity of their ADHD related problems in a way that each manual, when used separately, most likely cannot do.

1.4.3 Internet-based CBT

Up until now, most of the evaluated treatment programs for adults with ADHD have offered a high degree of interpersonal support during treatment [58], which reduces accessibility to evidence-based interventions such as CBT due to limited therapist resources [59]. However, in the last decade, internet-delivered cognitive behavior therapy (ICBT) has received increasingly robust empirical support as a treatment of various psychiatric conditions [60,61] such as depression [62], pathological gambling [63], comorbid anxiety disorders [64], irritable bowel syndrome [65], social anxiety disorder [66], tinnitus [67], insomnia [68], generalized anxiety disorder [69], and panic disorder [70]. The ICBT treatment is provided through an internet-based treatment platform which comprises the same main components as conventional CBT. The interpersonal communication goes through text messages and the therapist generally has no face-to-face contact with the participants during treatment.

Internet-based treatments are a promising solution to a number of mental healthcare delivery problems. While many people with mental illness go untreated due to the scarcity of trained CBT-therapists, ICBT provides enhanced access to evidence-based treatments with interventions delivered through a self-help format. However, programs with therapeutic guidance are often more effective than unguided programs [71]. Additionally, they can reach participants in areas where psychological or psychosocial treatment is not available. Furthermore, when compared with traditional face-to-face therapy, internet-based treatments have several other advantages in terms of greater cost-effectiveness [72], greater accessibility and convenience for the participants, as well as multimedia interactivity and continuous symptom monitoring.
Interventions delivered through internet are already in use in the regular health care systems in several countries such as Sweden and Australia, and because of these advantages, it is reasonable to assume that they will become increasingly available and provide a valuable alternative to many face-to-face treatments in the future [71,73].

1.4.4 Efficacy and use of smartphones in ICBT

Despite their proven effectiveness, current ICBT programs leave room for improvement. One way to potentiate ICBT might be to add smartphone applications. Research has shown that there are around 165 000 health care applications available for patients today, and that patients are interested in using mental health applications in their clinical care [74].

Smartphone applications bring the essential information, assignments, and measures/registrations much closer to the participants' everyday lives where the most important work takes place to change behaviors, thoughts, and emotional reactions.
The increased usage of smartphones creates an exciting and promising opportunity to extend the reach of psychological interventions and their effectiveness [75]. The emerging smartphone technology supports practice and use of therapy interventions outside of the session and into the real-life situations.
Smartphone applications may be used as stand-alone treatment or as supplementary ICBT components allowing novel features such as access to psychoeducational material, automated and tailored messages, reminders and feedback, as well as reporting of behaviors, thoughts and feelings unbiased by retrospective recall. The initial results from the relatively few studies on the use of smartphone in psychological treatment indicate that these interventions are effective [75]. Recently, a randomized controlled trial (RCT) contrasting smartphone- vs. computer-delivered self-help for depression found equal improvements in the two groups [76]. In another RCT [77], the effectiveness of two smartphone-delivered treatments was compared in the treatment of depression: one based on behavioral activation and other on mindfulness. After 8 weeks of treatment, the participants in both treatment groups reduced their depression symptoms significantly and the groups did not differ from each other. Other trials have shown promising results for smartphone-based interventions mainly focusing on increasing physical activity [78], and smoking cessation [79], among others.

In sum, although the evidence base for smartphone-administered interventions still is limited, it can be assumed that the combination of smartphone applications and ICBT can enhance and potentiate the flexibility and effectiveness of cognitive behavior therapy in a near future.

1.4.5 Self-help based treatments for ADHD

In the treatment of ADHD, only a few studies have investigated the effect of a more self-help based treatment. Stevenson and colleagues examined the effect of a self-help based psychosocial intervention with minimal therapist contact in a randomized controlled trial [80]. The participants were treated through a self-help book, containing education about ADHD and exercises covering strategies to cope with ADHD-related problems. Participants (n=35) were randomized to either a treatment group or a waiting-list control group. At the end of the 8-week treatment, the treatment group reported a significant reduction in ADHD symptoms, improved organizational skills and self-esteem and better anger control.

Only one study has to date examined the effect of ICBT in the treatment of ADHD. In a randomized controlled trial [58], the efficacy of two iCBT program formats was evaluated, where self-help with minimal therapist contact was compared to the same self-help program with weekly group-therapy sessions and to a wait-list control in an outpatient psychiatric care. The results were promising in that both types of support provided a significantly better outcome than a wait-list control.

The study by Pettersson and colleagues [58] indicates that self-help based psychosocial programs with a minimum of interpersonal support can also be a promising treatment alternative for adults with ADHD. However, there were several limitations of this study such as low power, lack of attention-matched control, and a dubious handling of missing data that inflated the treatment effects; all of which point to a need for further evaluations of ICBT for adult ADHD.

1.4.6 The use of smartphone in the treatment of ADHD

According to Hallberg [81], features such as alarm functions, calendars, to-do-lists, voice memos and camera can be useful tools for individuals with ADHD. A review of IT tools for adults with ADHD found that tools that give support for organization, structure and scheduling, and coordination of activities were the most desirable [82]. Several of these tools are available in their analog form as parts of Safren's CBT treatment [57]. Additionally, in a project conducted by inter alia Oslo university hospital, adult students with ADHD and Asperger’s syndrome learned to use a smartphone-based calendar synchronized with a computer. The result was a reduction in stress for the participants [83].

1.4.7 Unmet needs

The evidence base for the psychological treatment of adult ADHD is still limited and there is a need for more randomized controlled trials with larger sample sizes, active and credible controls, and long-term follow-up data, to provide evidence for the effectiveness of the treatment for this target group. Available interventions usually do not focus on the complexity and variety of problems related to the disorder and studies on psychological treatments usually separate CBT interventions from DBT in the treatment of ADHD. Thus, there is a need to develop new treatment manuals that target the wide range of difficulties experienced by adults with ADHD.
Furthermore, there are not enough psychologists and psychotherapists trained in CBT [59] in psychiatric healthcare. As a result, access to evidence-based psychological treatments is limited. Thus, given that the core symptoms of ADHD can lead to difficulties in a self-help based treatment setup, it is important to further develop and evaluate the efficacy of new technologies such as ICBT and smartphones in the treatment of ADHD in order to potentiate CBT and reach participants in areas where psychological or psychosocial treatment is not available.

1.5 AIMS

The primary aim of this thesis was to develop and evaluate the efficacy of new psychological interventions for adult ADHD, addressing a variety of related problems, with the intention to make these interventions accessible and available through internet.
The following research questions are targeted in this thesis:

- Are internet-based interventions a feasible way to treat adults with ADHD? (Study I and III)
- Can the use of smartphone applications teach adults with ADHD to improve their attention and organization skills? (Study I)
- Is a new treatment manual for adults with ADHD, combining methods from CBT and DBT, feasible and effective in reducing ADHD symptoms in adults? (Study II-III)
- Does the combined treatment manual produce specific or non-specific effects? (Study II-III)
- What are the long-term effects for the combined treatment? (Study II-III)

2 METHODS

"I wish I could show you, when you are lonely, or in darkness, the astonishing light of your own being." ~ Hafez

In each section below, elements that were shared between the studies are presented first, followed by a description of the unique and specific elements for each study.

2.1 DESIGN

Study I-III were clinical trials, conducted at the Internet Psychiatry Clinic at Psychiatry Southwest in Stockholm, Sweden.

Study I. In this randomized controlled study, 57 participants were randomized to either an internet-based course, teaching adults with ADHD or probable ADHD how to structure their everyday life through smartphone applications and online tools, or to a wait-list in a 1:1 ratio. The wait-list received the online course without therapeutic support after the post assessments. Assessments were made pre and post intervention. The primary outcome measures were also filled out weekly by the participants.

