Towards Digital Psychiatry in Adult Attention-Deficit/Hyperactivity Disorder

A Series of Clinical Intervention Studies using Mobile Health Applications and Virtual Reality

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Dedication

I dedicate this thesis to my friends and family who have supported me throughout my doctoral studies. I am very grateful to my parents, Elke and Walter, whose unwavering support made this work feasible, to my sister Lisa, and to Alicia for their continuous help and encouragement.

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List of abbreviations

ABP: App-based psychoeducation

ADHD: Attention-deficit/hyperactivity disorder

ADHS-SB: Attention-deficit/hyperactivity disorder self-assessment scale

ADP-IV: Assessment of DSM-IV personality disorders

AI: Artificial intelligence

App: Application

BAP: Brochure-assisted psychoeducation

BDI-II: Beck depression inventory II

CBP: Chatbot-based psychoeducation

CBT: Cognitive behavioral therapy

CCT: Computerized cognitive training

CPT: Continuous performance task

DASS: Depression, anxiety and stress scales

DP: Distractor phases

DSM: Diagnostic and statistical manual of mental disorders

EEG: Electroencephalography

fNIRS: Functional near-infrared spectroscopy

GART: Gaze-based attention refocusing training

HC: Healthy control

HMD: Head-mounted display

ICA: Independent component analysis

ICD: International classification of diseases

IDA-R: Integrated diagnosis of attention-deficit/hyperactivity disorder in adulthood

ISI: Inter-stimulus interval

LSL: Lab streaming layer

MD: Mean difference

mHealth: Mobile health

MINI-DIPS: Brief diagnostic interview for mental disorders

MWT-B: Multiple-choice vocabulary intelligence test

NDP: Non-distractor phases

RCT: Randomized controlled trial

SAP: Smartphone-assisted psychoeducation

SCID: Structured clinical interviews for DSM-IV

TBR: Theta/beta ratio

VR: Virtual reality

VRSQ: Virtual reality sickness questionnaire

VSR: Virtual seminar room

WFIRS: Weiss functional impairment scale

WHOQOL: World Health Organization quality of life questionnaire

WURS-k: Wender Utah rating scale, short version

1. Abstract

The field of digital psychiatry and psychotherapy has generated increasing interest given its potential to improve mental health care, for instance, by enhancing accessibility, scalability, and cost-effectiveness. In particular for heterogeneous disorders such as adult attention-deficit/hyperactivity disorder (ADHD), providing a large number of affected individuals early access to treatments with high personalization potential holds promise. In this project, digital psychoeducation and a novel attention training based on eye-tracking in virtual reality were evaluated in three separate clinical trials to determine their efficacy for the treatment of adult ADHD.

The first study aimed to evaluate a newly developed psychoeducation smartphone application (app) in a randomized controlled trial. To this end, 60 adults with ADHD were assigned to psychoeducation groups supported by either the smartphone app or traditional paper-based brochures. After eight weekly one-hour group sessions and additional homework, a significant reduction in the primary outcome measure, observer-rated ADHD symptom severity, was demonstrated. In addition, smartphone-based psychoeducation was found to be more effective in improving ADHD symptoms and showed higher homework compliance than brochure-based psychoeducation.

The second study examined digital, self-guided psychoeducation over a three-week period in 40 participants randomized to use either an interactive chatbot or the psychoeducation app employed in the first study. Results showed significant reductions in observer- and patient-rated ADHD symptoms but no interaction effects, thereby suggesting similar efficacy.

The third study investigated a novel gaze-based attention refocusing training in virtual reality in 18 adults with ADHD and 18 healthy controls under three different feedback conditions: gaze-based feedback, sham feedback, or no feedback. Although patients with ADHD showed more omission errors, higher reaction times, longer distractor-related gaze dwell times, and more head movements than healthy controls, the gaze-based feedback did not improve task performance.

In conclusion, the psychoeducation studies provided initial clinical evidence for the efficacy of digital psychoeducation and revealed no safety concerns. Specifically, the finding

from the first study that a psychoeducation app is superior to traditional paper-based materials in supporting clinical psychoeducation indicate the applicability of the digital format. Despite symptom improvements under both intervention types in the second study, further research is needed on the use of self-guided digital psychoeducation, particularly in the case of patient interaction with a chatbot. Regarding the use of virtual reality for the potential treatment of adults with ADHD, a single-session investigation of a novel gaze-based attention refocusing training in virtual reality did not result in immediate improvements in attention performance, but showed potential in the multimodal registration of ADHD symptoms. Results suggest that further refinement of the system could lead to improved outcomes in a future multisession treatment trial.

2. Introduction and aims

2.1 Background

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is characterized by symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2013). Individuals are diagnosed with the predominantly inattentive, predominantly hyperactive-impulsive, or the combined presentation based on their specific core symptom severity (American Psychiatric Association, 2013). The prevalence of ADHD is estimated to approximately 5.9% (Willcutt, 2012) in youth and 2.5% to 2.8% in adulthood (Faraone et al., 2021; Fayyad et al., 2017; Song et al., 2021). ADHD has a substantial impact on individuals' quality of life (Agarwal et al., 2012), academic performance, daily life functioning, and individuals are at increased risk for occupational failure and criminal behavior (Holst and Thorell, 2020). Moreover, comorbidities, such as anxiety, substance use and affective disorders are frequent (Chen et al., 2018), with at least 75% of individuals with ADHD diagnosed as having an additional comorbid disorder (Banaschewski et al., 2017). The increased strain on the healthcare system and the reduced productivity resulting from ADHD further pose a considerable burden for the economy (Barkley, 2020; Libutzki et al., 2019). However, despite its high prevalence and its considerable negative impact, ADHD is often underdiagnosed and undertreated in adults (Ginsberg et al., 2014; Rivas-Vazquez et al., 2023).

2.2 Diagnosis and treatment of ADHD in adults

The diagnosis of ADHD in adults is challenged by its heterogeneous presentation, overlap in symptoms with comorbidities, and difficulties in the retrospective self-evaluation of symptoms (Katzman et al., 2017). Given that no reliable biomarker for the disorder has yet emerged (Capuzzi et al., 2022; Chen et al., 2023), the diagnostic process requires a time-consuming, extensive procedure including the consideration of differential diagnoses, and examination of diagnostic criteria according to current versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013) or the International Classification of Diseases (ICD; World Health Organization, 2019). The basis for a diagnosis is an evaluation of current and past symptoms using retrospective rating scales and questionnaires, in which the patient has

to recall symptoms since childhood (Sibley et al., 2017). Self-reported and informant reports thereby have been shown to differ considerably (Martel et al., 2017).

The first-line treatment of adult ADHD is based on medication (German Association of the Scientific Medical Societies, 2017; National Institute for Health and Care Excellence, 2019). Although psychopharmacological approaches have generally been found to be effective in the treatment of ADHD symptoms (Cortese et al., 2018), research has also shown considerable non-responder rates (Wilens et al., 2011), adherence issues (Kooij et al., 2019), and individual outcome variability (Faraone et al., 2004; Philipsen et al., 2015; Selaskowski et al., 2022a). In such cases, or when tolerance is an issue or the patient makes an informed choice not to take medication, psychotherapy is offered (National Institute for Health and Care Excellence, 2019). In addition, psychoeducation is encouraged irrespective of the application of other treatments (German Association of the Scientific Medical Societies, 2017). These therapeutic and psychosocial approaches often have their own challenges, such as the need for specialized providers and the time-intensive involvement of clinical experts, long waiting times, and high administration cost. Two further intervention concepts that have been evaluated for the treatment of ADHD are computerized cognitive training (CCT) and neurofeedback. Here, the cognitive dysfunction associated with ADHD is addressed more directly via repeated training of attention tasks and acquiring of the ability to modulate one's own brain activity, respectively. Although these methods cause few, if any, side effects, the overall evidence for CCT (for a meta-analysis, see Elbe et al., 2023) and neurofeedback (for a meta-analysis, see Fan et al., 2022) is inconsistent and suggests relatively small effects. Considering that psychosocial symptoms persist to a significant degree even in patients who respond to first-line treatment (Brown et al., 2017), more holistic treatment options with greater efficacy are needed that can address both clinical symptoms and their impact on several domains of the patients' lives.

Heterogeneity of the disorder is a factor that significantly challenges the diagnosis and treatment of ADHD in adults. This is reflected in substantial inter-individual variability in neuropsychological impairments (Mostert et al., 2015), neurobiology (Li et al., 2021), and clinical profiles (Luo et al., 2019). Identifying biomarkers for reliable diagnosis and monitoring of treatment outcomes is therefore particularly demanding. Consequently,

developing a treatment that not only alleviates symptoms in a subset of patients, but achieves sustained remission in a large proportion of the ADHD population remains a priority in the field (Faraone et al., 2015). To approach this objective, research has focused on identifying more homogeneous subgroups within the disorder, for instance, based on emotional dysregulation as a fourth potential ADHD core symptom (Soler-Gutiérrez et al., 2023). However, such subgroup profiles are thought to be multifactorial, underscoring the urgent need to design rigorous studies that incorporate broad and comprehensive symptom monitoring to enable more personalized approaches (Buitelaar et al., 2022; Nigg et al., 2020). Modern technology could offer some potential in this regard, and the implementation of digital interventions may be a promising first step.

2.3 Digital interventions in psychiatry and psychotherapy

Digital interventions, such as mobile health (mHealth) solutions, have attracted increasing attention to improve accessibility, scalability, and cost-effectiveness of mental health care. This includes addressing existing barriers to treatment such as aforementioned long waiting times, need of in-person meetings with clinicians, or missing access to specialists (Rathbone and Prescott, 2017). In addition, these types of interventions have considerable potential to improve precision psychiatry by enabling more comprehensive, accurate, and individualized assessments and treatments. For instance, in clinically frequently applied therapeutic group treatments, such as psychoeducation, digital support materials might enable more individualized presentation of relevant topics. Differences in treatment progress could also be taken into account automatically and monitored more easily by the therapist. In individual psychotherapy, advantages could arise particularly for the time between therapy sessions or for phases with less frequent personal therapy sessions in order to maintain therapy effects. Additional clinician-independent, automatically collected data available to therapists may facilitate the identification of patients' individual needs, especially in heterogeneous disorders. The growing use of digital technologies and higher level of automated processing such as provided by artificial intelligence (AI), could thereby also enhance patient engagement and treatment adherence (Ray et al., 2022). However, digital interventions can also have their limitations such as lack of expert involvement in development stages and poor validation which ultimately might not only provide no benefit but harm (Akbar et al., 2020; O'Reilly-Jacob et al., 2021). Given the often low study quality and inconsistent scientific evidence (Marcolino et al., 2018), rigorous research is needed

to demonstrate the feasibility, safety, and efficacy of interventions that incorporate these technological advances (Torous et al., 2021).

2.4 Digital psychoeducation for adult ADHD

Psychoeducation provides general information about a disorder and introduces strategies to cope with its symptoms. Although recommended as a first step in the treatment of ADHD based on the few validated programs available to date, the development of additional programs and their rigorous evaluation have been suggested by the European Network for ADHD in Adults (Kooij et al., 2019). Psychoeducation may be particularly well suited for digital presentation given that it is typically delivered in a group format that does not involve a high level of interaction between the therapist and each individual patient. Consequently, a total of 23 apps for ADHD have already been released with a focus on psychoeducation, but none of them provided sufficient scientific evidence of their efficacy or safety (Păsărelu et al., 2020). Therefore, it is not known to what extent such apps are superior to traditional materials in supporting psychoeducation groups or might offer an opportunity for self-guided engagement with psychoeducation content. Most psycho-education apps present content in a format similar to a digital brochure (i.e., presenting different modules in which the user can proceed linearly from page to page), but there have also been initial attempts to use conversational agents (i.e., chatbots) to deliver therapeutic material (Jang et al., 2021; Nordberg et al., 2019). Although their ability to respond with contextual accuracy is still limited, chatbots could be capable of adding the level of interaction and personalization that might be essential for conveying information in dysfunctional learning behavior as associated with ADHD (Torous et al., 2021). A first study in this field, while not specifically addressing ADHD symptoms, showed that a chatbot can effectively improve symptoms of attentional dysfunction (Jang et al., 2021).

2.5 CCT and neurofeedback

While psychoeducation appears to be useful for providing patients with a basic understanding of the disorder and seems effective in delivering initial coping strategies, CCT and neurofeedback were developed to address ADHD-related cognitive dysfunction in a more direct manner. CCT focuses on improving cognitive functioning through repeated training of computer-based cognitive tasks. In neurofeedback, real-time feedback on aspects of a person's own brain activity is provided during performance of a

cognitive task. Although both approaches are generally considered promising (Keshavan et al., 2014), only few well-powered, rigorous studies have been conducted so far (Knouse et al., 2017), and their findings have been inconsistent (for reviews, see Cortese et al., 2016; Enriquez-Geppert et al., 2019; Fan et al., 2022). Both interventions aim to directly train impaired attentional functions through repeated learning sessions in laboratory settings, which might contribute to the inconclusive findings to date. Specifically, similar to the problems of eliciting and assessing ADHD symptoms in a laboratory context, successful training in these artificial environments might not be transferable to patients' everyday lives. Beyond that, these methods merely aim to train the sustainment of attention or the modulation of brain activity toward the attentional state, whereas the underlying impairments in metacognition of attentional deficits (i.e., awareness of one's own momentary inattention) are not addressed (Butzbach et al., 2021).

2.6 Virtual reality and eye-tracking for adult ADHD

Virtual reality (VR) has been proposed as a valuable tool for the assessment and treatment of ADHD in adults and can provide controlled, interactive, and immersive environments that may also offer increased ecological validity by simulating real-world situations in three dimensions (Jahn et al., 2021; Wiebe et al., 2022b). In addition, VR can be used simultaneously with a range of psychophysiological methods such as electroencephalography (EEG) or eye-tracking. Although this enables not only a comprehensive assessment of symptoms, but also personalized treatment attempts that can detect and adapt to individual differences online, few VR studies including adults with ADHD have been carried out so far (Wiebe et al., 2022b). In a first feasibility study on a virtual seminar room as a symptom assessment tool for adult ADHD based on a neuropsychological attention test, the continuous performance task (CPT), our research group has provided initial promising results (Wiebe et al., 2022a). Building on this, the system was expanded by VR-based eye-tracking in order to register deviations in patients' visual attention capacities. While eye-tracking has previously been used to successfully identify dysfunctional visual attention in adults with ADHD (Lev et al., 2022), the aim of the present study was to adopt a treatment-oriented approach by implementing a feedback mechanism that detects inattentional gaze behavior and guides the patient back to the CPT (Selaskowski et al., 2023a). This gaze-based attention refocusing training (GART) in

VR not only addresses the common issue of ecologically less valid laboratory settings, but also focuses on improving metacognitive attention functions in patients with ADHD.

2.7 Potential advantages of digital over traditional methods

Digital methods appear to offer some advantages over traditional methods in the assessment and treatment of ADHD. Regarding assessment, digital methods allow automatic, simultaneous recording of many parameters of interest without substantial additional cost or effort. Smartphone apps can not only assess individuals at different points in their daily life (often referred to as experience sampling method or ecological momentary assessment), and thereby minimize recall bias, but also allow for the collection of a variety of data beyond clinical symptoms (for a review, see Koch et al., 2021). This includes information characterizing the situation in which symptoms are assessed or other contextual data such as preceding sleep quality and level of physical activity. VR, in turn, is usually not applied to real-life situations, but can simulate these in realistic scenarios. As VR assessments retain the advantage of controlled environments, noise-sensitive measurements can still be combined, including EEG, functional near-infrared spectroscopy (fNIRS), and eye-tracking. With the rapidly increasing use of AI, additional tools are emerging that can support the analysis of large data sets obtained with these methods and the potential clustering into homogeneous subgroups to enable more personalized interventions.

2.8 Aims

In this PhD project, three separate clinical studies were conducted that aimed to examine the feasibility and efficacy of digital interventions for the treatment of adult ADHD:

- The first study (Selaskowski et al., 2022b) investigated the potential of a newly developed smartphone app for the psychoeducation of adults with ADHD. Specifically, it was investigated whether the smartphone app is more effective than a traditional paper brochure as support for a psychoeducation group. The clinical evaluation primarily focused on changes in ADHD symptom severity from pre- to post-intervention. For this purpose, 60 adults with ADHD were randomly assigned to an eight-week psychoeducation group supported by either a smartphone app or a brochure.