Study II was an uncontrolled pilot study where 18 participants underwent a 14 week intervention based on a manual combining CBT and DBT components. Assessments were made pre, post, one and six months after intervention.

Study III. In this randomized controlled study, 104 participants were consecutively randomized to either ICBT including a smartphone application to organize everyday life (n=36), to an equally long and active control treatment consisting of internet-based applied relaxation training (IART; n=37), or to treatment as usual (TAU; n=31). Assessments were made pre, post, three, and twelve months after intervention.

2.2 PARTICIPANTS

Recruitment of participants into study I was conducted through social media, postings on the National Association of Neuropsychiatry's website in Stockholm and via information on the website of Internet Psychiatry Clinic within Stockholm County Council. Participants in study II-III were enrolled through specialized neuropsychiatric units in Stockholm, and in study III also via the same sources as in study I.

Shared **inclusion criteria** in study I-III were:

- Aged at least 18
- Confirmed (or in study I, probable) diagnosis of ADHD according to DSM-IV or DSM-5
- Score of 17 points or more on the inattention and/or the hyperactivity/impulsivity subscale of Adult ADHD Self Report Scale version 1.1 [84] (ASRS v1.1; only the inattention scale for study I)
- Ability to participate in the study

Shared **exclusion criteria** in study I-III were:

- Severe depression as assessed by clinician (study II-III) or by scores greater than 30 in study I or greater than 34 in studies II and III, using the self-rated Montgomery-Åsberg Depression Rating Scale [85,86] (MADRS-S)
- Suicidality
- Somatic or psychiatric conditions that could seriously hamper participation in treatment
- ongoing non-pharmacological treatment for ADHD
- substance misuse (study I) during the last three months (study II-III)

Furthermore, in study I and III, common inclusion criteria were internet and smartphone access and ability to understand and read Swedish. In study II-III, stable or no psychotropic medication one month before baseline was required. Participants were also excluded in case of organic injury, and IQ ≤70 (study II) or IQ lower than 85 (study III). The final exclusion criterion in study III was a diagnosis of level 2 or 3 autism spectrum disorder according to DSM-5.

Baseline characteristics of the participants. A full comparison of the baseline characteristics can be seen in Table 1. Mean age ranged between 36-40 years, and a majority of the participants in the internet studies (I and III) were women. Sixty-one to eighty-three percent were stabilized on pharmacotherapy for ADHD before entering the studies. Furthermore, a majority of the participants worked/studied in all studies and had a high school (study II) or college/university degree (study I).
Comorbidity was most prevalent in study II where a majority of the participants had at least one comorbid disorder. Pretreatment scores of ASRS v.1.1 were similar between participants in study I-III, and most of the participants had a combination form of ADHD.

Table 1. A comparison of demographic characteristics of participants at baseline for the treatment studies

Baseline characteristics		**I** Living Smart (N=29)	**II** Group treatment (N=18)	**III** ICBT (N=36)	**III** IART (N=37)
Sociodemographic					
Gender	Women	22 (76%)	8 (44%)	25 (69 %)	30 (81 %)
Age	Mean (SD)	36.32 (11.1)	39.71 (8.2)	36.72 (11.4)	35.97 (9.4)
Highest education	Elementary school	1 (3%)	4 (22%)	2 (6 %)	6 (16 %)
	High school	11 (38%)	10 (56%)	16 (44 %)	15 (41 %)
	College/University/Other	17 (59%)	4 (22%)	18 (50 %)	16 (43 %)
Occupational status[a]	Working/studying	23 (67%)	13 (72%)	25 (70 %)	23 (62 %)
	Sick leave/disability retired	6 (21%)	3 (17%)	7 (19 %)	9 (24%)
	Unemployed	2 (7%)	2 (11%)	3 (8 %)	4 (11 %)
	Parental leave/housewife or house husband	3 (10%)	0 (0%)	1 (3 %)	1 (3 %)
Clinical					
Level of ADHD symptoms	ASRS v1.1 mean (SD)	50.6 (8.5)	45.8 (11.2)	48.5 (9.5)	48.7 (9.0)
Level of depressive symptoms	MADRS- S mean (SD)	7.1 (4.2)	15.1 (7.8)	16.4 (8.3)	15.4 (8.8)
Subtype ADHD	Combined	20 (69%)	13 (72%)	31 (86 %)	34 (92 %)
	Inattention	5 (17%)	5 (28%)	5 (14 %)	3 (8 %)
	Hyperactive	0 (0%)	0 (0%)	0 (0 %)	0 (0 %)
	Not reported	4 (14%)	0 (0%)	0 (0 %)	0 (0 %)
Psychiatric	Any diagnose	8 (28%)	11 (67%)	7 (19 %)	5 (14%)
	Depression	2 (7%)	5 (28%)	5 (14 %)	6 (16 %)
	Bipolar disorder	2 (7%)	4 (22%)	2 (6 %)	5 (14 %)
	Anxiety disorder	3 (10%)	3 (17%)	12 (33 %)	10 (27 %)
	Autism spectrum disorder	2 (7%)	3 (17%)	4 (11%)	2 (5%)
	Eating disorder	0 (0%)	0 (0%)	1 (3 %)	0 (0 %)
	Personality disorder	0 (0%)	1 (5.5 %)	1 (3 %)	0 (0 %)
ADHD medication	Stimulants and/or non-stimulants	24 (83%)	13 (72%)	22 (61%)	25 (68%)
Antidepressant medication	Any	7 (24%)	7 (39%)	6 (17 %)	12 (32 %)

Note: ICBT= Internet-based Cognitive Behavioral Therapy, IART= Internet-based Applied Relaxation Training, TAU= Treatment As Usual, ASRS= Adult ADHD Self Report Scale v1.1; MADRS-S = Montgomery-Åsberg Depression Rating Scale (self-report version).

[a] Multiple choice question, e.g. can be working and partially on sick leave

2.3 ASSESSMENTS

2.3.1 Diagnostic assessments

In all studies, licensed clinical psychologists and/or supervised final year clinical psychology students performed the diagnostic evaluations of the participants in the studies. The primary consideration in making participant eligibility decisions was a confirmed ADHD diagnosis. Therefore medical records and previous neuropsychiatric assessments were examined by the researchers to confirm their diagnostic status. If these could not be found, a copy of a neuropsychiatric report and/or a medical certificate was requested from the participant in order to determine eligibility to the study. Further evaluation of participant's current level of impairment and ADHD symptoms were made through ASRS-v1.1 [84] in all studies. In order to be included, participants also needed 17 or more points on the inattention or hyperactivity subscale using this measure (only the inattention scale for study I).
The specific diagnostic procedures for each study is described below.

Study I. ADHD diagnosis was confirmed through medical records for 29 (51%) of the 57 included participants. In cases where medical records were unavailable for evaluation, ADHD was evaluated through the DSM-IV diagnostic criteria in a structured telephone interview without performing neuropsychological testing or going through childhood anamnestic information in these cases.

After the telephone interview, an additional 28 individuals (49%) were deemed to have a very probable/probable ADHD diagnosis. However, due to bureaucratic delays, evaluation of medical records was performed after decision of inclusion in some cases. Thus, for 7 (12%) of the included participants who first were deemed to have a probable diagnosis after the telephone interview and thus were included in the study, diagnosis was not verified.

Study II. Medical records confirmed ADHD for all the participants in this study. Except for the ASRS v.1.1, clinician-rated ADHD Rating Scale IV for adults [87] was used during the assessment interview which preceded inclusion to the study, mainly to assess change in symptom severity from pre to post treatment.

Study III. Participants were only included if their ADHD diagnosis could be confirmed. In cases where verification of the ADHD diagnosis was not possible through medical records, a copy of a neuropsychiatric report and/or a medical certificate was requested from the participant in order to determine eligibility to the study. The ADHD Rating Scale IV was also used in this study during the assessment interview mainly to asses change in symptom severity. All the participants included had a verified ADHD diagnosis.

2.3.2 Outcome measures

This section describes a selection of the outcome and process measures most relevant for this thesis.

Primary outcome – self-rated ADHD Symptoms. Adult ADHD Self Report Scale version 1.1 (ASRS-v1.1, abbreviated as ASRS in this thesis) [84] was used as the primary outcome in Studies I-III, using the full scale ASRS as primary outcome in study II-III, and the inattention subscale for study I.
ASRS is a self-rating scale, containing the 18 symptom items for ADHD from the DSM-IV [15]. It includes two subscales, one measuring problems with inattention (nine questions), the other measuring problems with hyperactivity and impulsivity (nine questions). The options in the 5-point Likert scale are "never" (0), "rarely" (1), "sometimes" (2), "often" (3), or "very often" (4), as response types. The maximum score of ASRS is 72 and 36 points on the two subscales Inattention and Hyperactivity/Impulsivity, respectively. Test–retest reliability of ASRS is 0.88 [88]. Treatment response was defined as a reduction of at least 30% in the score of ASRS [39].

Clinician rated ADHD symptoms. The ADHD Rating Scale – IV [89] was administered in studies II-III. This measure consists of 18 items based on the DSM-IV criteria for ADHD, with the same response options as ASRS. It is a widely used clinician rated scale with acceptable psychometric properties [90.]

Clinical Global Impression – Improvement scale (CGI-I) [91]. Blinded clinicians in studies I and III rated post-treatment change in participant's illness severity relative to their baseline rates, using this 7 point scale ranging from 1 (very much improved) to 7 (very much worse). CGI-I is widely used in clinical research and medical care due to its face validity and practicability [92]. Clinical significant change was defined as much or very much improved.

Depression. In study I, researchers administered the Hospital Anxiety and Depression Scale (HADS) [93]; a self-report scale with good internal reliability using 14 items and two subscales to measure anxiety (HADS-A) and depression symptoms (HADS-D). Each subscale consists of seven questions (scores 0–3) with 7 or more points as cut-off. The scale has a sensitivity of 0.66, and a specificity of 0.97 to detect depression [94]. Only results for HADS-D is reported in this thesis.
Furthermore, Montgomery Åsberg depression rating scale – self rated version (MADRS-S) [85,86] was used to measure depression severity in study II-III. In these studies, MADRS-S was also administered weekly to detect suicidal ideation and risks. This instrument is widely used and validated for detecting and measuring change in depression severity. The MADRS-S contains nine items (scored 0-6) with total scores ranging from 0 to 54.

Level of functional impairment. To measure level of functional impairment (everyday functioning) in three life domains; work/school, social and family life, the Sheehan Disability Scale (SDS) [95] was used. Each domain score from 0 (not at all) to 10 (very much), reflects participants' level of impairment in these areas. Total score ranges from 0-30 (severely impaired level of functioning). This scale is sensitive in detecting treatment effects and has shown good psychometric properties [96].

Degree of stress. The Perceived Stress Scale (PSS) is a widely used psychological instrument for measuring degree of experienced stress in different life situations [97]. The PSS version used in study I had 10 items with response alternatives 0 (never) to 4 (very often) and an internal reliability of a Chronbach's alpha of 0.89. The 4-item version, also with acceptable psychometric properties [98] was used in study II-III.

2.3.3 Process measures

Adherence measures

Modules/sessions completed and therapist time spent on each participant

An analysis of how many modules/sessions each participant had completed during intervention was made in studies I-III. Furthermore, total therapist time spent on each participant reading and answering messages in the internet platform was analyzed for study I and III, as well as duration of supportive telephone calls to the participants in study II-III (planned weekly in study II).

Changes in medication and engagement in other therapeutic interventions. At post treatment, all participants in all studies were asked if they had made changes in their ADHD medication and/or had engaged in other therapeutic intervention related to their ADHD during their participation in each intervention.

Treatment credibility and satisfaction. Credibility was assessed with Treatment Credibility Scale [99] in study III for both treatment groups. The scale consists of five 10 point items. It assesses participants' perception of treatment credibility and how successful they deem the treatment will be in alleviating the target problems. The range of the test-retest reliability is between 0.75 and 0.82 and the internal question consistency (Cronbach's a) is between 0.69 and 0.83 [100].

Furthermore, client satisfaction was measured in studies II-III with the Client Satisfaction Questionnaire (CSQ-8) [101], consisting of eight items in which the item score ranges on a scale from 1-4 with a total possible score of 32. This scale has good internal consistency, is sensitive to treatment, and has good retest reliability [102].

Use, benefit and understanding of the treatment components. In study II, a questionnaire designed specifically for the study was used to measure the degree of use, understanding, and perceived utility of the treatment components. Previous session and homework assignments were rated by the participants each week by answering three questions related to each treatment

component. These questions assessed degree of use, benefit, and understanding of the components in each session. For use and benefit, the response options were: not at all (0), a little (1), to some extent (2), a lot (3), and very much (4). For level of understanding (comprehension), the response options were very difficult (0), difficult (1), neither difficult nor easy (2), easy (3), and very easy (4).

Furthermore, when reviewing homework, clinicians used the same 0-4 scale to rate participant's degree of use, benefit, and understanding. In order to enable comparisons between treatment components, the mean of all ratings of benefit and understanding was used. Total use of each component was summed considering that some of the components (e.g. the Safren components) were used more during treatment due to the treatment setup. Thus, these components received more weekly ratings and consequently higher totals. Finally, components that belong to either Safren's or Hesslinger's interventions were merged into two blocks (Organizing and DBT), and all the mindfulness exercises were merged into one block (Mindfulness).

2.4 INTERVENTIONS

In study I and III, the same internet platform was used to deliver the interventions. In study II-III, a novel treatment based on established therapeutic methods from CBT and DBT was evaluated.

The internet-based interventions. All of the internet-based interventions described in this section were developed and delivered through the Internet Psychiatry technical platform. After gaining access to the internet platform with a secure, double authentication log-in through 1177 (a governmental national eHealth site), participants took part of the course/treatment materials and secure messaging system in order to communicate with their therapist. The interventions were built on text-based chapters (modules) and in general, participants were instructed to work with each module for one week. Each module was devoted to a specific theme, was alternated with interactive work-sheets and ended with homework assignments. In addition, quick and often self-reflective exercises were built in the modules in study III to increase variation. After completing these, the work was sent to the therapist who reviewed the material and provided the participant written feedback and access to the next module often within 36 hours. In addition to the course/treatment materials, participants also filled out weekly web measures before getting access to the modules. This allowed the therapist to monitor symptom change during intervention. ADHD symptoms were rated weekly by the participants in study I and III. However, study III also used the MADRS-S to monitor progress and detect risks. Four points or higher on MADRS-S [85] suicide ideation item led to an additional structured telephone assessment by a clinician. In case of inactivity, participants were reminded and encouraged to continue their work via web-messaging or a personalized mobile text message. A phone call was made if this did not lead to resumed activity. Participants were also encouraged to write to their therapist whenever they needed support regarding their work.

Content of the combined treatment. The treatment manual evaluated in study II-III was developed by the author of this thesis. The first "block" of treatment addressed executive dysfunctions and was mainly based on Safren's manual [57]. The second "block" of treatment was based on Hesslinger's DBT treatment [103], with some adjustments in content. The mindfulness exercises were provided from Hogrefe Publishing House. Moreover, the author added other components to the manual such as valued living inspired by Acceptance and Commitment Therapy, [104] and communication training. In study III, a module on sleep hygiene was added to the treatment. The components are described in detail in Table 2.