- In the second study (Selaskowski et al., 2023b), a psychoeducation chatbot was designed to more specifically address ADHD-related dysfunctional learning behavior by increasing the level of interaction and allowing patients to co-determine the topics covered. Following up on the promising results of using a psychoeducation app to support clinical group sessions (Selaskowski et al., 2022b), this study examined the effects of a three-week self-guided psychoeducation. The primary research question was whether a newly developed psychoeducation chatbot or the previously validated psychoeducation app would be more effective in improving ADHD symptoms in adults through self-guided psychoeducation. To this end, 40 adults with ADHD randomized to either the psychoeducation chatbot or the psychoeducation app were assessed for changes in ADHD symptom severity from pre- to post-intervention.
- In the third study (Selaskowski et al., 2023a), VR was applied to extend common CCT approaches by a realistic three-dimensional environment. By evaluating eye movements to detect inattention during a CPT in the virtual seminar room and by providing immediate feedback on dysfunctional gaze behavior, an environment of high ecologically validity was created in which patients with ADHD could potentially improve their awareness of momentary inattention. This GART was investigated in 18 adult patients with ADHD and 18 healthy controls in three counterbalanced conditions: a condition in which the GART feedback was given, a sham feedback condition, and a condition in which no feedback was given at all. While CPT performance differences were evaluated as primary outcome parameters, recordings of physiological measurements (eye movements, EEG, head actigraphy) and subjective assessments were additionally conducted.

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3. Publications

3.1 Publication 1: Smartphone-assisted psychoeducation in adult attention-deficit/ hyperactivity disorder: A randomized controlled trial

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Smartphone-assisted psychoeducation in adult attention-deficit/ hyperactivity disorder: A randomized controlled trial

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ABSTRACT

Psychoeducation is generally recommended in the treatment of adult Attention-Deficit/Hyperactivity Disorder (ADHD), but only few studies have systematically assessed the effects of structured clinical psychoeducation. Moreover, although a considerable number of psychoeducational mobile applications exist, none have provided scientific evidence for their effectiveness or safety. Therefore, the present randomized controlled trial investigated a newly developed, free-to-use psychoeducation app for adults with ADHD as a support to a clinical psychoeducation group. 236 adults with ADHD were contacted for study participation, of whom 60 were finally randomized to a psychoeducation group supported either by our developed smartphone app ($n = 30$) or by traditional pen-and-paper brochures ($n = 30$). Psychoeducation treatments were conducted in groups of 10, with 8 weekly one-hour sessions between March 2019 and November 2020. Observer-rated ADHD symptom severity (IDA-R interview) was examined as the primary outcome parameter before and after treatment. Across both interventions, ADHD core symptoms were significantly reduced. Notably, the smartphone-assisted psychoeducation was significantly more effective in improving inattention and impulsivity and led to higher homework compliance than the brochure-assisted psychoeducation. No adverse events were reported.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity and impulsivity (American Psychiatric Association, 2013). ADHD has a prevalence of 5% in childhood and adolescence, and at least 75% of those affected are diagnosed with a comorbid disorder (Banaschewski et al., 2017). With an estimated persistence into adulthood of 40% to 50% (Sibley et al., 2016), ADHD causes significant individual suffering and substantial long-term health economic burden to society (Able et al., 2007; Capusan et al., 2019). In the US, for example, direct costs for adult ADHD alone amount to between 36.6 and 43.9 billion US dollars, without taking into account further secondary costs (Barkley, 2020). Consequently, more effective and cost-efficient treatments are needed to alleviate individual suffering and reduce the economic burden on society.

For the therapy of adult ADHD, guidelines recommend a pharmacological approach as a first-line treatment (German Association of the Scientific Medical Societies [AWMF], 2017; National Institute for Health and Care Excellence, 2018). Cognitive behavioral therapy is preferably applied in mild severity and, in more severe cases, combined with pharmacotherapy. Moreover, irrespective of symptom severity, comprehensive psychoeducation is advised (AWMF, 2017). The rationale of psychoeducation is to educate about the course of the disorder, its causes and maintenance factors, treatment options, and also to focus on the patient's individual strengths, resources and opportunities for development. Although psychoeducation generally shows promising results, the overall study quality is considered relatively low, and few studies have systematically examined effects in adult ADHD (Montoya et al., 2011; Powell et al., 2022; Vaag et al., 2019). Consequently, the European Network Adult ADHD considers psychoeducation to be effective in principle, but also emphasizes the need to further develop

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structured psychoeducation programs (Kooij et al., 2010; Kooij et al., 2019).

To date, few psychoeducation programs have been specifically designed for adult ADHD (e.g., D'Amelio, 2009; Hirvikoski et al., 2017; Matthäus and Stein, 2016). Commonly, these incorporate 8 to 12 weekly group sessions and some form of homework assignments. Homework is intended to promote content memorization and provides a structured opportunity to implement the learned strategies in everyday life. Also, while groups are generally considered supportive in the context of psychoeducation or therapy, they provide a learning environment in which the potential for distraction is substantially elevated. This in particular applies to individuals with ADHD, as disorder-related difficulties such as inattention and distractibility can be exacerbated in group environments (Barkley, 2008; Rogers and Tannock, 2018). Therefore, it seems reasonably relevant to patients with ADHD to individually recapitulate the introduced content at home. Moreover, homework has been recognized as one of the essential features of effective cognitive behavioral therapy (Helbig and Fehm, 2004). Homework compliance is thereby a key measure of therapy engagement and has been associated with better treatment outcomes for a variety of psychiatric disorders (Kazantzis et al., 2000; Lebeau et al., 2013; Mausbach et al., 2010). And yet, only 50% to 56% of assigned homework appears to be completed adequately (Gaynor et al., 2006; Helbig and Fehm, 2004; Tang and Kreindler, 2017). Several factors have been identified to contribute to this non-compliance, such as lack of motivation in the presence of negative emotions, insufficient instructions, and the effort associated with pen-and-paper homework (Tang and Kreindler, 2017). As a result, the authors recommend the state-of-the-art implementation of mobile apps with population-specific features that encourage learning and demand completion.

At least theoretically, the application of mobile apps in the field of psychoeducation and especially in the management of homework seems to offer various mHealth-specific advantages, such as high mobility, flexibility and user-friendliness. While this potential has been recognized and a growing number of digital health applications are entering the market, many of these fail to provide a sufficient scientific foundation (Lui et al., 2017; Torous et al., 2021). In fact, some of the health apps currently available have even been found to pose potential clinical risks to their users, with safety concerns related to factors such as the quality of information provided, lack of expert involvement, insufficient evidence base, and poor validation (Akbar et al., 2020). For ADHD specifically, 109 mobile apps (23 covering psychoeducation) were recently systematically reviewed, with none providing scientific evidence for their effectiveness (Păsărelu et al., 2020). Moreover, there has been no systematic research on the extent to which app-based processing of psychoeducational material in ADHD might be more beneficial than traditional processing based on brochures.

In the present study, we examined the potential of smartphone-assisted psychoeducation for adults with ADHD. Taking into account both the specific requirements of modern smartphone use and the aforementioned learning needs of patients with ADHD, we developed a psychoeducation app based on a previously validated manual (D'Amelio, 2009; Hoxhaj et al., 2018). To evaluate this psychoeducation app, we enrolled 60 adult patients with ADHD in this prospective randomized controlled trial (RCT). Specifically, we investigated whether smartphone-assisted or brochure-assisted group psychoeducation achieves greater therapeutic efficacy. ADHD symptom severity was considered the primary outcome measure and was assessed pre- and post-treatment after 8 weekly psychoeducation sessions.

2. Methods

2.1. Participants

The study was advertised via the Department of Psychiatry and Psychotherapy of the University Hospital Bonn and via publicly accessible media. Overall, 236 adults with ADHD were contacted for study participation, and 60 participants were finally enrolled in this RCT (for the detailed participant flow, see Fig. 1). To be eligible for the study, participants had to fulfill DSM-5 ADHD diagnostic criteria (American Psychiatric Association, 2013) as assessed with the Integrated Diagnosis of ADHD in Adulthood (IDA-R; Retz et al., 2014). In addition, they were not allowed to meet the criteria for a diagnosis of schizophrenia or other psychotic disorder, substance use disorder, antisocial personality disorder or severe affective disorder as assessed by means of the Structured Clinical Interviews for DSM-IV for Axis I disorders (SKID I, German version; Wittchen et al., 1997) and Axis II disorders (SKID II, German version; Fydrich et al., 1997). A further exclusion criterion was the presence of a severe neurological disorder. Participants were aged 18 to 65 years, had sufficient understanding of the German language and had access to a smartphone with Android OS. The intake of medication for ADHD was permitted, but an initial use or a change in dosage in the period from two weeks preceding baseline through the final examination resulted in exclusion from the study. Study participation was voluntary and participants received no compensation for their attendance.

The study was approved by the local medical ethics committee of the University of Bonn (protocol number: 232/18) and written informed consent was obtained from all participants. The study and all procedures contributing to this work were conducted in accordance with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The trial was registered in the German WHO primary

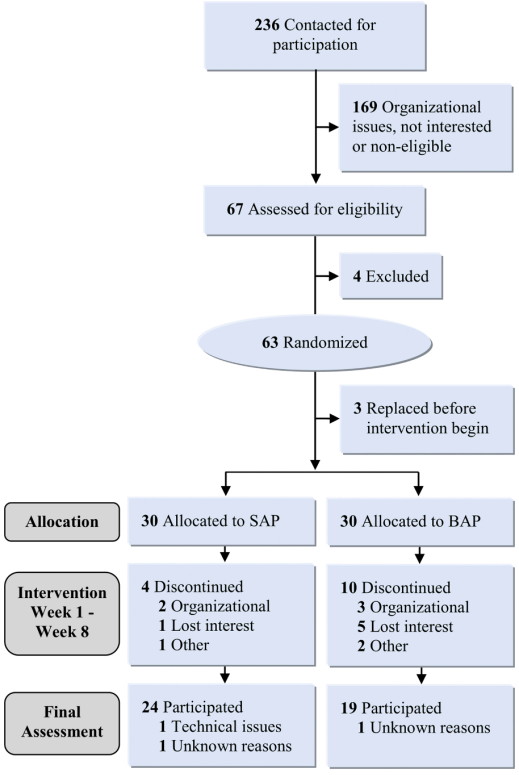

Fig. 1. Summary of the participant flow from initial contact to final assessment. 236 individuals were contacted for participation, 67 were screened for eligibility, and 30 started treatment in each intervention arm. 24 participants of the SAP and 19 participants of the BAP group with obtained baseline and final assessment data were considered for analysis. Abbreviations: BAP, brochure-assisted psychoeducation; SAP, smartphone-assisted psychoeducation.

register DRKS (identifier: DRKS00018026).

2.2. Study design

The study was conducted as a two-arm RCT with two measurement time points. The two intervention groups compared were: smartphone-assisted psychoeducation (SAP) and brochure-assisted psychoeducation (BAP). Both interventions consisted of 8 weekly psychoeducation group sessions and commenced with 10 individuals each. Missing more than two group appointments resulted in exclusion from further study participation. A total of three psychoeducation blocks were carried out per intervention, with each new block covering one group of each intervention. Two parallel psychoeducation groups started in the same week and were held on consecutive weekdays at similar times of the day over a period of 8 weeks. Group allocation was conducted by permuted block randomization in blocks of 20. Outcome parameters were evaluated at baseline prior to intervention begin (T0) and after the intervention (T1). The change in ADHD symptom severity from T0 to T1 was considered the primary outcome of the study. Secondary study outcomes included: acquired psychoeducational content knowledge as measured by content quizzes, change in symptoms of depression, change in functional impairment, number of study dropouts, and the quantitative extent of homework completed and group sessions attended. Blinded clinical experts assessed the primary outcome at T0 and T1. For group therapists and participants, the study was open for allocation to SAP or BAP.

2.3. Procedures and interventions

Each of the 8 group psychoeducation sessions lasted one hour and covered one psychoeducation module. Each group was led by two experienced therapists in the Department of Psychiatry and Psychotherapy at the University Hospital Bonn. The same two therapists (MS, ML) generally conducted both parallel psychoeducation groups within each block to ensure a high degree of comparability. However, in one of the three blocks, only one of the two therapists (ML) was involved in both parallel groups and was joined by two different therapists (HR, LG). Identical content based on a validated manual by D'Amelio (2009) was presented in both intervention groups by means of customized PowerPoint slides (Microsoft Corporation, Redmond, WA, USA). The two intervention groups only differed in the format of the work materials handed out. Specifically, the SAP group received psychoeducation content in digital form via the smartphone app (see Fig. 2), whereas the BAP group was provided with traditional pen-and-paper brochures. The app was written in the Java Native Interface Programming Framework and is available for free from the Google Play Store ("AwareMe ADHS"; https://play.google.com/store/apps/details?id=de.awareme.pse). Each of the 8 separate modules contained a comprehensive outline of the psychoeducation content covered, corresponding homework assignments, a content quiz, and addressed one of the following topics: basic information on ADHD, personal resources, mindfulness and attention control, self-organization, stress management, mood regulation and impulsive behavior control, relationships, and a final evaluation. On a weekly basis, following each group session, the SAP app modules were unlocked and the BAP material was distributed. Compared to the more extensive presentation of content in the brochures of the BAP group, the app contained a more condensed form of language, but was equal in terms of structure and psychoeducational content presented. The underlying purpose was to adapt for relatively small screen sizes of smartphones and resulting usability implications.

Both groups received identical homework assignments within each module. These were designed to have the participants reflect individually on the psychoeducation content, promote deeper learning, and encourage the application of learned strategies to everyday life. For instance, participants were asked to describe their personal experiences and difficulties in relationships or to provide a description of their personal resources and those they would like to develop. Moreover, apart from the module on personal reflection and evaluation (module 8), both groups were presented with four single-choice quiz questions at the end of each module. The inclusion of quiz questions in learning

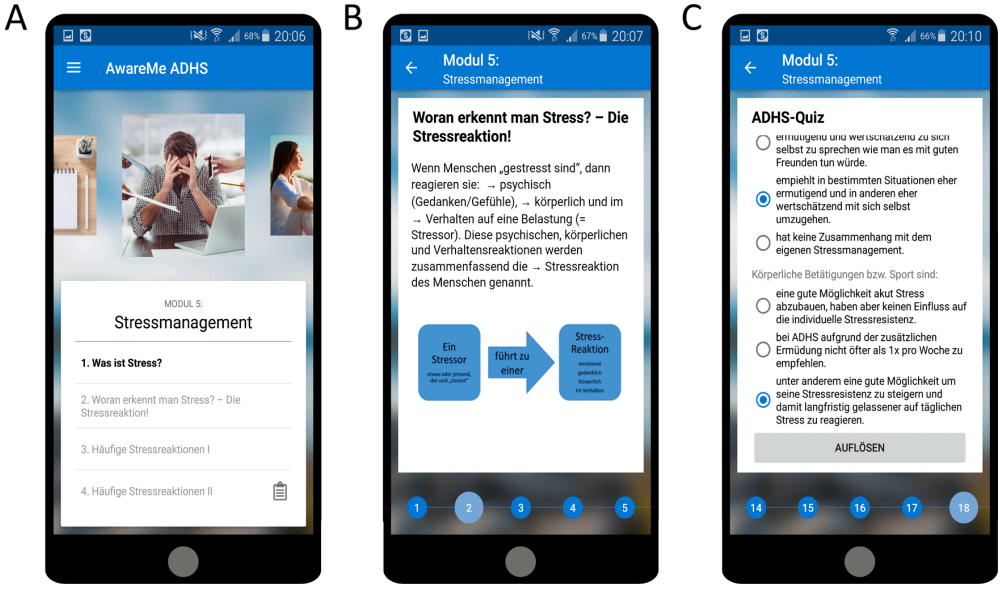

Fig. 2. Functionality of the developed psychoeducation app for ADHD. The "AwareMe ADHS" Android app was developed in German language for adults with ADHD. The App is available as a free download in the Google Play Store. (A) The user can choose between 8 modules by swiping the images in the upper section. The title of the chosen module is presented at the center, with a brief depiction of subchapters in the order of presentation below. (B) After opening a module, the numbers in the bottom area can be used to navigate in the subchapters. The content is presented in the center and includes written texts, illustrations and tasks that require answers to be filled in. (C) At the end of each module, a four-question single-choice content quiz is presented to check successful learning.

applications has previously been associated with increased motivation and self-regulation, and reduced mind wandering (Delen et al., 2014; Rice et al., 2019; Szpunar et al., 2014).

2.4. Clinical outcome assessment

The ADHD symptom severity was assessed based on the observer-rated IDA-R total score before (T0) and after (T1) the intervention. In addition, the IDA-R inattention score (sum score of E1 items), IDA-R hyperactivity score (sum score of E2.1 - E2.5 items) and IDA-R impulsivity score (sum score of E2.6 - E2.9 items) were derived. In addition, current symptoms of depression were examined by the German version of the Becks Depression Inventory II (BDI-II; Beck et al., 1996) and functional impairment by the self-rated Weiss Functional Impairment Scale (WFIRS; Weiss, 2000). The subscale 'School' was thereby not considered for the present adult sample. Exclusively at T0, the MWT-B was administered to estimate verbal intelligence (Merz et al., 1975), and the WURS-k to assess childhood ADHD symptoms (Retz-Junginger et al., 2002).

2.5. Missing data handling

Of 60 patients originally included, 17 dropped out of the study before T1 and were not considered for the present analysis. We obtained complete primary outcome IDA-R data in the remaining 43 participants. Quiz data of three participants of the SAP group could not be processed due to transmission errors. Missing values in the quiz data often occurred in a chapter-by-chapter pattern, indicating unaddressed questions rather than unknown answers, and were evaluated as the percentage of correct answers of all answers given. In addition, one participant did not complete BDI-II and WFIRS scores and was therefore not considered for the analyses of these specific questionnaires.

2.6. Statistical analyses

The IDA-R sum score served as the primary outcome parameter. We additionally analyzed ADHD core symptoms separately based on the respective subscores: IDA-R inattention score, IDA-R hyperactivity score, IDA-R impulsivity score. Further secondary outcome parameters included were the percentage of correct quiz responses, the percentage of missing quiz responses, the BDI-II sum score, the WFIRS sum score, the number of dropouts during the course of the study, the number of homework assignments submitted, and the number of psychoeducation group sessions attended.

On each of the IDA-R, BDI-II and WFIRS scores separate 2 × 2 mixed ANOVAs were carried out, with Intervention Group (SAP, BAP) as a between-subjects factor and Time (T0, T1) as a within-subjects factor. In all cases, there was homogeneity of covariances and error variances, except for the BDI-II baseline, as determined by Levene's test ($p = .047$). In addition, BDI-II data were right skewed, resulting in non-normal distributed data for T0 and T1 scores (Shapiro-Wilk, $p_{T0} = .002$, $p_{T1} = .001$). BDI-II variables were therefore Johnson-transformed (Johnson, 1949) and included into the present analysis, after a reassessment of ANOVA assumptions indicated normal distributed data (Shapiro-Wilk, $p_{T0} = .33$, $p_{T1} = .18$).

Separate independent t-tests between intervention groups were carried out on the percentages of correct responses and percentages of missing responses in the quiz. Moreover, Pearson correlations were separately calculated within each intervention group for an exploratory examination of potential associations between ADHD symptom severity (IDA-R sum score), depression symptom severity (BDI-II score), functional impairment (WFIRS sum score), and psychoeducational content knowledge (percentage of correct quiz responses). For this purpose, difference scores between T0 and T1 were first individually calculated for the IDA-R, BDI-II, and WFIRS scores, and subsequently these difference scores and the percentage of correct quiz responses were correlated. Finally, study dropouts and study compliance were evaluated. A chi-square test was conducted to examine the number of dropouts between groups. Independent t-tests were performed to compare both groups on the number of homework assignments submitted and the number of psychoeducation group sessions attended.

All reported statistical tests were performed two-sided and based on a significance level of $\alpha = 0.05$. Except for the exploratory correlation analysis, we report adjusted p-values based on the Benjamini-Hochberg procedure controlling the false discovery rate for all outcome analyses (Benjamini and Hochberg, 1995; Glickman et al., 2014). Partial eta-squared and Cohen's d are reported as estimates of effect size for ANOVA procedures and independent t-tests, respectively. Statistical analyses were carried out with SPSS software version 21.0 (IBM Corp., 2012) and Matlab version 2021b (The MathWorks Inc., Natick, MA, USA). Visualization of the correlation matrix was conducted by means of R version 3.6.1 (R Core Team, 2021) using the Corrplot package for R version 0.84 (R Package "Corrplot", 2017).

3. Results

3.1. Sample characterization and demographics

43 patients with ADHD (20 female, 23 male; $M_{age} = 38.2$, $SD_{age} = 11.9$) completed their study participation in either the SAP ($n = 24$) or BAP ($n = 19$) group between March 2019 and November 2020 and were considered for analyses. The clinical and sociodemographic baseline characteristics of both groups are depicted in Table 1. Both intervention groups were widely balanced in several characteristics including age, sex, education and ADHD subtype presentations.

3.2. ADHD symptom severity

ADHD total symptoms, as measured by the IDA-R, are depicted in Fig. 3A. The 2 × 2 mixed ANOVA revealed a significant interaction of Time and Intervention Group ($F(1,41) = 8.51$, $p = .019$, $\eta p^2 = .17$), thereby indicating a greater reduction in ADHD total symptoms from T0 to T1 in the SAP group as compared to the BAP group. More specifically, ADHD symptoms improved by 33.4% in the SAP group and by 17.3% in the BAP group. A decrease in total symptoms from T0 to T1 was also observed across intervention groups ($F(1,41) = 69.71$, $p < .001$, $\eta p^2 = .63$). Both groups, in turn, did not differ significantly across measurement points ($F(1,41) = 0.22$, $p = .74$).

A significant interaction was also found in the separate analysis of inattention symptoms ($F(1,41) = 8.44$, $p = .019$, $\eta p^2 = .17$), in that there was a greater decrease in IDA-R inattention scores (see Fig. 3B) from T0 to T1 in the SAP group (40.4%) than in the BAP group (24.9%). Across intervention groups, symptoms of inattention decreased from T0 to T1 ($F(1,41) = 136.35$, $p < .001$, $\eta p^2 = .77$), but no main effect of Intervention Group was revealed ($F(1,41) = 2.25$, $p = .30$).

For symptoms of hyperactivity (see Fig. 3C), we observed no interaction between Time and Intervention Group ($F(1,41) = 1.88$, $p = .30$), but we did find a significant effect of Time ($F(1,41) = 8.27$, $p = .019$, $\eta p^2 = .17$). Here, a reduction in IDA-R hyperactivity scores of 17.2% from T0 to T1 across groups was revealed. There was no main effect of Intervention Group ($F(1,41) = 0.78$, $p = .52$).

An interaction was found between Time and Intervention Group for impulsivity symptoms ($F(1,41) = 7.15$, $p = .030$, $\eta p^2 = .15$). Concretely, the reduction of the IDA-R impulsivity scores from T0 to T1 was greater in the SAP group (25.6%) than in the BAP group (2.7%), as depicted in Fig. 3D. Also, across intervention groups, symptoms of impulsivity improved from T0 to T1 ($F(1,41) = 11.88$, $p = .006$, $\eta p^2 = .23$). No main effect of Intervention Group was observed ($F(1,41) = 0.48$, $p = .60$).

3.3. Content quiz

The percentage of correct and missing responses of the content quiz

Table 1
Baseline demographic and clinical characteristics of study participants.

Characteristic	No. (%) BAP (n = 19)	SAP (n = 24)	*P* value[a] Group comparison
Age, y			
Mean (SD)	41.0 (13.5)	35.9 (10.1)	.17
Range	20 - 61	19 - 56	
Female	9 (47.4)	11 (45.8)	.92
University entrance diploma (year 5 to 12/13)	15 (78.9)	20 (83.3)	.71
Full- or part-time employment	8 (42.1)	14 (60.9)	.35
Verbal IQ, mean (SD)	104.5 (10.7)	104.3 (11.1)	.95
IDA-R total ADHD symptoms, mean (SD)	37.0 (7.3)	39.5 (7.0)	.25
WURS-k childhood ADHD symptoms, mean (SD)	31.2 (15.1)	32.0 (11.3)	.85
ADHD presentation			.30
Inattentive	6 (31.6)	4 (16.7)	
Hyperactive-impulsive	0	0	
Combined	13 (68.4)	20 (83.3)	
Psychopharmacological treatments			
Methylphenidate	3 (15.8)	11 (45.8)	.052
Amphetamine	3 (15.8)	3 (12.5)	.76
Other psychostimulants	0	0	
Atomoxetine	0	1 (4.2)	.37
Antidepressant	7 (36.8)	4 (16.7)	.17
Mood stabilizers, sedatives, neuroleptics, others	9 (47.4)	8 (33.3)	.53
Comorbid axis I disorders[b]			
Affective disorders	14 (73.7)	15 (62.5)	.45
Anxiety disorders	10 (52.6)	14 (58.3)	.80
Substance abuse	0	5 (20.8)	.022
Comorbid axis II disorders			
Schizoid, schizotypal, paranoid	0	2 (8.7)	.38
Borderline, narcissistic, histrionic	1 (5.3)	1 (4.2)	.87
Avoidant, OC, dependent	10 (52.6)	6 (25.0)	.11
Other, depressive, negativistic, NOS	5 (26.3)	2 (8.3)	.14

[a] Independent t-tests or chi-square tests were conducted in dependence of variable types.
[b] Some patients were diagnosed with more than one disorder according to DSM-IV, current or in remission.
Abbreviations: BAP, brochure-assisted psychoeducation; OC, obsessive-compulsive; SAP, smartphone-assisted psychoeducation; WURS-k, Wender Utah Rating Scale, short version.

across all psychoeducation modules are presented in Fig. 4. While the SAP group answered 75.9% ($SD = 12.3$) of the quiz questions correctly, the BAP group had 80.2% ($SD = 14.7$) correct responses. This descriptive difference, however, did not turn out significant ($t(38) = 1.03$, $p = .45$). Likewise, similar percentages of missing responses were observed between groups ($t(38) = -0.37$, $p = .79$). Specifically, 4.6% ($SD = 7.7$) and 3.8% ($SD = 5.4$) of the quiz questions were not answered in the SAP and BAP group, respectively.

3.4. Symptoms of depression and functional impairments

At T0 and T1, in both intervention groups, similar scores were observed for Johnson-transformed BDI-II ratings of depression symptoms as well as for functional impairment ratings as measured by the WFIRS. That is, neither for symptoms of depression ($F(1,40) = 1.64$, $p = .33$) nor for functional impairment ratings ($F(1,40) = 5.09$, $p = .30$), an interaction of Time and Intervention Group was found. Moreover, no significant main effects were revealed.

3.5. Correlation analysis

Pearson correlations between IDA-R difference scores (i.e., ADHD total symptom severity), BDI-II difference scores (i.e., depression symptoms), WFIRS difference scores (i.e., functional impairment), and percentage of correct quiz responses are presented in Fig. 5. Positive correlations were found between the ADHD total symptom severity and the percentage of correct quiz responses in the BAP group ($r = 0.53$, $p < .05$) as well as between symptoms of depression and functional impairment in the SAP group ($r = 0.55$, $p < .01$). Apart from that, no further significant correlations were found.

3.6. Study dropouts and compliance

Although a total of 17 participants dropped out between T0 and T1, no unintended consequences or adverse events were reported. Descriptively, more participants dropped out of the BAP group ($n = 11$) than the SAP group ($n = 6$), however, no significant difference was found between the two groups ($\chi^2(1) = 2.05$, $p = .30$).

With regard to therapy compliance, participants who completed the study attended a similar number of group sessions in the SAP ($M = 6.7$, $SD = 0.8$) and BAP ($M = 6.9$, $SD = 0.8$) group ($t(41) = 0.59$, $p = .56$). Homework compliance, in turn, differed between groups ($t(38) = -4.35$, $p < .001$, $d = -1.38$), in that participants of the SAP group submitted 93.9% ($SD = 17.8\%$) and participants of the BAP group submitted 66.2% ($SD = 22.4\%$) of their homework assignments.

4. Discussion

In this RCT, we investigated whether group psychoeducation for adults with ADHD is more effective in reducing ADHD symptoms when supported by a purpose-designed smartphone app or traditional paper brochures. To this end, 60 patients with ADHD were randomized to either a smartphone-assisted 8-week group psychoeducation or to the same group psychoeducation but with handed-out brochures as support material. Analysis of the 43 participants who completed the final assessments revealed considerable reductions in ADHD symptoms across intervention groups, with some particularly pronounced improvements related to use of the smartphone app.

Specifically, and also the key finding of this study, the decrease in ADHD symptoms from T0 to T1 was greater in the SAP group than in the BAP group. That is, patients who received their work materials via the smartphone app showed stronger improvements than patients who received the same work materials via pen-and-paper brochures. This indicates that the use of digital health apps for ADHD is promising and may facilitate everyday life transfer of learning content conveyed in a group psychoeducation session. Notably, we kept work materials and included homework almost identical in both interventions and refrained from implementing supplementary app functions. Consequently, group differences most likely result from the type of media employed (app-based vs. brochure-based). While an app-based engagement with information presumably offers greater flexibility and thereby allows for an enhanced interaction with the psychoeducational content, further studies involving a detailed tracking of user behavior are needed to determine the exact causes.

To further specify the above result, the greater decrease in ADHD symptoms from T0 to T1 in the SAP group compared to the BAP group was symptom specific. That is, while we did not observe any group differences with respect to hyperactivity, we found a greater reduction in symptoms of inattention and impulsivity particularly in the SAP group. Hence, the use of our app seems to specifically reduce these two ADHD core symptoms. In turn, symptoms with a stronger motor and less pronounced cognitive component, such as hyperactivity, may be more difficult to address through psychoeducational content in general, as possibly indicated by the smaller effect of across-group symptom improvements. Besides that, although a large RCT indicated differences in multimodal treatment effects (Selaskowski et al., 2022), few studies report these core symptom-specific outcomes for adult ADHD. The present findings thereby add to what has previously been described as one of the key gaps in evidence regarding the treatment of ADHD in adults (Peterson et al., 2008). Future confirmatory studies need to

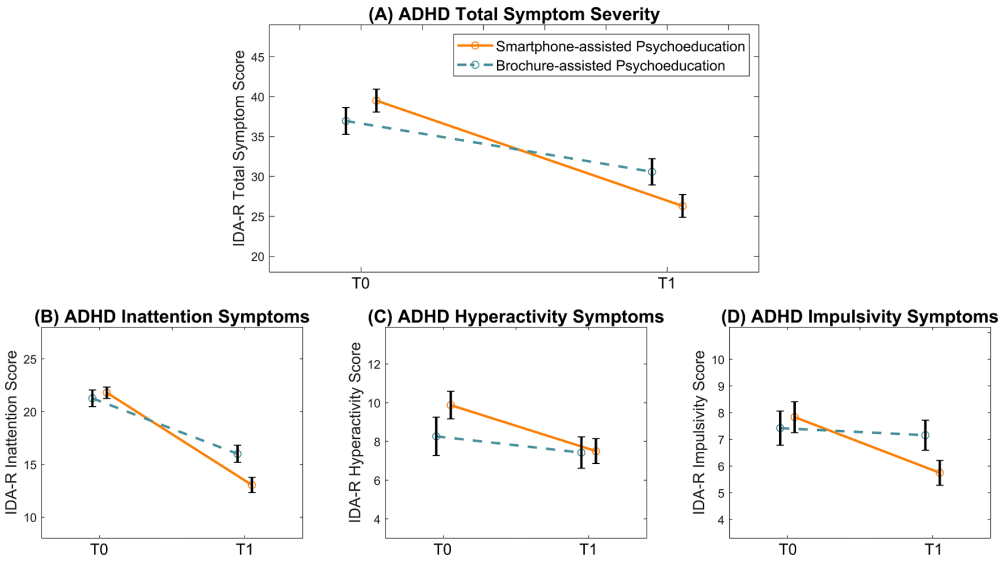

Fig. 3. ADHD symptom severity before and after group psychoeducation. Symptoms were assessed at baseline (T0) and after the 8-week psychoeducation (T1). (A) The IDA-R total symptom score and the derived IDA-R subscores for symptoms of (B) inattention, (C) hyperactivity and (D) impulsivity are presented for the smartphone-assisted psychoeducation group (orange line) and the brochure-assisted psychoeducation group (green dashed line). Significant Time × Intervention Group interactions were found for ADHD total symptoms ($p = .019$, $\eta p^2 = .17$), inattention symptoms ($p = .019$, $\eta p^2 = .17$) and impulsivity symptoms ($p = .030$, $\eta p^2 = .15$). The score range for the IDA-R total score is 0 to 54. Maximum values for the inattention score, the hyperactivity score and the impulsivity score are 27, 15 and 12, respectively. Error bars indicate standard errors of the mean. Abbreviations: IDA-R, Integrated Diagnosis of ADHD in Adulthood