Table 2. Content of the combination treatment

Content	Description
Psychoeducation	Prevalence, etiology, symptom description, evidence based treatments and content description
Attention training (Mindfulness)	Paying attention to thoughts and feelings without judging. Practicing self-compassion and acceptance.
Valued Living	Setting up personal goals as desired treatment outcomes. Learn how these goals can be rooted in deeper values (inspired by Acceptance and Commitment Therapy).
Planning and organizing everyday life	Learn how to use to do-lists and prioritize activities. Break down activities to reduce procrastination. Incorporate the to-do list in a calendar. Use efficient reminders.
Behavior analysis	Understanding and changing dysfunctional behavior patterns.
Impulse control	Increasing control over dysfunctional patterns due to impulsivity.
Emotion regulation	Learning about basic emotions and their values. Practicing how to regulate emotions through self-monitoring and self-validation.
Communication	Practicing communication skills in order to enhance listening and participating during conversations.
Sleep hygiene	Learning about a variety of habits and practices that enhance good nighttime sleep quality as well as full daytime alertness (only in Study III).
Problem solving	Using problem solving as a tool to increase mental and behavioral flexibility when dealing with obstacles in everyday life (only in Study II).
Relapse prevention	Learning about how to prevent setbacks and relapses. Planning how to work with achieved skills after treatment.

2.4.1 Study I – Living Smart

The content of the course Living Smart was inspired by specific parts of an existing manual for ADHD [57] and on the findings from previous studies regarding important IT tools for ADHD [81-83]. During the six-week therapist guided program, participants took part of seven chapters (text modules) where they learned how to use different online and smartphone applications in order to enhance their attention and organization skills. The main focus of the course was an online calendar app named Google Calendar. The content of the course modules, including all smartphone applications and their functions, are presented in Table 3.

Table 3. Content of Living Smart.

Module	Content	Smartphone Application
1	Introduction to the course, goal setting	
2	Introduction to Google Calendar, shared calendar and weekly planning	Google Calendar (Time management)
		N-back (improving working memory)
3	Smartphone calendar, using reminders, daily planning	Google Calendar
		Evernote (Notes to aid memory)
4	Using to-do-lists, working with difficult tasks	G-tasks (to-do-list)
		Google Tasks (organization)
5	Reducing distractions and stopping procrastination	Stayfocusd (block distractions)
		SimplyNoise (reduce distractions)
6	Problem solving, advanced features and repetition	Dropbox, Banking apps
7	Summary of the course, planning for the future	All applications

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2.4.2 Study II – The combination treatment

The group treatment lasted 14 weeks and each session followed the same structure. The weekly three hour session was led by one senior therapist and one co-therapist. They started with a mindfulness exercise and were followed by a homework review from the previous session. Participants' degree of use, comprehension, and benefit, were also rated by two observers. After a 15-minute break, the new session theme (described in Table 2) was introduced through power point and white board, and at the end of the session, new homework assignments were given to the participants. The assignments were tailored later during an individual phone call, placed by one of the therapists 2-3 days after the group session. These calls focused on support and solving problems related to treatment. Participants were instructed to work 30-60 minutes per day with their homework assignments. As a reminder to attend the session, a text message was sent to the participant´s mobile phone the day before. During the sessions, target behaviors such as attention training, impulse control and time management were practiced in group, however, participants were encouraged to use these skills beyond the session context as well.

2.4.3 Study III – Internet-based treatment for adults with ADHD

ICBT and IART were given as add-ons to treatment as usual. Both treatments lasted 12 weeks and were further matched for treatment format, number of standard modules given to the participants, therapists, and their supervision.

Internet-based cognitive behavior therapy (ICBT). ICBT was based on the combination manual described in Table 2. Mindfulness exercises were conveyed through audio clips. Thirteen standard and two optional modules were available. Additionally, a new smartphone application inspired from applications from study I was developed and used in ICBT as an aid to organize daily life. This included a flexible to-do list where tasks were categorized, prioritized, and managed, with functions for calendar-scheduling, reminders, and planning techniques. These features were intended to replace web-work sheets in Safren's modules. In case of treatment inactivity, the therapist sent an encouraging text message after 2-3 days and if the participant remained inactive, he/she was contacted by telephone.

Internet-based applied relaxation training (IART). This treatment was designed as an active control treatment with a thorough and credible rationale, based on the well-established relaxation program, applied relaxation [106]. This program has shown effects similar to traditional CBT for conditions such as generalized anxiety disorder and panic disorder [107-109].
In a study of adult ADHD, relaxation was used as control treatment [39], with inferior effects compared to individual CBT sessions. The intervention was presented as a stress reducing technique aimed at breaking the vicious circles fueled by ADHD symptoms.

Treatment as usual (TAU). The treatment as usual condition consisted of each participant's standard medication and/or standard psychiatric care. Participants were only contacted for assessments. Initially, 71% of participants were undergoing ADHD medication.

2.5 STATISTICAL ANALYSIS

All analyses were performed according to intent-to-treat. T-tests and Chi-squared tests were conducted to compare the groups at baseline. Effect sizes were calculated as Cohen's d (study I) and Hedges' g (study II-III). The significance level set for all statistical analyses was $p < .05$.

Study I. Outcome differences were analyzed through a two-way repeated measures ANOVA, with time (pre-post) as within subject variable and group as between subject factor.

Additionally, sensitivity analyzes for all of the outcome measures were conducted without including the seven participants who did not fulfill all criteria for ADHD. At post treatment assessments, last-observation-carried-forward was used to replace missing data for the primary outcome to evaluate the effect of missing data.

Study II. Primary outcome was analyzed through a one-way repeated measures ANOVA including four time-points (pre, post, one month, and six months follow-up), and Bonferroni-corrected post-hoc tests were used to evaluate differences between the pre-measure and each following time-point. An ANOVA was also used to compare differences between use, comprehension, and benefit for all the treatment components. Moreover, their relationships with various outcome measures were analyzed with Pearson's correlations.

Study III. Hierarchical Linear Mixed-effect models were used to test if change over time differed between groups. Since TAU had received treatment after the three-month follow-up and thus could not act as a control group at the 1-year follow-up, two separate models were used. The first model included all groups but only used the data from pre, post, and three month assessments.
Two dummy variables were used to compare each active treatment to TAU, which was set to zero in both dummies. The second model included only ICBT and IART and compared their slopes over a time period covering all the assessment points (pre, post, three and twelve months). The best model fit was found when random intercept, random slopes, and a squared time parameter was included. A sensitivity analysis included the baseline variables that were correlated to missingness, to control for non-random missing data.

3 RESULTS

"If it doesn't challenge you, it doesn't change you." ~ Fred Devito

3.1 STUDY I

3.1.1 Primary outcome

From pre to post treatment, participants in the Living Smart condition showed a significantly larger decrease in the ASRS subscale for Inattention when compared to the wait-list condition ($p < .001$). The sensitivity analysis in which the seven participants without an ADHD diagnosis were removed did not alter the results. The within group effect size was large (d=1.18) as well as the between group effect (d=1.21).

3.1.2 Secondary outcomes

Participants in Living Smart condition improved significantly on hyperactivity and depressive symptoms compared to wait-list ($p < .05$), although the between group effect sizes were small (d=0.19-0.23). No significant interactions were found on experienced stress or level of functional impairment. Eight participants (33%) reached a clinical significant change according to blinded ratings on CGI-I, mainly assessing improvement in attention and organization skills. No participant in the wait-list group made a clinically significant change.

3.1.3 Process measures

Participants completed on average 3.7 of the seven modules (53%). Each week the therapist spent on average 8.5 min on each participant in the platform. No correlation between therapist time spent and change in outcome was found. Changes in medication or engagement in other therapeutic intervention did not differ between the groups. Furthermore, many participants requested a longer treatment time in the qualitative evaluation.