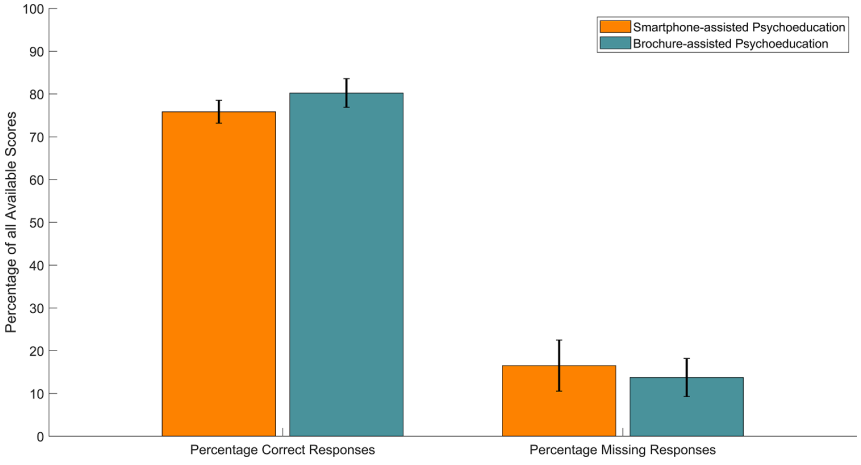

Fig. 4. Results of the psychoeducation content quiz. The percentages of correct responses and missing responses relative to all available scores are depicted. At the end of each of the psychoeducation modules 1 to 7, a four single-choice questions quiz was presented to evaluate the psychoeducational content knowledge in both groups. None of the parameters differed significantly between the smartphone-assisted psychoeducation group and the brochure-assisted psychoeducation group ($p_{correct} = .45$; $p_{missing} = .79$). Error bars indicate standard errors of the mean.

further examine the potential superiority of app-based psychoeducation on specific ADHD core symptoms.

In the content quizzes administered to assess the acquired psychoeducational knowledge in both groups, similar accuracies in answering the questions were observed. This suggests that group differences in symptom reductions are related less to the basic learning of the psychoeducational content but rather to its implementation into daily routine. In this aspect in particular, the mobility of a smartphone allows the user to engage with the content in a more flexible manner, and this may be especially the case in times of elevated motivation to actually attempt the strategies in practice.

In depressive symptomatology, both SAP and BAP showed no improvements. This finding is in contrast to a previous study that used the same manual (Hoxhaj et al., 2018) and another non-digital psychoeducation study (Hirvikoski et al., 2015), both of which found reductions in depression symptoms after 8 sessions of psychoeducation in adults with ADHD. Of note, however, these two studies applied less strict exclusion criteria for comorbid depression. The reported higher baseline symptoms may have facilitated improvements in this outcome in comparison with our study. Consequently, interpretations with respect to the effectiveness of the present interventions for comorbid depression are limited.

Likewise, functional impairments did not improve in either group over the course of the study. This finding needs further exploration in upcoming trials, especially as it contradicts previous evidence and general assumptions regarding psychoeducation in ADHD (Kooij et al., 2010; Vidal et al., 2013).

Our exploratory correlation analysis on primary and secondary

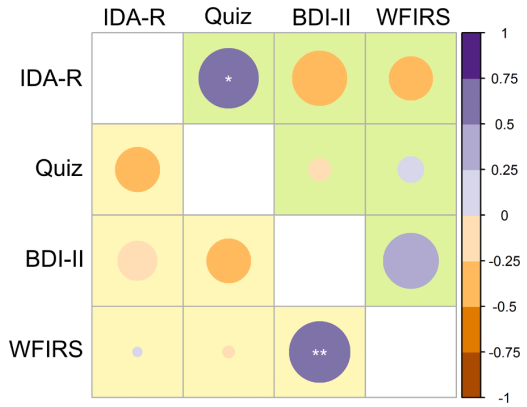

Fig. 5. Correlation matrix of primary and secondary study outcome parameters. Pearson correlations (r) between primary and secondary outcome measures (IDA-R total ADHD symptom score, percentage of correct responses in the content quiz, BDI-II depression symptoms score and Weiss Functional Impairment Rating Scale total score) for the smartphone-assisted psychoeducation group (below diagonal in yellow color) and brochure-assisted psychoeducation group (above diagonal in green color) are presented. Analyses are based on difference scores from T0 to T1. Abbreviations: BDI-II, Becks Depression Inventory II; IDA-R, Integrated Diagnosis of ADHD in Adulthood; WFIRS, Weiss Functional Impairment Rating Scale. *p < .05, **p < .01.

outcome parameters yielded a positive correlation of the percentage of correct quiz answers and the difference in ADHD total symptoms in the BAP group. This may suggest that such knowledge examinations are valid assessments of the quality of psychoeducational content in addressing specific symptoms. In addition, higher reported depression symptoms were associated with higher functional impairment in the SAP group.

In light of the present results, our study not only confirms previous findings that indicate beneficial effects of psychoeducation in adult ADHD (Hoxhaj et al., 2018; Vidal et al., 2013), but beyond that, supports the implementation of mobile apps in routine clinical care. There were no reports of symptom aggravation related to the interventions throughout the study, and no adverse events were reported. Dropouts were a factor, with descriptively more participants of the SAP completing the study. Although this difference was not significant, it potentially holds clinical interest for future investigations as it may indicate higher adherence to treatment in app-assisted psychoeducation. Consistent with this, being satisfied with the information received was the strongest predictor of overall satisfaction in an evaluation of ADHD health care experiences (Solberg et al., 2019). Notably, this effect was independent of medication or treatment outcome thereby emphasizing the need for effective psychoeducation. In our evaluation of treatment compliance, participants of both groups attended a similar number of group sessions. Homework compliance, instead, was considerably higher in the SAP group, which may also account for the superiority in improving ADHD symptoms.

This study has some limitations. First, although relatively strong effects were found, there was no comparison with a control condition that was more distinct to our group psychoeducation intervention. While we therefore cannot rule out an impact of within-group effects, we consider this unlikely based on the high level of equality in the procedure and the structured nature of the implementation. Second, there were descriptively more patients treated with medication for ADHD in the SAP than in the BAP group. Since participants were not allowed to initiate medication intake or change dosage during the study, we expect only minor effects in this regard. Third, the generalizability of the sample may be limited by the fact that a number of interested individuals were unable to participate in the study for organizational or technical reasons. Specifically, those who were not sufficiently mobile, for instance because they lived far from the study site or because they could not adjust their work schedules to attend the group sessions, were not able to participate in the study. In addition, access to a smartphone was a prerequisite for participation in the study and we thereby potentially primarily addressed those who were already familiar with smartphones. Consequently, the present results may not be generalized to patients who do not have access to or are less familiar with the use of a smartphone. While the participants' age did not differ significantly between groups, smartphone familiarity may be age-dependent, and future studies should investigate the extent to which the present results can be generalized to elderly patients in particular. Finally, our RCT design did not include a follow-up measurement. As a result, our current study cannot provide information on the extent of long-term improvements in ADHD symptoms which is important to address in future trials.

On a further note, we retained the way psychoeducation content is delivered in both interventions, although numerous helpful additional features could be integrated into the app. For instance, calendar functions and push-up messages could substantially improve the organizational difficulties in everyday life. Also, in its current form, the smartphone app is structured similar to a digital brochure with individual modules to be completed one by one. Successful acquisition of such monotonous content requires a sufficient level of motivation and the ability to self-regulate, which is a particular challenge in ADHD (Reaser et al., 2007). A higher extent of individualization and interaction could therefore be a promising approach to increase self-motivated engagement, such as via a chatbot (i.e., a conversational agent). There is some initial evidence that this approach can improve attention deficits (Jang et al., 2021).

In summary, we provide first evidence that smartphone apps are effective and safe in delivering psychoeducational content as a support to group settings and reduce symptoms in adult ADHD. Moreover, inattention and impulsivity improved stronger when participants were assisted by a smartphone app as compared to traditional brochures. Our findings suggest that group psychoeducation should find further application in regular patient care of adult ADHD and could be successfully enhanced through the use of mobile apps.

Author contributions

Study conception and design: BS, MSC, AP, NB. Data collection: BS, MS, ML. Analysis and interpretation: BS, NB. Draft manuscript preparation: BS, MS, NB. Supervision: AP, NB. Review and editing: MS, MSC, ML, BA, HR, KK, AW, TW, SB, SL, AP. All authors approved the final version of the manuscript prior to submission.

Data availability statement

The analysis data set of this study is available upon reasonable request for non-commercial purposes. Sharing with third parties requires approval. All data requests should be addressed to the corresponding author.

Declaration of Competing Interest

BS and NB received funding by BONFOR and the German Federal Ministry of Education and Research. Over the past three years, AP received funding by the German Federal Ministry of Education and Research, Horizon2020, and DFG; she reports serving on advisory boards for Takeda, Medice, and Boehringer; and delivering lectures sponsored by Medice, Takeda; and being the author of books and articles on psychotherapy. All other authors declare no conflict of interests.

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3.2 Publication 2: Chatbot-supported psychoeducation in adult attention-deficit hyperactivity disorder: randomised controlled trial

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Chatbot-supported psychoeducation in adult attention-deficit hyperactivity disorder: randomised controlled trial

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Background

Although psychoeducation is generally recommended for the treatment of adult attention-deficit hyperactivity disorder (ADHD), participation in clinical psychoeducation groups is impeded by waiting times and the constrained number of patients who can simultaneously attend a group. Digital psychoeducation attempts are promising, but the rapidly expanding number of apps lack evidence and are mostly limited to only a few implemented interactive elements.

Aims

To determine the potential of digital, self-guided psychoeducation for adult ADHD, a newly developed interactive chatbot was compared with a previously validated, conventional psychoeducation app.

Method

Forty adults with ADHD were randomised, of whom 17 participants in each group completed self-guided psychoeducation based on either a chatbot or conventional psychoeducation app between October 2020 and July 2021. ADHD core symptoms were assessed before and after the 3-week interventions, using both the blinded observer-rated Integrated Diagnosis of ADHD in Adulthood interview and the self-rated ADHD Self-Assessment Scale (ADHS-SB).

Results

Observer- and patient-rated ADHD symptoms were significantly reduced from pre- to post-intervention (observer-rated: mean difference −6.18, 95% CI −8.06 to −4.29; patient-rated: mean difference −2.82, 95% CI −4.98 to −0.67). However, there were no group × intervention interaction effects that would indicate a stronger therapeutic benefit of one of the interventions. Likewise, administered psychoeducational knowledge quizzes did not show differences between the groups. No adverse events were reported.

Conclusions

Self-guided psychoeducation based on a chatbot or a conventional app appears similarly effective and safe for improving ADHD core symptoms. Future research should compare additional control interventions and examine patient-related outcomes and usability preferences in detail.

Key words

Attention-deficit hyperactivity disorder; chatbot; smartphone-assisted psychoeducation; conversational agent; digital health.

With a prevalence of approximately 5.9% in youth and 2.5% in adulthood,[1,2] attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder associated with substantial individual suffering and economic burden.[3,4] Clinical complexity is further aggravated by high rates of comorbid disorders, such as substance use disorder, depression, bipolar disorder and anxiety disorders.[5] Pharmacological treatment has effectively reduced ADHD symptoms and is considered the first-line treatment.[6–8] Yet, it is associated with side-effects,[9] risks of multimorbid pharmacotherapy and issues with adherence.[10] In addition, the non-medical use of prescribed stimulants has emerged as a major public health concern.[11] Cognitive–behavioural therapy (CBT) is recommended in cases of low pharmacological treatment benefit or to specifically address functional impairment.[6] Regardless of conducting other treatments, guidelines generally recommend comprehensive psychoeducation.[7]

The basic principles of psychoeducation are to provide knowledge about the disorder and treatment procedures, as well as emphasise the patient's personal strengths and potential for growth. Although psychoeducation generally shows promising results, few rigorous examinations of treatment effects on ADHD core symptoms exist. One of these studies compared psychoeducation with mindfulness training in adults with ADHD,[12] and another study assessed psychoeducation against CBT in medicated but still symptomatic adults.[13] Both studies found all interventions to be similarly effective in improving ADHD core symptoms. Compared with other treatments, psychoeducation has the advantage of having hardly any side-effects as well as being easily scalable through digital provision without significantly increasing costs. A psychoeducation mobile app, for instance, could significantly reduce the time and effort associated with conducting clinical psychoeducation.

Current state of digital health applications

In general, advances in digital health have led to the development of a substantial number of mobile health (mHealth) apps, which can reduce the need for in-person meetings with a clinician, shorten waiting list times, promote self-care[14] and be economically beneficial because of their low-cost scalability, especially in low-income countries.[15] However, although mHealth is growing in popularity, scientific evidence of its efficacy is inconsistent, study quality is often low[16] and, moreover, safety concerns related to incorrect information, lack of expert involvement and poor validation have been reported.[17] Consequently, the risk of low-value care – that is, services that provide little benefit to patients or that even cause

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harm – is particularly high.[18] This risk also applies to mental mHealth, where many applications seem to have no scientifically valid foundation,[19] and can appear to suggest evidence-based treatments by using misleading scientific language.[20] Regarding ADHD, for instance, Păsărelu et al.[21] identified 109 apps, including 23 that focused on psychoeducation, but none provided proof of their effectiveness.

Digital psychoeducation in adult ADHD

To address this issue, our research group recently conducted a randomised controlled trial (RCT), in which we evaluated an 8-week psychoeducation group programme that was either assisted by traditional paper brochures or by a newly developed psychoeducation app for adult ADHD.[22] Although the app was more effective in improving ADHD symptoms and no adverse events were reported, we cannot directly transfer these results to self-guided psychoeducation without a concomitant psychoeducation group. Moreover, the app used may be less suitable for self-guided learning in ADHD because it was developed as a digital, but hardly interactive, instructional format. Thus, the potential benefits of mHealth applications, such as considering individual patient differences in learning behaviour, have not yet been incorporated.

Considering that motivation-related and dysfunctional learning behaviours occur in adult ADHD, the implementation of a psychoeducation chatbot may be of particular value. A chatbot (i.e. a conversational agent) is a computer program that can simulate conversations with human users. Potential benefits for psychoeducation include the possibility of interactively self-guiding the learning path, and receiving individualised responses and feedback that are not achievable with a 'conventional' psychoeducation app. Although these properties appear valuable for several mental disorders, there is limited evidence for the use of chatbots in mental health.[23] Regarding attention deficits, although not specifically addressing patients with ADHD, only one previous study conducted a chatbot-assisted psychoeducation, and found stronger improvements of ADHD-related symptoms than a self-help book control group.[24]

Aims

In this study, we implemented a new chatbot that, based on validated psychoeducational content, interacts in such a way that the patient co-determines the topics addressed. We hypothesised that this approach might lead to greater symptom improvement than conventional module-based content presentation, given the increased potential for self-guidance through the preferred psychoeducational content, as well as the higher level of interaction and individualisation offered by a chatbot. For clinical evaluation, we conducted an RCT to evaluate the effects of a 3-week self-guided, chatbot-based psychoeducation (CBP) in adults with ADHD compared with our previously validated psychoeducation app, which is based on a module-by-module content presentation.[22]

Method

Participants

A total of 139 adult out-patients with ADHD were contacted for study participation, of which 40 participants were randomised to the intervention groups and 34 participants completed the study (for the participant flow chart, see Supplementary Fig. 1 available at https://doi.org/10.1192/bjo.2023.573). The study was advertised via the Department of Psychiatry and Psychotherapy of the University Hospital Bonn, via the website 'Central ADHD Network' (https://www.zentrales-adhs-netz.de), and via other publicly accessible media. Individuals were eligible to participate if they met DSM-5 ADHD diagnostic criteria,[25] as assessed by the observer-rated Integrated Diagnosis of ADHD in Adulthood (IDA-R);[26] were aged 18–65 years; had access to a smartphone with Android OS (version 5.0 or higher) and had sufficient command of the German language.

Individuals were ineligible to participate if they met the diagnostic criteria for schizophrenia or other psychotic disorders; severe affective disorder; moderate-to-severe substance use disorder, as assessed by the Brief Diagnostic Interview for Mental Disorders (Mini-Dips-OA, German version);[27] or antisocial personality disorder, as evaluated by the Assessment of DSM-IV Personality Disorders (ADP-IV, German version).[28] Intake of medication for ADHD was permitted, but had to be stable from 4 weeks preceding the start of study through to the final examinations. The participants received no compensation for their participation in the study.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by the local medical ethics committee of the University of Bonn (protocol number: 123/19). All participants provided written informed consent. The study was preregistered in the German Clinical Trials Register (DRKS; identifier: DRKS00022287) on 13 August 2020. An *a priori* sample calculation in G*Power version 3.1 for Windows[29] (Faul F, Erdfelder E, Buchner A and Lang A-G, Heinrich Heine University, Düsseldorf, Germany; see https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower) was performed to determine the required sample size of 34 participants, which was based on an alpha error probability of 0.05, a power of 80% and a moderate effect size ($f = 0.25$). To account for study drop-out, a randomisation of $n = 40$ was pursued. The first participant was enrolled on 29 September 2020.

Study design

Two interventions were compared in this parallel-group RCT: a self-guided CBP and a self-guided, app-based psychoeducation (ABP). All participants underwent an extensive baseline assessment (time point 0) and were allocated to one of the intervention groups by permuted block randomisation in blocks of two, to maintain balanced group sizes. Sequence generation and participant enrolment were performed by different study personnel. Participants were asked to engage with the psychoeducation content as much as possible during the self-guided 3-week psychoeducation period. Afterwards, a final assessment (time point 1) was conducted. The relative change in ADHD total symptom severity from time point 0 to time point 1, as examined by a blinded clinical rater on the IDA-R, was considered the primary outcome parameter of the study. Participants' remarks about app specifics during the final assessment (time point 1), which provided indications of their respective assigned group, were the cause for not maintaining rater blinding for five cases in the CBP group and four cases in the ABP group. Participants were not blinded for assignment to CBP or ABP.

Clinical outcome assessment

Besides observer-rated ADHD symptoms as measured via the IDA-R,[26] self-rated ADHD symptoms were obtained via the ADHD Self-Assessment Scale (ADHS-SB).[30] Further outcome parameters included the subscales of the World Health Organization Quality of Life questionnaire (WHOQOL)[31] and the Depression, Anxiety and Stress Scale (DASS-21).[32] The Multiple-choice Word Test

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(MWT-B) was conducted at time point 0 exclusively, to estimate verbal intelligence.[33]

Procedures

Following baseline assessments at time point 0 (approximately 2 h), participants received a download link to either the conventional psychoeducation app or the chatbot, and time point 1 final assessments were scheduled. However, because of organisational constraints of some participants, these could not be exactly planned after 3 weeks in all cases. As a result, there were marginal differences in the duration of possible use between participants (see 'Results'). Both the CBP and ABP groups were not limited in the amount or duration of material usage during the intervention period. Processing of all psychoeducational content was estimated to require about 16 h. Following the self-guided 3-week intervention periods, final assessments (approximately 1 h) of the outcome parameters were conducted.

Interventions

The psychoeducation content of both interventions was based on a validated manual,[34] and consisted of eight separate modules that contained a comprehensive summary of the psychoeducation content, assignments and a content quiz. In line with a recent Delphi consensus study on digital psychoeducation for adult ADHD,[35] a comprehensive summary on various aspects of ADHD was implemented, including multiple illustrations to facilitate understanding. The following topics were addressed: basic information about ADHD, personal resources, mindfulness and attention control, self-organisation, stress management, mood regulation and impulsive behaviour control, relationships and a final evaluation. Within each module, the conventional psychoeducation app presented the content linearly (i.e. module by module), whereas the chatbot interactively presented content based on user input (see Fig. 1). The chatbot also offered to present all the information of each module, but the user could skip the content more easily compared with the conventional app. Both the chatbot and the conventional app included identical quiz questions at the end of each module (except for evaluation module eight), to evaluate the acquired psychoeducational knowledge.

The conventional psychoeducation app of the ABP group is available in the Google Play Store ('AwareMe ADHS'; https://play.google.com/store/apps/details?id=de.awareme.pse) and has previously been presented in detail.[22] The chatbot (CBP group) was based on the open-source conversational artificial intelligence platform Botpress version 12.2 for Windows (Botpress, Quebec, Canada; see https://botpress.com).

Statistical analyses

Full IDA-R and questionnaire data were obtained from all 34 participants who completed the study. In the CBP group, however, 14 of the 17 participants were provided only partial access to module seven of the psychoeducation programme, because of technical errors. Module seven data for both groups was therefore dismissed from analyses.

Separate two × two mixed analyses of variance (see Supplementary Table 1) with group (CBP, ABP) as a between-subjects factor and time (time point 0, time point 1) as a within-subjects factor, were conducted for the following outcome parameters: IDA-R total, inattention (sum score of E1 items), hyperactivity (sum score of E2.1–E2.5 items) and impulsivity (sum score of E2.6–E2.9 items) scores; ADHS-SB total,

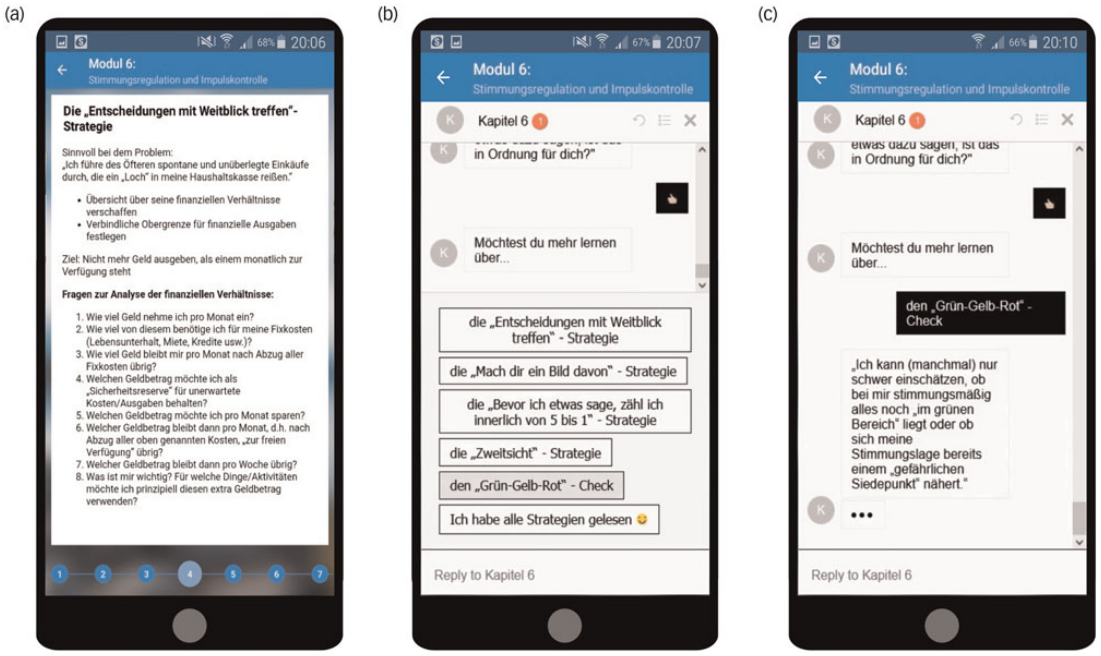

Fig. 1 Functionality of the two psychoeducation systems. (a) Presentation of a slide from the emotion regulation module used in the app-based psychoeducation group. The content is presented linearly within each module. The Android app 'AwareMe ADHS' was evaluated in a previous study.[22] (b) Illustration of the chatbot used in the chatbot-based psychoeducation group. Here, participants engaged in 'digital conversations' within each module, interacting mainly based on predefined response options, as shown in the bottom section. (c) After selecting an answer, the chatbot responded and presented psychoeducational content or asked additional questions to further narrow down the participant's preferred content.

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inattention, hyperactivity and impulsivity scores; the sum scores of the DASS-21 subscales (depression, anxiety and stress) and the sum scores of the WHOQOL subscales (physical health, psychological health, social relationships and environment).

Data from the DASS-21 scales for symptoms of depression and anxiety were considerably right-skewed, resulting in non-normal distributions for scores at both time points (Shapiro–Wilk test, $P < 0.05$). Therefore, the DASS-21 variables of these two scales were Johnson-transformed[36] and subsequent tests for normal distributions revealed no violations (Shapiro–Wilk test, $P_{T0} = 0.33$, $P_{T1} = 0.18$). Transformed data were used for all statistical analyses.

The percentage of correct responses and the percentage of missing responses of the quiz were compared by using separate independent *t*-tests between both groups. Moreover, an exploratory correlation analysis was conducted between primary and secondary outcome parameters, using time point 0 to time point 1 difference scores. Pearson correlations between each difference score were calculated separately for each intervention group.

Statistical analyses were conducted with SPSS software version 21.0 for Windows[37] and MATLAB version 2021b for Windows (The MathWorks, Massachusetts, USA; see https://de.mathworks.com/products/matlab.html). Visualisation of the correlation matrix was performed with R version 3.6.1 for Windows (R Core Team, Vienna, Austria; see https://www.R-project.org),[38] using the Corrplot package for R version 0.84.[39] Reported statistical tests were two-sided and based on a significance level of $\alpha = 0.05$.

Results

Sample characterisation and demographics

In total, 34 participants (18 women, 16 men; mean age 29.6 years, s.d. 8.4) completed the RCT between October 2020 and July 2021. Table 1 provides a presentation of the balanced clinical baseline and demographic characteristics for the CBP ($n = 17$) and ABP ($n = 17$) groups. The exact duration from time point 0 to time point 1 in which the participants could access the psychoeducation content on their smartphones was 22.5 days (s.d. 2.2) in the CBP group and 23.8 days (s.d. 4.3) in the ABP group ($t(32) = 1.16$; $P = 0.25$).

ADHD symptom severity

Changes in observer- and self-rated ADHD symptoms from time point 0 to time point 1 are shown in Fig. 2. The analysis of observer-rated ADHD symptoms showed that IDA-R total scores decreased from time point 0 to time point 1 (mean difference −6.18, 95% CI −8.06 to −4.29) across groups ($F(1,32) = 44.44$; $P < 0.001$; $\eta p^2 = 0.58$), with reductions of 20.8% in the CBP group and 23.9% in the ABP group. Neither a group × time interaction ($F(1,32) = 0.04$; $P = 0.84$), nor a significant main effect of group ($F(1,32) = 3.47$; $P = 0.072$) was found.

In line with this, the separate analyses of each core symptom (i.e. IDA-R subscale scores) showed no significant group × time interactions for inattention ($F(1,32) = 0.17$; $P = 0.68$), hyperactivity ($F(1,32) = 0.16$; $P = 0.69$) or impulsivity ($F(1,32) = 0.15$; $P = 0.70$), but only showed main effects of time. That is, across groups, inattention improved by 20.3% ($F(1,32) = 30.30$; $P < 0.001$; $\eta p^2 = 0.47$), hyperactivity improved by 20.7% ($F(1,32) = 18.30$; $P < 0.001$; $\eta p^2 = 0.36$) and impulsivity improved by 29.9% ($F(1,32) = 34.90$; $P < 0.001$; $\eta p^2 = 0.52$) from time point 0 to time point 1. No main effect of group on any core symptom was revealed.

Self-rated ADHD total symptoms (i.e. ADHS-SB total score) also improved (mean difference −2.82, 95% CI −4.98 to −0.67) over time ($F(1,32) = 7.12$; $P = 0.012$; $\eta p^2 = 0.18$), but no group × time interaction ($F(1,32) = 0.03$; $P = 0.88$) was observed. Here, ADHD total symptoms decreased by 12.6% in the CBP group and

Table 1 Demographic and clinical sample characteristics

Characteristic	*N* (%) CBP ($n = 17$)	*N* (%) ABP ($n = 17$)	*P*-value[a] Group comparison
Age, years			
Mean (s.d.)	29.6 (7.6)	29.7 (9.5)	0.99
Range	19–44	20–52	
Female	9 (52.9%)	9 (52.9%)	0.92
University entrance diploma (year 5 to 12/13)	12 (70.6%)	16 (94.1%)	0.72
Full- or part-time employment	8 (47.1%)	11 (64.7%)	0.30
Verbal IQ, mean (s.d.)	106.5 (13.1)	109.7 (14.0)	0.48
Previous psychoeducation experience	4 (23.5%)	6 (37.5%)	0.38
ADHD presentation			0.30
Inattentive	2 (11.8%)	3 (17.7%)	
Hyperactive–impulsive	0	1 (5.9%)	
Combined	15 (88.2%)	13 (76.5%)	
Psychopharmacological treatments			
Methylphenidate	10 (58.8%)	5 (29.4%)	0.08
Amphetamine	0	3 (17.6%)	0.70
Other psychostimulants	0	0	
Atomoxetine	0	1 (5.9%)	0.31
Antidepressant	2 (11.8%)	6 (35.3%)	0.11
Anticonvulsants, anxiolytics, antipsychotics, others	3 (17.6%)	2 (11.8%)	0.63
No medication	3 (17.6%)	4 (23.5%)	0.67
Comorbid mental disorders			
Affective disorders	8 (47.1%)	11 (64.7%)	0.30
Anxiety disorders	5 (29.4%)	8 (47.1%)	0.29
Comorbid personality disorders			
Schizoid, schizotypal, paranoid	1 (5.9%)	1 (5.9%)	0.38
Borderline, narcissistic, histrionic	4 (23.5%)	1 (5.9%)	0.15
Avoidant, obsessive–compulsive, dependent	4 (23.5%)	3 (17.6%)	0.67

CBP, chatbot-based psychoeducation; ABP, app-based psychoeducation; ADHD, attention-deficit hyperactivity disorder.
a. Based on independent *t*-tests or chi-squared tests.