3.2 STUDY II

3.2.1 Primary outcome

Participants improved significantly regarding ADHD symptoms between pre and post treatment, using full scale ASRS v.1.1 as primary outcome ($p < .001$). Within effect size was large at post (d=1.29). Improvements were maintained and still significant compared to baseline at both follow-up assessments; one and six months after treatment (d=1.45-1.35). Post treatment responder analysis identified 11 participants (61%) as responders.

3.2.2 Secondary outcomes

Significant improvements were observed at post treatment for all secondary outcome measures assessing depression severity, degree of stress, level of functional impairment ($p < .05$), and clinician rated ADHD symptoms ($p < .01$). Within group effect sizes ranged from moderate to large (d=0.45-1.46).

3.2.3 Process measures

On average, participants completed twelve of the fourteen sessions (86%). Each weekly telephone conversation with the participant lasted about 20 min. Moreover, average ratings of participant's satisfaction with treatment were 29.33 (SD= 4.28) out of maximum 32, which was considered to be "excellent satisfaction" [110].

Organizing components were rated by the participants as more used and comprehensible than DBT ($p < .01$). Organizing was also rated as more comprehensive and beneficial than the Mindfulness block ($p < .01$). Change in ASRS correlated significantly with total use of all treatment components ($r = 0.51$; $p < .05$). Moreover, the usage of Organizing and DBT components correlated significantly with reductions in ADHD symptoms, but this relationship was not found with the Mindfulness component. No change in medication or engagement in other therapeutic interventions was reported by the participants at post treatment assessments.

3.3 STUDY III

3.3.1 Primary outcome

ICBT and IART showed a larger reduction in ASRS comparing to TAU over the period from pre to three month follow-up ($p < .01$). Between groups effect size for ICBT was moderate (d=0.42) as for IART (d=0.57). However, the treatment effects were similar without any significant interaction between the two treatment groups when compared over all four assessment points, showing that both treatments were equally effective in reducing ADHD symptoms. Response rate was 25% in each treatment group compared to 3% in TAU at post treatment.

3.3.2 Secondary outcomes

When comparing all three conditions, there was a significantly larger reduction in clinician rated ADHD symptoms over time for ICBT and IART (d=0.35-0.40; $p < .001$) in comparison to TAU. Furthermore, ICBT showed superiority over TAU for depression severity, (d=0.6; $p < .01$) perceived stress (d=0.07; $p < .01$ and level of functional impairment (d=0.45; $p < .01$), while IART did not.

When comparing ICBT to IART from pre to one year after treatment, no significant interactions were found except for level of functional impairment favoring ICBT ($p < .01$). According to blinded ratings, 30% of participants reached clinically significant change on CGI-I in ICBT after treatment, compared to 9% in IART, when assessing improvement on ADHD symptoms in total. The difference was not significant ($p=.14$, Fisher's exact test).

3.3.3 Process measures

On average, participants in both treatment groups completed seven of the 13 standard modules (56%). Total weekly therapist time spent per participant reading and answering messages was on average 11.2 minutes in ICBT and 7.3 minutes in IART, which was significantly less ($p < .01$). In total, duration of each telephone call from therapist to the participant was 17.1 minutes in ICBT, significantly longer than the 7.3 min in IART ($p < .01$). Overall rates for satisfaction were higher for ICBT than the control treatment, and ICBT were also deemed as more credible after five weeks of treatment.
No differences were found between the groups regarding change in ADHD medications and/or engagement in other therapeutic activities.

3.4 SUMMARY OF RESULTS

Figure 1 illustrates change on the primary outcome for study I-III and Table 4 summarizes the number of patients and effect sizes (with confidence intervals) for ADHD symptoms, depression and level of functional impairment for study I-III. As a reference, some data from the previously published ICBT study [58] are also included in the table. Response rates are also compared between studies.

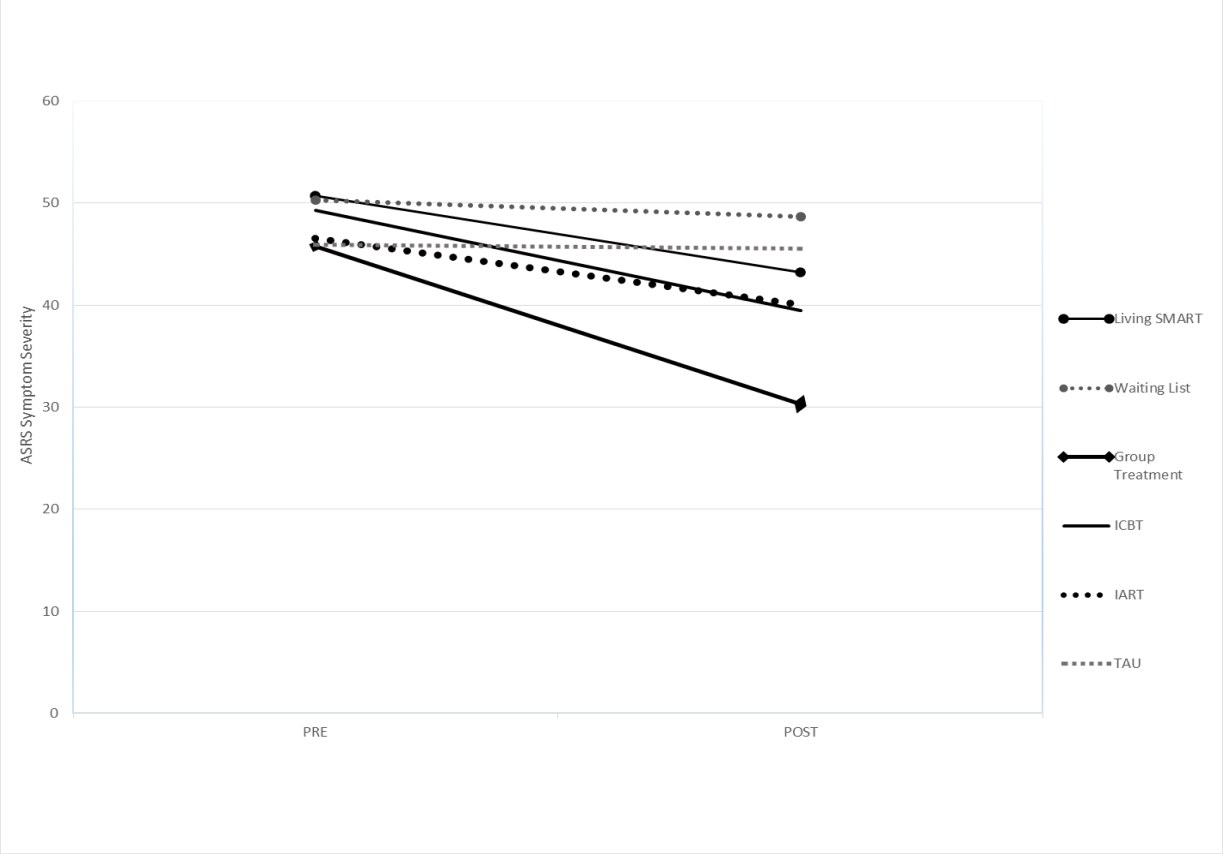


Figure 1. Change on ASRS v1.1 from pre-treatment to post-treatment – a comparison between study I-III, observed means.

3.4.1 Attrition

In study I, response rate for Living Smart was 90% and 96% for the wait-list control at post treatment assessments. In study II, response rate was 100% at post, 83% at one month follow-up and 100% at six month follow-up assessments.

In study III, the total response rates at post was 90%; for ICBT 89%, IART 86% and TAU 97%. At three month follow-up assessments, the total response rate was 86%; for ICBT 78%, IART 84% and TAU 97%. Finally, the total response rate at twelve months follow-up was 79%; for ICBT 81%, and for IART 78%.