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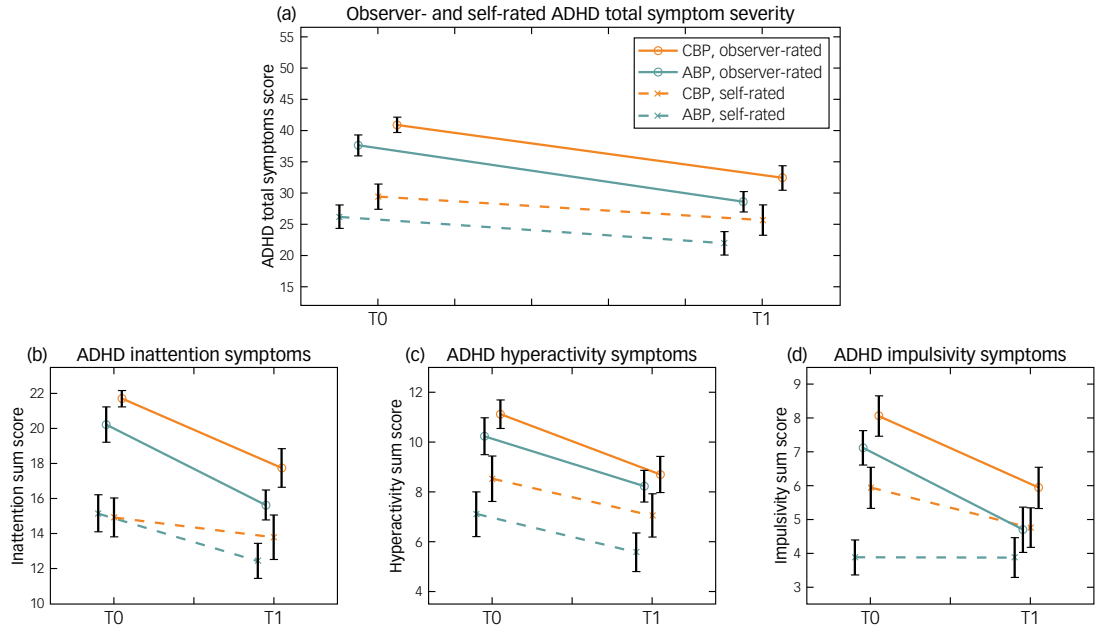

Fig. 2 Observer- and self-rated ADHD symptom severity before (time point 0) and after (time point 1) the 3-week psychoeducation interventions. The (a) ADHD total symptom scores and subscores for symptoms of (b) inattention, (c) hyperactivity and (d) impulsivity based on IDA-R observer ratings (solid line) and ADHS-SB self-ratings (dashed line) are presented. The chatbot-based psychoeducation group (orange line) and the app-based psychoeducation group (green line) are depicted separately. The IDA-R and ADHS-SB total scores ranged from 0 to 54. The maximum values for inattention, hyperactivity and impulsivity scores were 27, 15 and 12, respectively. Error bars indicate standard errors of the mean. ABP, app-based psychoeducation; ADHD, attention-deficit hyperactivity disorder; ADHS-SB, ADHD Self-Assessment Scale; CBP, chatbot-based psychoeducation; IDA-R, Integrated Diagnosis of ADHD in Adulthood; T0, time point 0; T1, time point 1.

16.4% in the ABP group, with no significant main effect of group on total symptom severity ($F(1,32) = 1.93$; $P = 0.17$).

In the separate analyses of self-rated ADHD core symptoms (i.e. ADHS-SB subscale scores), no group × time interactions were found, but time had a significant main effect. Specifically, we observed improvements of 12.7% for inattention ($F(1,32) = 6.77$; $P = 0.014$; $\eta p^2 = 0.18$) and 19.2% for hyperactivity ($F(1,32) = 7.64$; $P = 0.009$; $\eta p^2 = 0.19$), but only a descriptive reduction of 12.0% for impulsivity ($F(1,32) = 1.65$; $P = 0.21$; $\eta p^2 = 0.05$). For impulsivity, in turn, a significant main effect of group ($F(1,32) = 4.84$; $P = 0.035$; $\eta p^2 = 0.13$) was found, in that mean impulsivity symptoms were higher in the CBP group (mean 5.35, 95% CI 4.39 to 6.31) than in the ABP group (mean 3.88, 95% CI 2.91 to 4.85).

Psychoeducational knowledge quiz

The percentages of correct and missing answers in the content quizzes are presented in Supplementary Fig. 2. Of the questions, 21.1% were not answered in the CBP group and 6.9% were not answered in the ABP group. This difference in the percentage of missing responses was, however, not statistically significant ($t(22,5) = -1.85$, $P = 0.078$, $d = -0.78$). Both groups also performed similarly on the content quiz ($t(32) = 0.62$, $P = 0.54$, $d = 0.22$), as measured by the proportion of correct answers, which amounted to 76.4% in the CBP group and 79.4% in the ABP group.

Symptoms of depression, anxiety and stress

The analyses of comorbid symptoms (i.e. DASS-21 scales) did not reveal any group × time interactions with regard to symptoms of depression ($F(1,32) = 2.47$; $P = 0.13$), anxiety ($F(1,32) = 0.72$; $P = 0.40$) or stress ($F(1,32) = 0.01$; $P = 0.94$). Besides a significant group effect indicating higher stress symptoms in the CBP group ($F(1,32) = 5.79$; $P = 0.02$; $\eta p^2 = 0.15$), we did not observe significant main effects of time or group (see Supplementary Table 1).

Quality of life

The domain-specific analysis of self-rated quality of life (i.e. WHOQOL scales) demonstrated no significant group × time interactions for physical health ($F(1,32) < 0.01$; $P = 0.95$), psychological health ($F(1,32) = 0.47$; $P = 0.50$), social relationships ($F(1,32) = 0.36$; $P = 0.55$) or environment ($F(1,32) = 0.12$; $P = 0.73$). Instead, the analysis of variance only revealed a significant main effect of group on quality of life concerning social relationships ($F(1,32) = 4.27$; $P = 0.047$; $\eta p^2 = 0.12$). Concretely, the ABP group (mean 73.53, 95% CI 65.85 to 81.21) reported higher quality of life than the CBP group (mean 62.50, 95% CI 54.82 to 70.18).

Correlation analysis

A detailed matrix of Pearson correlations between time point 0 to time point 1 difference scores of primary and secondary outcome parameters is depicted in Fig. 3. In both groups, positive correlations were found between changes in observer- and self-rated ADHD symptom severities ($r_{CBP} = 0.64$, $P_{CBP} < 0.01$; $r_{ABP} = 0.59$, $P_{ABP} < 0.05$), and between changes in DASS-21 scores for symptoms of depression and anxiety ($r_{CBP} = 0.70$, $P_{CBP} < 0.01$; $r_{ABP} = 0.62$, $P_{ABP} < 0.01$). In the CBP group, *inter alia*, DASS-21 difference scores for depression symptoms were further positively correlated with those of stress ($r = 0.56$, $P < 0.05$), and larger difference scores of stress ($r = 0.70$, $P < 0.01$) and depression ($r = 0.56$, $P < 0.05$) were

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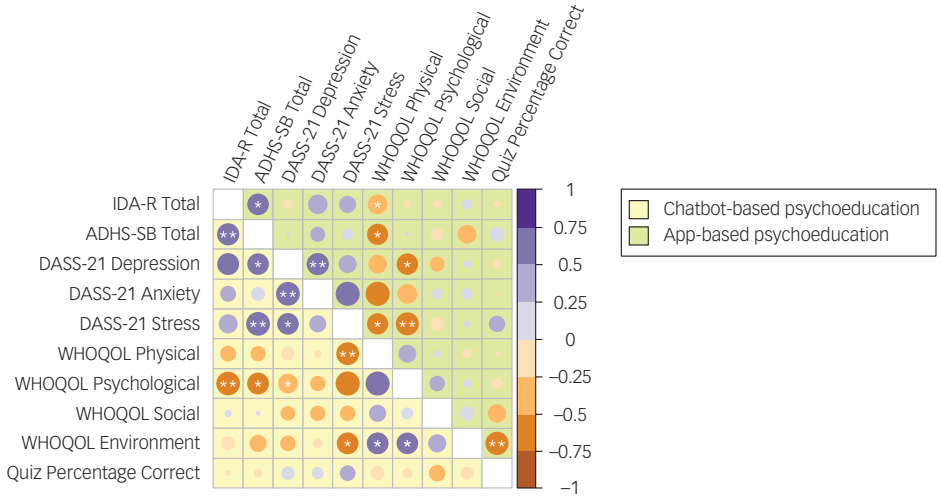

Fig. 3 Correlation matrix of study outcome parameters. Pearson correlations (*r*) are depicted separately for the chatbot-based psychoeducation group (below the diagonal, in yellow) and the app-based psychoeducation group (above the diagonal, in green). Correlations between difference scores of observer-rated (IDA-R total score) and self-rated (ADHS-SB total score) ADHD symptoms; symptoms of depression, anxiety and stress (separate DASS-21 subscale scores); quality of life (separate WHOQOL subscale scores for physical health, psychological health, social relationships and environment) and psychoeducational content knowledge (percentage of correct quiz responses) are presented. Except for percentages of correct quiz responses, analyses were based on difference scores from time point 0 to time point 1. ADHD, attention-deficit hyperactivity disorder; ADHS-SB, ADHD Self-Assessment Scale; DASS-21, Depression, Anxiety and Stress Scale; IDA-R, Integrated Diagnosis of ADHD in Adulthood; WHOQOL, World Health Organization Quality of Life questionnaire. $^{*}P < 0.05$, $^{**}P < 0.01$.

associated with larger difference scores of self-rated ADHD symptoms.

Study drop-outs and adverse events

In each group, three participants did not complete the study for unknown reasons, as a reestablishment of contact was unsuccessful. However, no unintended consequences or adverse events related to any intervention were reported.

Discussion

In this RCT, we examined the efficacy of self-guided digital psychoeducation for adults with ADHD. Specifically, we compared a newly developed chatbot with a previously validated psychoeducation app in addressing ADHD symptoms in a 3-week psychoeducation. A total of 34 participants completed the study and, although both interventions yielded strong effects in the reduction of ADHD core symptoms, neither proved superior.

Effects of digital psychoeducation on ADHD core symptoms

The symptom improvements found across intervention groups were evident in both observer ratings (approximately 22%) and patient ratings (approximately 15%), with underestimates of self-rated effects being a common finding in adult ADHD, according to a previous meta-analysis.[40] However, although these results appear promising, it has to be considered that the two interventions in this study were not compared with further control conditions (e.g. a waiting list group). Therefore, we cannot completely rule out potential improvements caused by incidental treatment effects independent of our specific interventions.

Notably, in the current study, we find similar effect sizes in terms of ADHD symptom reductions as in our previous app study.[22] However, although we previously assessed our conventional psychoeducation app in combination with an 8-week psychoeducation group, in the current study, we tested the app and the chatbot as self-directed psychoeducation approaches without face-to-face meetings or involvement of clinical experts in the treatment process. Therefore, although we earlier demonstrated the effectiveness of a psychoeducation app as an adjunct to a group intervention, here, we provide first evidence that ABP or CBP for adults with ADHD may also be effective in a self-guided setting without continuous clinical supervision.

Regarding symptom-specific effects, our analyses revealed significant and strong effects on observer-rated inattention, hyperactivity and impulsivity, as well as self-rated inattention and hyperactivity across intervention groups. These results contrast with the only other study that examined a psychoeducation chatbot in individuals with attention deficits, which primarily found significant improvements in impulsivity symptoms compared with reading a self-help book, but no improvements in inattention and hyperactivity in their per-protocol analysis.[24] However, their generalisability may be limited given that they did not include patients with ADHD and only included individuals with attention deficits regardless of psychiatric diagnosis. Still, a recent pre–post feasibility study of a conventional mHealth app for CBT psychoeducation found that adults with ADHD viewed the content delivered via an app positively, and self-reported a decrease in ADHD symptoms after 7 weeks of use.[41] Also, our results are generally consistent with other psychoeducation studies in adult ADHD, in which all core symptoms improved after the intervention.[12,13]

Psychoeducational knowledge and secondary outcome evaluation

The evaluation of psychoeducational knowledge transfer showed similar results in terms of knowledge acquisition and content

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completion in both groups. This is contrary to our expectation, as we hypothesised that a greater emphasis on interaction and the individual selection of topics associated with the use of the chatbot would lead to a greater increase in psychoeducation content knowledge compared with the use of the conventional app. Yet, it is also conceivable that greater involvement and constant interaction may have instead led to a decreased learning capacity in patients with ADHD that overshadowed potential positive effects of individual learning pathways. Future psychoeducation research should additionally focus on the patients' specific learning styles.

Further secondary outcomes included changes in depression, anxiety, stress and quality of life. In line with our previous study,[22] which yielded improvements in ADHD core symptoms, but not in secondary outcomes (e.g. depression and functional impairments), we found no enhancement in any secondary outcome in the present study. Although we used narrow inclusion criteria for affective disorders in both our studies and therefore did not expect great reductions in depressive symptoms, improvement in quality of life was particularly anticipated based on previous, non-digital psychoeducation in ADHD.[12,13] One explanation for this difference could be that in these studies, quality of life was considered as health-related rather than global, as was done in this study by using the WHOQOL. In addition, our correlation analysis found that symptoms of ADHD and symptoms of depression and stress, as well as subdomains of quality of life, generally correlate well with each other. In particular, the health-related subdomains of the WHOQOL (i.e. physical and psychological health) were correlated with changes in other symptom scores. Hence, despite not finding time effects across groups, improvements in ADHD symptoms may be associated with improvements in other secondary domains. As this has relevance for clinical application, future research should target this issue and investigate the extent to which there are potential deviations from non-digital psychoeducation.

In general, both groups reported no adverse events or unintended consequences and had equal drop-out rates. As mentioned above, the chatbot was more prone to technical errors. Consequently, in this study, the conventional psychoeducation app appeared to have advantages in terms of overall usability. Given the similar clinical efficacy, this may also illustrate the potential therapeutic benefit that a more individualised approach, such as a chatbot, could have if the technical foundation allows for a flawless and natural flow of conversation. On the other hand, there is the possibility that the preferred method of content delivery, and ultimately the clinical efficacy, also depends on individual patient characteristics. For example, patients who have no prior experience with psychoeducation may prefer an app that offers a more structured format, whereas more experienced patients may have specific questions and interests that can be addressed more efficiently with a chatbot.

Limitations and future directions

This study has some limitations. First, the total duration of interventions was rather short and could therefore be responsible for the lack of improvements in secondary outcomes. In particular, changes in quality of life could possibly be perceived in a delayed manner. Second, for technical reasons, we could not limit the duration of app use to precisely 3 weeks. As a result, the average duration of app access was approximately 1 day longer in the ABP group than the CBP group. We assume only minor implications, as completing the amount of psychoeducational content was manageable within the intervention period. Moreover, we were technically unable to measure the exact amount of time each participant spent using the app. Future research should incorporate these measurements, as they may provide important insights into the behaviour of patients with ADHD. Third, although the conventional app worked without errors, the chatbot had some technical issues in one of the modules that eventually led to the exclusion of this module from the analysis and may have resulted in fewer symptom improvements, as well as negative associations with CBP among affected participants. Chatbots appear particularly susceptible in this regard, and conducting pilots with a wide range of devices is recommended. Fourth, the chatbot was compared with an active control intervention that had only been validated once, along with group psychoeducation. Further evaluation of the chatbot against a traditional group psychoeducation or treatment as usual is recommended. Finally, the relatively moderate sample size may have contributed to the failure to detect certain effects, which also complicates more detailed subgroup analysis. However, with respect to the primary end point, we assume that none of the interventions proved superior, given that effect sizes were considerably small.

Overall, taking into account the similar outcome of the digital psychoeducation forms examined in this study, a chatbot may offer the greater potential for development, especially considering the current pace of innovation in the non-clinical chatbot market. Future research should also focus on the implementation of different add-ons that might help patients organise their personal digital psychoeducation, such as notifications that provide exercise reminders and recap psychoeducational content to help deepen knowledge.[14] In addition, specific participant characteristics that might affect treatment outcomes should be examined, as, for instance, different age groups might have different preferences regarding usability and content presentation, or education level might be related to certain preferred learning styles. In addition, the generalisability of the present results may be limited by the above-average educational level of the sample, which should be addressed in future studies.

In conclusion, we found both a conventional module-based psychoeducation app and an interactive chatbot to be safe, feasible and effective for self-guided psychoeducation, although neither can be favoured based on the present findings. Strong effects on ADHD core symptoms were observed, providing a first step toward implementing these scalable and cost-effective applications in clinical practice; for instance, to provide treatment during therapy waiting times or as an augmentation to medication. Secondary outcome effects, such as on symptoms of depression, anxiety and stress and quality of life, need to be given stronger consideration in the further development of digital psychoeducation, as they did not improve in this study.

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Supplementary material

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Data availability

The data that support the findings of this study are available on request from the corresponding author, B.S. Sharing with third parties requires approval.

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Author contributions

B.S., M.S., T.W., S.B., S.L., A.P. and N.B. conceived the study. B.S. and N.B. were responsible for the study methodology. B.S., M.R. and B.A. conducted data collection. B.S., K.K. and A.W. were responsible for formal analysis. B.S. and N.B. conducted data interpretation. B.S., M.R. and N.B. drafted the manuscript. M.S., B.A., K.K., A.W., T.W., S.B., S.L. and A.P. reviewed and edited the manuscript. S.L., A.P. and N.B. supervised the study. All authors read the final manuscript, approved its submission and agreed to take responsibility for the integrity and veracity of the work.