Table 4. Within group effect sizes and number of treatment responders

Study	N [a]	Total ASRS		ADHD Symptoms (ASRS/CSS) Follow-up [c]		ADHD Rating Scale		Depression [g]		Sheehan Disability Scale		Responders	
		Effect [b]	*95% CI*	*Effect* [b]	*95% CI*	*Effect* [b]	*95% CI*	*Effect* [b]	*95% CI*	*Effect* [b]	*95% CI*	*ASRS* [d]	*CGI-I* [e]
I Living Smart	29	0.72	0.15-1.28					0.11	-0.43 - 0.65	0.47	-0.08 - 1.02	4 (17%)	8 (33%)
II Group Treatment	18	1.29	0.54 -2.01	1.35	0.63 -2.07	1.46	0.73 -2.20	0.45	-0.23 - 1.13	0.76	0.08 - 1.43	11 (61%)	
III													
ICBT	36	0.68	0.19 -1.17	0.79	0.29 -1.30	0.79	0.24 -1.34	0.62	0.12 -1.12	0.82	0.31 - 1.34	8 (25%)	7 (30%)
IART	37	0.93	0.43 -1.42	0.92	0.41-1.43	0.79	0.25 -1.32	0.33	-0.15 - 0.82	0.35	-0.13 - 0.84	8 (25%)	2 (9%)
Previous ICBT study [58]													
iCBT-G	14	0.42 [f]	-0.33 -1.16	0.41	- 0.34 -1.16			0.52	-0.23 - 1.27				
iCBT-S	13	0.61 [e]	-0.18 -1.40	0.57	-0.21 -1.35			0.24	-0.53 -1.02				

Note: The table contains data that has not been reported previously. Abbreviations: ASRS= Adult ADHD Self Report Scale v1.1; CSS= Current Symptoms Scale (self-report); CGI-I=Clinical Global Impression – Improvement Scale. ICBT= Internet-based Cognitive Behavior Therapy. IART= Internet-based Applied Relaxation Training; iCBT-G=Internet-based Cognitive Behavior Therapy-Group format; iCBT-S= Internet-based Cognitive Behavior Therapy-Self-help format.

[a] Sample size at intervention/treatment start

[b] Within group effect sizes comparing pre to post and pre to six or twelve month follow-up, shown as Hedge´s G, based on observed, non-imputed m and SD (pooled)

[c] Follow-up assessment points: study II and previous ICBT study = six month follow-up; study III = twelve month follow-up. The effect size for the ASRS at six month follow-up has been corrected since it was found inaccurately reported in Table 3 in the published article (study II)

[d] 30% reduction or more on total ASRS

[e] Clinical significant change defined as much or very much improved on CGI-I (for study I, only change in inattention and organization problems).

[f] ADHD-symptoms assessed with CSS

[g] Effect sizes for Hospital Anxiety and Depression Scale (HADS-D) in study I, Montgomery-Åsberg Depression Rating Scale (MADRS-S; self-report version) in study II-III, and Beck Depression Inventory (BDI-II) for the previous ICBT study

4 DISCUSSION

"She had not known the weight until she felt the freedom." ~ The Scarlet Letter

4.1 Are internet-based interventions a feasible way to treat adults with ADHD?

The very nature of symptoms like inattention, impulsivity, and hyperactivity, can undoubtedly interfere with the delivery of internet based interventions to patients with ADHD. Thus, one of the main objectives of this thesis was to investigate the feasibility aspects of the treatment format.

In conclusion, results from studies I and III show that internet treatment seems to be a feasible treatment format - but with some caveats. In total, therapist spent between 8.5 (study I) -11.2 (study III) minutes weekly per participant reading and answering messages. The treatment credibility for ICBT was higher than in the control condition after five weeks of treatment, with satisfaction ratings on par with the ratings in study II, indicating "excellent" treatment satisfaction [110]. This suggests that ICBT is a feasible treatment format for this participant group. Results from study I and III also show that internet-based psychological interventions have the potential to improve ADHD symptoms with moderate (study III) to large (study I) within group effect sizes on the primary outcome and less therapist time compared to "conventional" face-to-face behavioral interventions for ADHD [48,111]. A majority of participants had ongoing medication for their ADHD symptoms, indicating that the achieved treatment effects most likely were add-on effects to medication. This is promising, considering that pharmacotherapy has been shown to be insufficient for 50-70% of the participants [37].

Moreover, there are even some clear advantages of internet-based interventions over face-to-face treatment for this group of participants. For example, while inattention may cause ADHD patients to miss relevant information in traditional therapy sessions, the possibility to work at home with the treatments and taking short breaks while working with the material can be a better fit for their attentional style. Furthermore, the text format makes it possible for the participants to repeat and retain the treatment content for later use; clear advantages for a patient group that generally has problems managing time, concentrating during face-to-face therapy sessions, and recall the session content. Additionally, through the technical platform text messages can be sent to the patients, in order to remind and encourage them to continue their work.

Despite these advantages, participants in both interventions only completed slightly above 50% of the total number of modules, suggesting that strategies designed to increase adherence could be an important target area for improvement. This is comparable with the previously published ICBT study [58], somewhat lower than a study on ICBT for depression in routine psychiatric care

(72%) [112], and also lower than in the face-to-face format in study II where participants on average completed 86% of the sessions.

The overall qualitative evaluations (described more in the manuscripts) showed that the majority of the participants were satisfied with the interventions. However, recurring feedback pointed out the need for less extensive content (study III) and prolonged treatment time. In study III, the average ICBT participant was exposed to six different techniques, each with its own educational material and homework, which could have possibly lead to fragmentation. Moreover, some participants tried out the new smartphone application which did not work optimally due to technical problems, causing additional stress for the participants in ICBT Therefore, it seems clear that future studies need to evaluate the effects of more refined treatments with reduced content. This approach could increase adherence and ameliorate negative experiences of treatment such as feelings of failure and stress, thus enhancing the effects and increasing the potential for internet-based interventions as an addition to a multimodal treatment for adult ADHD.

Indeed, clinical observations together with participant's experiences of treatment agree that the ambitious and demanding treatment set-up combined with the rapid speed of ICBT could have been stressful and overwhelming for a participant group that has difficulties with attention and working memory. Most probably, these factors could explain the more frequent interaction between therapists and participants in ICBT compared to the control treatment, but given the finding therapist contact time was not related to treatment outcome, this would not have altered the results.

Although attempts were made to adapt the combination manual from a face-to-face setting to an internet-format, the non-optimal effects of ICBT suggest that further adjustments have to be made in future studies in order to enhance the treatment effects and allow ICBT to show its full potential in changing ADHD symptoms. While longer treatments have not been associated with larger effect sizes in general [113], some promising ways to improve efficacy and feasibility could be reducing the amount of written text, adding illustrations and sound files, and identifying and removing non-essential treatment modules. An attempt to extract the most useful, comprehensible and beneficial treatment components was made in study II, and a similar evaluation would consequently be valuable to enhance the internet treatment format in further studies. Moreover, evidence from anxiety and depression ICBT trials [114,115] suggests that exploring a tailored treatment approach may be the most important line of inquiry. Therefore, while there is a clear need to continue to refine ICBT treatment for ADHD, there are a number of promising avenues to pursue this mission.

Nevertheless, the specific deficits in this patient population call for a very particular approach in treatment development. This begs the question, "Is less more when it comes to delivering psychological interventions on internet for adults with ADHD?" Future studies are necessary to answer this. However, given the problems with working memory, attention, and the general novelty seeking tendencies in individuals with ADHD, it seems likely that a major challenge in

creating new psychological interventions for this group will be finding a balance between introducing new components in treatment and repeating them in order to maintain their motivation.

4.2 Can the use of smartphone applications teach adults with ADHD to improve their attention and organization skills?

Compared to the wait-list condition, participants in Living Smart showed larger improvements on the primary outcome, measuring attention and organization skills, with a large between group size. None of the participants in the wait-list condition reached the criteria for clinical significant change, as measured with CGI-I, compared to 33% in the intervention group. Furthermore, although decrease in depression and hyperactivity was significant, effects on these areas were low, indicating that the intervention had a rather "narrow" effect on inattention and organizational skills. This finding is in line with the primary aim of the study, which was to reduce problems with inattention and improve organization skills.
Moreover, the between group effects on inattention were larger compared to study III (*d*=0.46 for ICBT) and to Pettersson and colleagues' study [58] where the between size effects for the ICBT self-help group (based on observed means) were *d*=0.24 compared to a wait-list condition. This supports the specificity of the Living Smart intervention. It is notable that these effects were retained even after removing the seven participants without ADHD diagnosis in the sensitivity analysis.

Given that participants only completed 50% of the course content (on average three out of six modules), with Google Calendar as the most used application during this time, the results show that advantageous effects can be obtained also with rather limited means. It also indicates the potential of smartphone applications as a tool to enhance attention and organization skills for adults for ADHD.

There are several obvious advantages of the smartphone as a potential addition in a multimodal treatment model for adult ADHD. Today, the smartphone is a highly common and affordable device which provides access to free applications [75, 77]. This makes it possible for the individual to use the phone as a flexible treatment tool without any economic considerations. Furthermore, some of the applications, like the calendar system used in the intervention, can be shared with another individuals such as parents and spouses, which can facilitate everyday organization and planning for adults with ADHD.

However, it is important to be aware of some of the limitations of this study. The response rate on full scale ASRS was lower than in study II and III, partly due to the low effects on the hyperactivity subscale, suggesting that the intervention only provided limited effects on ADHD symptoms in total. Thus, this finding indicates that the selected smartphone applications in study I would be more useful for the individuals who primarily have problems with attention

and organization skills. However, this was not problematic given that it was the main objective of the study. Furthermore, although all participants had pronounced difficulties with inattention and organization, not all had a verified diagnosis of ADHD. In addition, they had actively sought the intervention and many of the participants were highly educated. These factors may limit the generalizability of the results to a clinical and more impaired sample.

Moreover, it is likely that an individual with executive difficulties will, at least initially, need a higher degree of guidance when selecting and learning to use smartphone applications. This indicates that the applications should be accompanied by clear step-to-step instructions (as in the intervention). Thus, the smartphone applications used in this study may not be as effective if they are recommended to the individual "as they are" and without any guidance. The new smartphone application developed for study III attempted to integrate useful applications with user instructions and rationales, however, due to recurrent technical problems in the administration of the new application, adherence information could not be collected and analyzed.

In conclusion, the smartphone applications used in study I seem to be promising in improving attention and organization skills. However, while the amount of time therapist spent on reading and answering messages showed no correlation with primary outcome, non-specific factors such as therapist support and attention could have affected the results. Thus, these mechanisms need to be further investigated in future studies so that the scope and potential of using the smartphone as a treatment aid for adults with ADHD can be clarified.

4.3 Is the new treatment manual for adults with ADHD, combining methods from CBT and DBT, feasible and effective in reducing ADHD symptoms in adults?

The primary purpose of developing a new treatment manual with combined methods from CBT and DBT was to address the variety and complexity of problems often associated with adult ADHD. However, a combined approach could also increase stress and mental "overload" for a patient group who has problems with attention and working memory. From the results from study II-III, we can conclude that the combined treatment manual was feasible with positive effects on both self-reported and observer-rated ADHD symptoms. In study II, participants completed 86% of the sessions with high overall ratings of use, comprehension, and perceived benefit related to the treatment techniques (described more in the study II article) indicating good adherence. In study III, the combined treatment was perceived as more credible than the control after five weeks of treatment, and treatment satisfaction was rated as "excellent" in both studies [110].
Moreover, the within group effect sizes on primary outcome were moderate (study III) to large (study II), and the latter was comparable to studies on both Safren's and Hesslinger's manual [39,50].

Thus, the findings indicate that the combined manual could be a promising treatment option for adults with ADHD. Positive effects were found also on secondary outcomes measuring depression severity, perceived stress and level of functional impairment in both studies.

Furthermore, the results from study II showed a correlation between use and change on primary outcome as well as on depression severity and perceived stress, indicating the relevance of the treatment components. Comparison of the level of use, comprehension, and benefit of the treatment components, also suggested an advantage for organization tools in the combination manual. This is possibly because they were introduced first and repeated during the whole treatment. Moreover, compared to DBT, these components were also experienced as more emotionally neutral and more concrete. Due to these experiences, the DBT components were somewhat adjusted in the ICBT manual. Furthermore, a recently published study [113] suggest that treatments based on DBT for ADHD including mindfulness and self-regulation skills may be associated with lower effect sizes than other treatment types, which thus could be due to the more complex and emotional approach of the components in this treatment.

However, although the results seems promising for the combined treatment, adherence data from study III leaves room for improvement and some of the participant's reports of negative treatment experiences (as mentioned previously) indicate that further adjustments should be made in the ICBT treatment manual order to increase adherence and acceptability in the future. Moreover, there is a possibility that the effects found on ADHD symptoms were mainly caused by non-specific factors such as participant expectations, therapist's contact, a credible rationale, or active engagement in any kind of new activity.

4.4 Does the combined treatment manual produce specific or non-specific effects?

Since study II was uncontrolled, it is difficult to rule out whether the large effect sizes on ADHD symptoms could have been influenced by factors such as the relationship between therapists and participants. Moreover, although ICBT was superior to the control treatment on some of the secondary outcomes, the overall changes were very similar in both treatments, indicating that the effects could be mainly non-specific. However, evidence for the efficacy of the control treatment in treating a variety of psychiatric disorders [107,109,116,117], suggests that applied relaxation might also be a legitimate treatment option in the treatment of adult ADHD that is capable of producing specific effects for this disorder.

Indeed, the promising findings for IART could be the result of several advantageous features of this treatment compared to ICBT. For example, the content was available not only in text, but also through sound files and it was more experientially oriented and less intellectually demanding due to the recurring themes throughout treatment. These factors show the potential for IART as a treatment option for adults with ADHD with a within group effect size of *d*=0.93 at post, which was higher than the within group effect for relaxation training in Safren's study (*d*=0.68) [39]. This could possibly explain the difficulties for ICBT in showing superiority regarding change in ADHD symptoms.
Nonetheless, participants in IART rated the treatment as less credible and satisfactory than ICBT, probably because of the narrow and repetitive scope of the treatment.

Another probable explanation for the comparable results between ICBT and IART in study III is that the wide array of therapeutic techniques that were presented in the ICBT treatment may have been mentally and emotionally overwhelming for the participants when presented in the internet-format without the same therapeutic guidance as in study II (described more in detail in 4.1). Although adjustments had been made to facilitate these components in the ICBT version, it is still possible that ICBT did not succeed in reaching its full potential and could have even produced non-optimal effects as a result of these issues.

In conclusion, the question if the combined treatment produce specific effects remains to be answered in future trials. Considering that study II was uncontrolled and the combined treatment in study III most probably was not implemented optimally, it is likely that the combination treatment did not succeed in reaching its full potential in the internet-format.

4.5 What are the long-term effects for the combined treatment?

An analysis of the long-term effects for the combination treatment in studies II-III, showed sustained, and slightly increased effects in both studies regarding change on ADHD symptoms up to one year after treatment (see Table 4). This suggests that beneficial treatment gains can be obtained even after the end of the intervention. The within group effects on ADHD symptoms one year after treatment were larger for ICBT in study III (*d*=0.79) than effects on ADHD symptoms six month after treatment (based on observed means; *d*=0.57) reported in a previously published ICBT study [58]. Moreover, sustained effects were also found over time for ICBT on the secondary outcomes mentioned above, when compared to TAU.