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3.3 Publication 3: Gaze-based attention refocusing training in virtual reality for adult attention-deficit/hyperactivity disorder

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RESEARCH

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Gaze-based attention refocusing training in virtual reality for adult attention-deficit/hyperactivity disorder

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Abstract

Background Attention-deficit/hyperactivity disorder (ADHD) is characterized by substantial interindividual heterogeneity that challenges the systematic assessment and treatment. Considering mixed evidence from previous neurofeedback research, we present a novel feedback system that relies on gaze behavior to detect signs of inattention while performing a neuropsychological attention task in a virtual seminar room. More specifically, an audiovisual feedback was given whenever participants averted their gaze from the given task.

Methods Eighteen adults with ADHD and 18 healthy controls performed a continuous performance task (CPT) in virtual reality under three counterbalanced conditions in which either gaze-based feedback, sham feedback, or no feedback was provided. In all conditions, phases of high and low virtual distraction alternated. CPT errors and reaction times, proportions of gaze dwell times (e.g., task focus or distraction focus), saccade characteristics, EEG theta/beta ratios, head movements, and an experience sampling of ADHD symptoms were analyzed.

Results While patients can be discriminated well from healthy controls in that they showed more omission errors, higher reaction times, higher distraction-related dwell times, and more head movements, the feedback did not immediately improve task performance. It was also indicated that sham feedback was rather associated with an aggravation of symptoms in patients.

Conclusions Our findings demonstrate sufficient suitability and specificity for this holistic ADHD symptom assessment. Regarding the feedback, a single-session training was insufficient to achieve learning effects based on the proposed metacognitive strategies. Future longitudinal, multi-session trials should conclusively examine the therapeutic efficacy of gaze-based virtual reality attention training in ADHD.

Trial registration drks.de (identifier: DRKS00022370).

Keywords Virtual reality, Eye-tracking, ADHD, Adults, Attention training, Treatment, Therapy, Continuous performance task, Distractors, Self-regulation, Metacognition, EEG

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Introduction

With an estimated prevalence of 5% [1, 2], attention-deficit/hyperactivity disorder (ADHD) is the most common mental disorder in childhood. It is characterized by pervasive patterns of inattention, hyperactivity, and impulsivity that interfere with functioning [3]. In

adults, the global prevalence is estimated at 2.58% [4] and symptoms of inattention are most pronounced [5]. Considerable psychosocial and health economic implications have been reported [6], particularly given the wide range and high rate of comorbidities associated with adult ADHD [7].

Stimulants are recommended as a first-line treatment in ADHD [8], whereas cognitive behavioral therapy is recommended in cases of low treatment benefit of medication or mild symptomatology. However, both treatment modalities have limitations. In adults, psychostimulants are reported to have mean response rates of only about 60% and are less effective and less well tolerated than in children and adolescents [9, 10]. Additionally, psychostimulant treatment responses have been found to depend on individual symptom profiles [11], might relate to genetic factors [12] and, while the risk of serious harm is considered low, some adverse effects have been reported [13, 14]. Psychotherapeutic interventions, in turn, are often restricted to cognitive behavioral approaches that improve coping mechanisms for ADHD symptoms and related difficulties [15], but address ADHD core symptoms less directly.

Moreover, ADHD is a disorder with substantial heterogeneity in clinical profiles, neurocognitive impairments and treatment responses [10, 16]. Consequently, a systematic review highlighted the need to integrate multilevel information for an effective exploration and treatment of the varying degrees of dysfunction and their respective symptom expression [17]. Given that treated patients with ADHD still report considerable burden of their symptoms in everyday life [18, 19], the development of more effective and specific therapeutic approaches is needed. Two relatively new treatment approaches, computerized cognitive training (CCT) and neurofeedback, thereby intend to directly target cognitive dysfunction associated with ADHD.

CCT aims to enhance various cognitive functions such as attention, reaction speed, or behavioral inhibition through repetition of computer-based cognitive tasks. Most of these trainings have been developed for children and adolescents with ADHD [20, 21] but almost none for adults [22]. In the few cognitive training programs available for adults with ADHD, effects were either not superior to an active control group or could not be generalized beyond performance enhancements within the specific training paradigm [23, 24]. This may be linked to the concept of CCTs often being developed to directly address neuropsychological symptoms, rather than to create awareness of environmental triggers and the specific consequences. Specifically, cognitive tasks for the treatment of ADHD often address the patients' difficulties in sustaining attention, but few focus on impairments in the metacognition of attentional functions or deficits in self-regulation, such as recognizing attentional misdirection and dealing with limited attentional capacity [25, 26].

Another underlying cause for the insufficient evidence for CCT in adult ADHD might derive from its abstract nature and lack of transferability to real-world situations, especially since the neuroscientific foundation of cognitive training appears well-grounded. Until now, CCT has been delivered almost exclusively on classic computer screens. Therefore, given the higher achievable degree of perceived realism and ecological validity, it would be of particular interest to offer CCT by using virtual reality (VR). VR is defined by the capability of a seemingly real user interaction with computer-generated simulations of an environment. A recent systematic review of neuropsychiatric rehabilitation based on cognitive training in fully immersive VR provided some promising evidence of its cognitive benefits [27].

In neurofeedback, in turn, a cognitive task is performed and real-time feedback on some specific aspects of one's own, otherwise covert, brain activity is simultaneously received [28]. Repeated training is thought to result in an increase in the ability to modify one's own brain signal and to thereby improve cognitive functioning. While various EEG-based [29], fMRI-based [30] and fNIRS-based [31] protocols have been developed for neurofeedback application, a modulation of the theta/beta ratio (TBR) in EEG is often the therapeutic objective in ADHD [32, 33].

In summary, however, although the general concept appears plausible, the existing evidence for neurofeedback is inconsistent, particularly with respect to long-term improvements in clinical outcomes of adult ADHD [29]. One of the contributing factors seems to be the unsolved issue of which brain signal should be considered for feedback and from which brain modality it should best be derived [28, 33]. In addition, various technological shortcomings such as the relatively low signal-to-noise ratio of EEG, the sensitivity of fMRI to motion artifacts and the rather low temporal resolution of fNIRS hinder the optimal implementation of neurofeedback. Moreover, while state-of-the-art neuroscientific research methodology provides a valid foundation for measures of attention [34] and ADHD symptoms have been differentiated for adulthood and characterized in detail [35], a gap remains for treating attention disorders at the clinical level. Therefore, interventions based on valid assessment methodology that explicitly aim at inattention behavior by initiating metacognitive learning processes, e.g., by improving attentional modulation, might be a promising approach to improve attentional dysfunction.

Conceivable advancements in the treatment of dysfunctional metacognition and self-regulation in ADHD

might be achieved through eye-tracking, which features a high temporal resolution, a comparatively good signal-to-noise ratio and a user-friendly, unobtrusive application. While unlike in EEG, fMRI, or fNIRS, no measures of brain activity are captured directly, the objective quantification of eye movements is of particular value in the field of attention research [36, 37]. In this context, it is highly useful that humans are naturally inclined to pursue shifts in overt attention, i.e., physically directing their eyes to stimuli [38]. In ADHD, oculomotor inhibition, i.e., the ability to select relevant information and to reflexively suppress attending irrelevant or distracting stimuli, has been discussed as a potential biomarker of the disorder [39].

The assessment of eye movement behavior in ADHD is often conducted during the performance of a neuropsychological attention task, such as the continuous performance task (CPT). Here, participants must react upon infrequent target stimuli and withhold their responses to frequent non-target stimuli [40]. Adults with ADHD were found to gaze more at task-irrelevant areas than healthy individuals while performing a CPT during concurrent presentation of distractors [41]. While such distractibility is considered bottom-up driven, i.e., by environmental stimuli, mind wandering is a spontaneous, unintentional shift away from a task toward internal thoughts [42]. Spontaneous mind wandering is associated with increased functional impairments in ADHD [43] and has led to variations in eye movement behavior during attentional task performance in healthy individuals [44, 45]. Therefore, for the systematic detection and subsequent feedback provision that renders the awareness of both types of inattention, gaze tracking during a CPT may be a promising approach.

Consequently, the aim of this study was the development and evaluation of what is, to our knowledge, the first gaze-based attention refocusing training in virtual reality (GART) for patients with ADHD. This system builds upon existing CCT and neurofeedback principles, but is intended to specifically target metacognitive and self-regulatory functions. More specifically, we applied our developed virtual seminar room (VSR) [46], and extended it with a gaze-based feedback system that intervenes each time a person stops attending a VSR-embedded CPT (see Fig. 1). To evaluate this GART, 18 adult patients with ADHD and 18 healthy controls (HC) performed our virtual CPT (including alternating phases of additional distraction) in three counterbalanced feedback

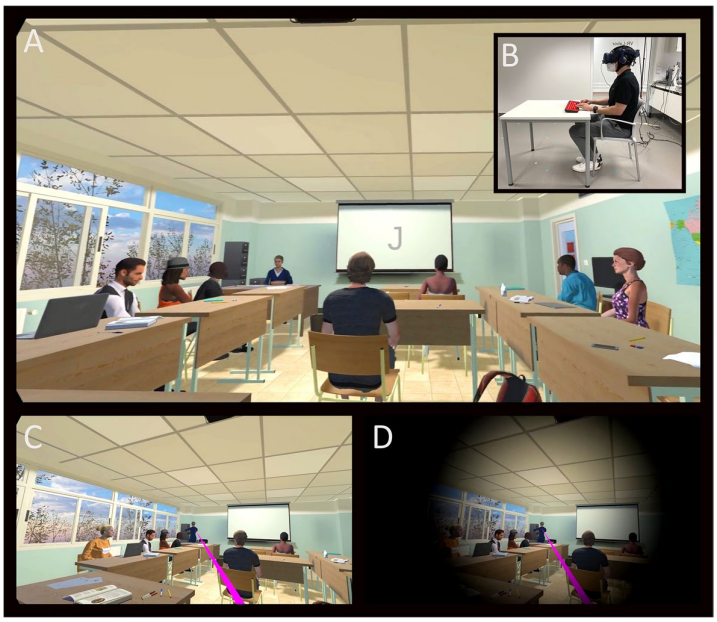

Fig. 1 The virtual seminar room (VSR) into which the participants immersed via a head-mounted display. **A** First-person view of the virtual seminar room in which the continuous performance task is presented on the canvas at the front wall. **B** Real world side view of participant in the virtual reality lab. **C** One of the distractor events played during a distractor phase: avatar in the front is standing up and walking to a cabinet, thereby attracting the attention of the participant as indicated by the visualized pink gaze vector (not visible for study participants). **D** Gaze-based feedback provision. Whenever the participant's gaze shifted away from the canvas for more than 2 s or the gaze was directed at a distractor for at least 0.5 s, audiovisual feedback was automatically played (combined black fade-in and sound effect). For a video presentation of this feedback, see Supplementary Material 1

conditions: a *real feedback* condition, in which audiovisual feedback was given as soon as participants averted their gaze from the task-relevant canvas; a *sham feedback* condition, in which the feedback was triggered with a quasi-random delay; and a *no feedback* condition in which no feedback was given at all. A multimodal offline evaluation of CPT performance measures, psychophysiological measures (eye movements, EEG, head actigraphy) and subjective ratings was conducted.

Methods

Participants

The study was advertised via the adult ADHD specialist outpatient clinic of the Department of Psychiatry and Psychotherapy of the University Hospital Bonn and via publicly accessible media. Of 40 participants who entered the study between February 2021 and August 2021, 36 completed the participation (for the participant flow, see Fig. 2). To be eligible, participants had to be between 18 and 65 years of age, have normal or corrected-to-normal vision, adequately understand the study content and language, not be pregnant, not have epilepsy, not have oculomotor atypicalities, and not have rashes on the scalp. Moreover, all participants assigned to the ADHD group had to meet the DSM-5 diagnostic criteria for ADHD as assessed with the revised, German version of the Clinical Interview for the Integrated Diagnosis of ADHD in Adulthood (IDA-R) [3, 47]. Additionally, they had to be free of a schizophrenia spectrum disorder, severe affective disorder, antisocial personality disorder, or moderate-to-severe substance abuse. Also, participants had to discontinue taking their ADHD medication 48 h before the experiment. Healthy participants, in turn, were ineligible if they had a psychiatric diagnosis as mentioned above or a diagnosis of ADHD. Therefore, before study participation, all potential participants were screened with the Brief Diagnostic Interview for Mental Disorders (Mini-Dips-OA, German version) [48] and the Assessment of DSM-IV Personality Disorders (ADP-IV, German version) [49].

The study was conducted in accordance with the Helsinki Declaration as revised in 2013, and approved by the local medical ethics committee of the University of Bonn (protocol number: 297/20). A required sample size of 36

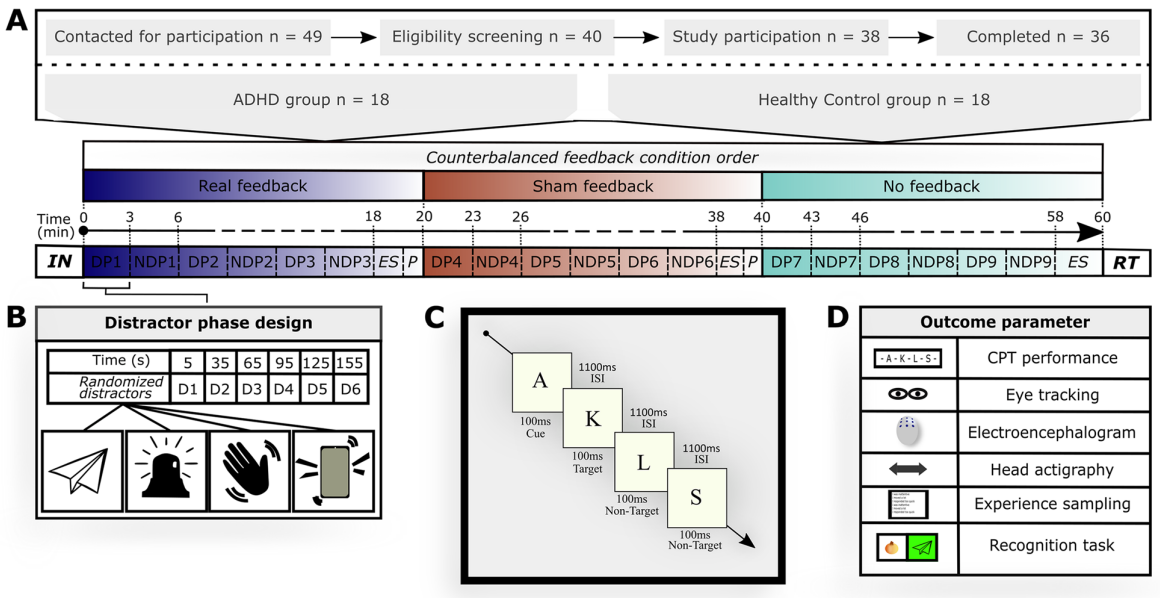

Fig. 2 Participant flow and experimental design. **A** 36 participants underwent all three feedback conditions in counterbalanced order on experiment Day 2. First, instructions were shown and a short continuous performance task (CPT) trial block was run. Then, the task block started, combined with either the real feedback, sham feedback, or no feedback. Following each 18-min CPT block, participants underwent experience sampling (ES) and a short break (P). Within each feedback block, time phases with distracting events (DP) and phases without distracting events (NDP) were alternated in three-minute cycles. At the end of the experiment, the VRSQ was completed and a recognition task (RT) regarding presented distractors was conducted. **B** Distractor phase design. Audio, visual, or audiovisual distractors were presented every 30 s during DP. **C** Implementation of the CPT. The CPT was presented on a canvas with a stimulus interval of 100 ms and an interstimulus interval of 1100 ms. **D** Outcome parameters of the study. *Abbreviations:* ADHD: Attention-deficit/hyperactivity disorder, ES: Experience sampling, D: Distractor, DP: Distractor phase, HC: Healthy control, ISI: Interstimulus interval, NDP: Non-distractor phase, P: Pause, RT: Recognition task, VRSQ: Virtual Reality Sickness Questionnaire

participants was revealed by an a priori sample size calculation in G*Power [50], based on an alpha error probability of 0.05, a power of 0.9 and a moderate effect size. Written informed consent was obtained from all participants. Information that could identify participants is not published. For compensation, participants had the opportunity to enter a draw (2 × 50 €). The trial was preregistered in the German WHO primary registry DRKS on 01–12-2020 (identifier: DRKS00022370).