From these results we can conclude the combination manual seems to be promising in reducing ADHD symptoms over time, but this finding begs the question of why this might be the case. One possible explanation could be that participants who initially benefited from treatment continue to work with and remind themselves of the principles of treatment [118] which could lead to maintained treatment effects over a longer period of time. Additionally, a clear advantage of the internet-based programs is the possibility to access treatment even after the treatment has

ended which enables continued work through repeating the text material and rehearsing exercises. However, due to the fact that the long-term effects were uncontrolled in both studies (i.e. the last controlled comparison in study III was at three month follow-up assessments), future trials are needed to support the long-term effects for the combination treatment.

4.6 LIMITATIONS

General limitations of study I-III are described in the following section.

Can the results be generalized to the entire ADHD population in psychiatric healthcare? All participants included in study II-III were assessed and diagnosed in specialized ADHD units, and in study II the participants were also recruited directly from such a unit, indicating high generalizability to the ADHD population in psychiatric healthcare. However, in the internet-based studies, the participants were more often women, self-referred, more highly educated and with lower comorbidity rates compared to those in study II. Moreover, a difference between the participants in study II and the internet-based interventions was that the latter more actively sought treatment without the involvement from caregivers, possibly decreasing generalizability to a clinical and more impaired sample. This could also indicate that internet-based interventions attract more highly educated people because of the text and self-help based format.

Another limitation is that 12% of the participants in study I did not prove to have an ADHD diagnosis, and for some other participants, diagnosis could not be confirmed. Nevertheless, 88% of the participants had either confirmed or highly probable ADHD, and the sub-analysis where those without ADHD diagnosis were removed did not change the results.
However, it is reasonable to conclude that the results from study I primarily are generalizable to individuals with ADHD who primarily have significant problems with organization and attention.

Using ASRS v.1.1 as the primary outcome. In all studies, the use of participant-rated ASRS as primary outcome could have influenced the results, due to possible expectancy effects. To control for these effects, blinded observer ratings had been preferable as the primary outcome. However, the outcome from ASRS was actually verified in study II-III, where observer rated ADHD Rating scale (blinded in study III) showed highly similar results.
Furthermore, ASRS has primarily been used to measure symptom change in pharmacological studies [119] which could imply that ASRS is not as effective in measuring function improvement and change which often is the target in psychotherapy trials. To date, except for Adult ADHD Quality of Life Questionnaire [120] which only partially measures impairment in function, there is no function scale developed for this target group which had been preferable to use in study I-III. However, the general functional disability measure (SDS) showed moderate to large within group effect sizes in all three studies, indicating that the participants improved in symptoms as well as their functioning, after the interventions.

Engagement in other medical and/or therapeutic interventions. In study I and III, some of the participants reported that they had been engaged in other medical and/or therapeutic interventions during their treatments. Unfortunately, we were not able to control these engagements, which could have influenced the results. However, no differences in this respect were found between the groups in study I and III.

Statistical power. In study III, power analysis was calculated on 140 participants, but the study was discontinued after recruiting 104 participants due to shortage of time and resources. Thus, the question is if we had enough power to find an effect between the treatment groups. However, preliminary analysis and clinical observations indicated that adding 36 individuals (13 in each group) most probably would not have altered the results.

4.7 FUTURE DIRECTIONS

Suggestions for future research are presented below based on the questions that have emerged from study I-III.

- *Does the combined treatment produce specific effects?*
  As described in the Discussion (4.4), the specific effects of the combination treatment should be further evaluated in future controlled trials.

- *Do participants without ADHD medication benefit from the combination treatment*? In study II, a sub-analysis revealed no differences between medicated (n=13) and non-medicated (n=5) participants, indicating that the combination treatment can also be effective for non-medicated individuals. However, this result must be interpreted with some caution due to the low statistical power. Larger studies should examine the effect of CBT and the combination treatment, especially on adults with ADHD who cannot take medication for any number of reasons.

- *Could future versions of the ICBT treatment benefit from the treatment set-up and content of IART?* One hypothesis that emerged from study III is that a more repetitive, "narrow" and experientially oriented content could be beneficial for adults for ADHD, due to their problems with i.e. attention and working memory. Another suggestion is to include components from applied relaxation training in the combination manual because of the effects seen in study III. This could potentially be used as an alternative to mindfulness exercises for participants who prefer this method. However, adding new components to the combined treatment must be handled with some caution due to the risk of overwhelming the patients, which is an important lesson learned from study III. Furthermore, a future suggestion is also to make the technical platform responsive to mobile phones to increase adherence.

- *Would larger effects be achieved with a tailored internet-treatment based on the combination manual?* The results from study III indicate that reducing the number of techniques presented in the ICBT treatment could be beneficial for the participants. However, the techniques that would be beneficial to use still need to be determined. Further studies should focus on evaluating the use, understanding, and benefit of the treatment modules in order to extract the most effective treatment components, similar to study II.

- *Who benefits most from treatment, and which mechanisms are responsible for the change of ADHD symptoms?* Clinical observations indicate that participants with predominantly inattentive symptoms, had more adherence difficulties during treatment, and that participants with comorbid, high functioning ASD did well. However, there is still so much more to understand about who responds to treatment and why. Thus, potential predictors and mediators should be explored to increase knowledge about mechanisms of change.

- *How important is the therapeutic guidance in ICBT?* In study III, there were major differences between degree of therapist time spent in the treatments between ICBT and IART. However, these differences did not alter the highly comparable results for ICBT and IART in outcome. Clearly, this can be explained by several factors mentioned in the discussion section, but it would be interesting to examine if less therapist time spent would alter the results for ICBT. If future ICBT treatments produce effective results despite less therapist effort, the cost-effectiveness would increase which would be beneficial for the individual and society.

- *Should the group-treatment based on the combination manual or ICBT for adults with ADHD be implemented within regular psychiatric health care?* All participants in study II were recruited directly for specialized ADHD units, thus, this indicates that the promising results found in study II are generalizable to the ADHD population in psychiatric healthcare. However, if we think of the group treatment as a replacement to the standard Safren [57] or Hesslinger [103] treatments which are usually provided in psychiatric healthcare, we need to evaluate it in non-inferiority trials before implementation. Furthermore, if future trials further strengthen the evidence for ICBT treatment, it could be offered to the patients as a supplementary to other therapeutic interventions in psychiatric health-care (and not as a replacement, due to the limitations in generalizability mentioned before).

- *Can the interventions evaluated in studies I-III all be parts of a multimodal, stepped-care treatment approach for adults with ADHD?* If future studies verify our findings, interventions in studies I and III could be presented to interested individuals directly after diagnosis, followed by the group treatment evaluated in study II for individuals who are still in need of more support and therapy after these interventions.
  This stepped-care approach could thus be effective in saving therapist resources in psychiatric health care, and lead to a higher accessibility and availability of evidence-based psychological treatment to a participant group that needs other interventions than just medication.

5 CONCLUSIONS

The primary aims of this thesis were to develop and evaluate the efficacy of new psychological interventions for adult ADHD, addressing a variety of related problems, with the intention to make these interventions accessible and available through the internet.
The following conclusions can be drawn from studies I-III:

- Internet-based interventions seem to be a feasible way to treat adults with ADHD. In general, treatment satisfaction and adherence were good, but the findings indicate that there must be further adjustments in content in order to enhance adherence and effects.
- Smartphone applications and online tools can help adults with ADHD and individuals with pronounced problems with inattention and organization to improve these skills.
- The new combination manual based on interventions from CBT and DBT seems to be feasible and effective in the treatment of adult ADHD when provided in a group setting and through the internet. However, the effects can also be explained by non-specific factors and therefore, future controlled trials are needed to evaluate the specific effects of the combined treatment.
- The reductions of ADHD symptoms were maintained and slightly increased up to one year after treatment, suggesting lasting treatment gains.

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~ Alfred Lord Tennyson

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