Study design

The study was designed as a two-armed controlled trial, in which two groups (patients with ADHD, HC) received three feedback conditions in counterbalanced order: real feedback, sham feedback, and no feedback. The real feedback condition thereby served as the main intervention of interest, during which audiovisual feedback was triggered as soon as an eye-tracked gaze behavior was registered that indicated a loss of task focus (details below). The sham feedback and no feedback conditions, in turn, served as control conditions. Whereas in the sham feedback condition, the same type of audiovisual feedback was provided as in the real feedback condition, except that here the feedback was provided with a quasi-random delay (20—30 s) after inattention registration, the no feedback condition provided no feedback at all. Otherwise, all three conditions were identically structured: Participants were immersed into the VSR, i.e., a virtual testing environment of high ecological validity for the multimodal assessment of ADHD-associated symptoms, and performed a CPT while distracting events occurred. Participants were blind to which CPT block represented which condition, but were informed that feedback could appear at any time and in any condition.

Study participation was scheduled over two days: Day 1 served for the eligibility testing and clinical characterization of our participants and was conducted online as a result of COVID-19 restrictions for some participants. Day 2 included the experiment and occurred at the virtual reality laboratory of the Department of Psychiatry and Psychotherapy of the University Hospital Bonn. The total duration was approximately 1.5 h and 2.5 h for Day 1 and 2, respectively.

Clinical characterization

ADHD symptoms were evaluated based on both the observer-rated clinical interview IDA-R [47] and the self-rating behavior questionnaire ADHS-SB [51]. Moreover, the World Health Organization Quality Of Life questionnaire (WHOQOL) [52] and the Depression, Anxiety and Stress Scales (DASS) [53] were completed for further clinical characterization. Demographic data were collected with a lab-internal questionnaire.

Experimental procedure and virtual environment

The experimental procedure on Day 2 was as follows: First, participants were prepared for the EEG recordings, before they were seated at a 1 × 1 m table with a keyboard in front of them. Next, the head-mounted display (HMD) was placed on the participants' heads. The HMD used was the HTC Vive Pro Eye (HTC Corporation, Taoyuan City, Taiwan), which has 1440 × 1600 pixels per eye image resolution, a 90 Hz screen refresh rate, a 110-degree field of view and an embedded eye-tracking system. Immersed into the VSR, participants found themselves seated at a virtual table from where they could follow the VSR scenery from a first-person perspective (cf. Fig. 1). Besides the canvas, which was located at the front of the VSR and on which the CPT was presented, typical seminar room equipment and animated study mates were included. The VSR has been self-assembled by our lab using Unity 3D 2019.1.10f1 (Unity Technologies, San Francisco, CA, USA) and C# based on pre-existing assets (e.g., 3D Everything's School Classroom which is available in the Unity Asset Store). Its complete functionality and validation has previously been described in detail [46]. After the participants had briefly accustomed to the virtual environment, a short calibration sequence for the eye-tracking system followed, before a first trial run of the ensuing CPT task was conducted. Next, the three feedback conditions were run, with two-minute breaks and recalibrations of the eye-tracker between each condition. All three conditions consisted of performing a CPT for 18 min (cf. section continuous performance task), while additional distractor events occurred (cf. section implementation of distracting events) and, if applicable, audiovisual feedback was given. Each condition ended with an experience sampling, in which the participants were briefly surveyed about their subjective experiences via a VR-embedded survey tool. In addition, after all CPT blocks were completed, the Virtual Reality Sickness Questionnaire (VRSQ) [54] was presented, before participants removed the HMD. In total, participants remained in the virtual environment for about one hour. Finally, participants completed a recognition test regarding perceived distractor stimuli during the virtual experiment via a desktop screen.

Continuous performance task

The CPT was directly presented on a canvas at the front wall of the VSR (cf. Fig. 1). Specifically, a sequence of single letters was presented centrally and iteratively on the canvas, with a stimulus duration of 100 ms and an interstimulus interval of 1100 ms, resulting in 900 trials per block. The task required pressing a key as quickly as possible when a "K" was shown after an "A", while withholding the response for any other sequence

of letters. Compared to our previous VSR study [46], in which we found a ceiling effect (i.e. a very low error rate), a faster stimulus sequence was applied by decreasing the interstimulus interval by 800 ms. In each CPT block (i.e. each condition), 30% target sequences and 70% non-target sequences were presented. Of the latter, 50% were pseudo-targets containing only one of the two target letters. For analysis, reaction times (in ms) of all responses, commission errors (as an estimation of impulsivity) and omission errors (as an estimation of inattention) were derived.

Implementation of distracting events

Each CPT block (i.e., condition) was further divided into alternating distractor phases (DP) and non-distractor phases (NDP), with each of these phases lasting three minutes. Whether a CPT block started with a DP or NDP was counterbalanced across participants. During an NDP, the seminar room was presented unchanged. During each DP, a total of six different visual, auditory, and audiovisual distractors were randomly selected (from a pool of 18 visual, 18 auditory, 18 combined audiovisual distractors) and presented in intervals of 30 s. The distractors represented events with high everyday relevance, such as a smartphone ringing or birds flying past the window and were widely balanced (28:26) in terms of their content reflecting a social (e.g., a person entering the room) or non-social (e.g., a passing fire truck) context.

Eye-tracking recording

Eye movements were recorded with a sampling frequency of ~ 50 Hz via the infrared-based Tobii eye-tracker (Tobii Technology, Stockholm, Sweden) built into the HMD. The eye-tracker has an accuracy estimation of 0.5°—1.1° and allows the additional wearing of glasses, which was required in 39% of patients and 11% of healthy participants. Participants were asked not to wear any eye makeup. Eye-tracking data were recorded by a combination of three different software packages: SRanipal SDK version 1.3.1.1 (HTC Corporation, Taoyuan, Taiwan), Tobii XR SDK version 1.16.36.0 (Tobii Technology, Stockholm, Sweden), and Lab Streaming Layer (LSL; https://github.com/sccn/labstreaminglayer). SRanipal SDK provided access to the raw eye-tracking data within Unity. Tobii XR SDK was used to track the participant's momentary gaze focus on specific virtual objects within Unity. Technically, this tracking was realized by the SDK's *IGazeFocusable* interface that builds upon Unity's collider system and allows to register whenever a specified collider (3D object) is hit by a raycast representing the participant's gaze direction. Using this functionality, three different eye gaze states were defined and tracked:

- *Task focus:* The participant's gaze was fixed on the canvas on which the CPT was presented.
- *Distractor focus:* The participant's gaze was shifted to the collider of a 3D object, which was played as an animated distractor. In the case of purely auditory distractors, generous colliders were placed in the area where the sound source was located in the 3D environment.
- *Gaze wandering:* The participant's gaze was neither directed to the canvas nor to a distractor-related 3D object, but to somewhere else in the virtual space. Gaze wandering here is intended to provide an eye movement-based estimate of mind wandering.

For each recorded time stamp, only one of the three possible gaze direction states (excluding blinks) was thereby possible at a time. Finally, LSL was used to save the eye-tracking data along with the other data collected.

Implementation of the gaze-based online feedback

As stated, during both the real feedback and sham feedback conditions, audiovisual feedback was triggered whenever gaze locations indicated a loss of task focus. A loss of task focus was assumed as soon as a participant did not look at the canvas for more than 2 s or as soon as a participant gazed at a distractor for more than 0.5 s. In the real feedback condition, this resulted in an immediate provision of audiovisual feedback. In the sham feedback condition, an initial delay of 20—30 s was implemented before feedback initiation to ensure a similar frequency compared to the real feedback. The audiovisual feedback itself consisted of a 0.5 s black fade-in effect to a maximum of approximately 35% of the screen size combined with a chime-like sound effect (for a video presentation, see Supplementary Material 1). It was automatically stopped as soon as either the gaze was redirected to the canvas or 2 s passed. In addition, following feedback, there was a refractory period of 5 s during which no further feedback could be played to prevent over-extensive initiation of feedback.

Eye-tracking offline analysis

Eye-tracking offline analyses were conducted in Matlab 2021b (The MathWorks Inc., Natick, MA, USA). Detection of saccades and fixations was based on a custom Matlab script that implemented an adaptive data-driven algorithm for velocity-based detection (for details, see [55]). Specifically, the three-dimensional gaze coordinates of each eye were used to calculate sample-to-sample velocities and accelerations [56]. A second order Savitzky-Golay finite impulse response filter was applied for data smoothing [57]. Invalid data as indicated by the SRanipal validity score were discarded from analysis.

Interpolation across gaps of 75 ms maximum duration was performed linearly. Loss of data from one side was compensated using valid data from the other eye, and subsequently the data from both eyes were averaged. Implicitly detected fixations with a duration of less than 60 ms were discarded and fixations were merged on the basis of inter-fixation intervals of maximum 40 ms. Mean data loss was 2.75% (SD = 1.98%) per participant. For analysis, the average number of saccades and average saccade durations (in ms) were derived for each condition and phase.

The analysis of the gaze direction behavior, in turn, focused on the three gaze direction states, which were already online determined in Unity during the experiment and tracked by LSL. For statistical analyses, the following dwell times were separately derived for each group and each feedback condition and, additionally, a composite distractibility score was calculated:

$$Distractibility\ score = \frac{Time\ of\ distractor\ focus\ (in\ \%)\ +\ Time\ of\ gaze\ wandering\ (in\ \%)}{Time\ of\ task\ focus\ (in\ \%)}$$

A high distractibility score thereby indicates a high level of distraction.

EEG recording and analysis

The EEG was gathered via a wireless EEG system (Smarting®, mBrainTrain®, Belgrade, Serbia) and electrodes were placed by means of an EEG cap (EASYCAP, Herrsching, Germany) according to the 10–20 system and included 24 Ag/AgCl sintered ring electrodes: Fp1, Fp2, AFz, F3, Fz, F4, T7, C3, Cz, C4, T8, CPz, P7, P3, Pz, P4, P8, POz, O1, O2, M1, and M2, with the ground electrode (DRL) at FPz and the reference electrode (CMS) at FCz. With impedances kept < 10 kΩ, EEG data was digitized via LSL at a 500 Hz sampling rate and a 24-bit step-size resolution.

For the offline analysis, Matlab 2021b and EEGLAB 2021.0 [58] were used. First, the EEG datasets were temporally filtered between 0 and 35 Hz, detrended, and subsequently screened for noise in EEG channels. In each of 4 datasets, one noisy EEG channel was identified and replaced via spherical interpolation. Next, for calculating an independent component analysis (ICA), the continuous EEG data was epoched into 2 s time windows and non-stereotypic artifacts were removed using built-in EEGLAB functions. After that, an ICA was computed and components containing stereotypical artifacts such as ocular, cardiac, or muscle activity, were visually identified, backprojected to the continuous EEG data, and then rejected. The visual inspection of the components was thereby conducted by a trained EEG researcher and based on built-in functions of EEGLAB and focused on the components scalp topographies, spectral characteristics and time courses. The ICA-corrected continuous EEG datasets were cut into six separate subsets (either all DP or NDP within one feedback condition). Subsequently, every subset was epoched into as many non-overlapping five-seconds segments as possible, these segments were baseline corrected and all segments containing nonstereotyped artifacts were rejected. A continuous wavelet transformation was calculated on each retained segment for channel Fz. The time resolution amounted to 4 ms and the frequency range ranged from 0.1 to 35.0 Hz in 85 steps on a log scale. Finally, the average theta (4—7 Hz) and beta (13—30 Hz) power across segments was calculated between 0.5 and 4.5 s and the TBR was derived by dividing the theta power values by the beta power values.

Head actigraphy recording and analysis

Head movement as a measure of actigraphy was obtained from built-in positional tracking of the HTC Vive system. The Euclidean 3D coordinates were recorded via LSL with a ~ 90 Hz sampling rate. For offline analysis in Matlab 2021b, the raw data was first downsampled to ~ 10 Hz and then the Euclidean distances between each consecutive 3D position of the HMD were computed. Finally, the mean distances of head position shifts were obtained.

Experience sampling

After each feedback condition, a gesture-controlled user interface was provided to assess the participant's momentary ADHD core symptoms. The user interface showed up as a semi-transparent overlay directly within the VSR and evaluated the participant's symptoms of inattention, hyperactivity, and impulsivity on a 7-point Likert scale from -3 (no symptoms) to 3 (serious symptoms). Also, satisfaction with the GART and cybersickness via the VRSQ were inquired via this user interface.

Recognition task

After completion of the experiment, a recognition task was administered in which 60 visual or auditory distractors were shown. Of these, 50% represented actual distractors played during the experiment and 50% represented distractors that were unplayed. Upon each presented distractor, participants had to decide whether this distractor was encountered during the experiment, or not. The recognition accuracy, i.e., the proportion of

correct responses out of all possible correct responses, was derived for analysis.

Statistical analyses

Complete data sets were available for all variables except the recognition task, which was not completed by two participants. The corresponding analysis of the recognition task was based on the remaining complete data sets.

With regard to ANOVA assumptions, visual inspection of Q-Q plots and histograms indicated non-normally distributed data in some cases. However, no serious violations were detected, and given the robustness of ANOVAs to non-normality [59], analyses were continued as planned. Sphericity violations were adjusted with the Huynh field correction for $\varepsilon > 0.75$ and Greenhouse–Geisser corrections in the remaining cases (see Supplementary Material 2).

To investigate potential differences between groups, feedback conditions, and phases, separate $2 \times 3 \times 2$ mixed ANOVAs with the between-subjects factor Group (ADHD vs. HC) and the within-subject factors Feedback Condition (real feedback vs. sham feedback vs. no feedback) and Phase (DP vs. NDP) were carried out on commission errors, omission errors, reaction times, saccade durations, number of saccades, TBR values, and head movements. Moreover, 2×3 mixed ANOVAs (Group × Feedback condition) were conducted on gaze dwell time percentages (task focus, distractor focus, and gaze wandering), the composite distractibility score, and on the separate ADHD core symptom outcome scores of the experience sampling (inattention, hyperactivity, and impulsivity). Post-hoc comparisons were based on Bonferroni-adjusted t-tests. Independent samples t-tests were conducted to assess group differences with respect to VR-related cybersickness and satisfaction with the GART. Additionally, one-sample t-tests were carried out against "0" (moderate cybersickness/satisfaction) to determine differences from neutral responses. The accuracies of the recognition task were compared between both groups by using an independent samples t-test.

Finally, for an investigation of potential associations between measures, Pearson and Spearman's rank correlations with Benjamini–Hochberg corrected p-values were calculated separately for each group and feedback condition for several outcome parameters [60]. These included all previously described CPT and eye movement parameters, EEG theta power and beta power, head movements, the number of feedback triggered (except for the no feedback condition), and the ADHD total symptom scores as measured by experience sampling, the IDA-R, and the ADHS-SB. Age and education were the only demographic parameters evaluated.

All statistical tests were performed two-sided with a significance level of $\alpha = 0.05$. Due to the exploratory nature of this study, which, to our knowledge, is the first to implement such simultaneous recording of multimodal physiological and behavioral data streams in VR, and which is intended to act hypothesis-generating for future confirmatory trials, unadjusted p-values are presented (except for the correlation analyses) with respect to multiple testing [61, 62]. Analyses were performed in SPSS 21.0 (IBM Corp., Armonck, NY, USA), except for the correlation analyses, which were performed in Matlab 2021b (The MathWorks Inc., Natick, MA, USA) and R software 3.6.1 [63] and visualized by means of the Corrplot package for R version 0.84 [64].

Results

The detailed results of each ANOVA are summarized in Supplementary Material 2 (Supplementary Tables 1—5).

Sample characteristics

Overall, 18 adult outpatients with ADHD (6 females) and 18 HC (7 females) participated in the present study. All of them were recruited in Germany and identified as of White European ethnicity. Detailed sample characteristics are presented in Table 1.

CPT performance

The results of the behavioral CPT performance are depicted in Fig. 3 (A—C). No significant main effect of Feedback Condition or interactions between Phase, Feedback Condition and Group were detected for reaction times, omission errors or commission errors.

For omission errors, a significant main effect of Phase ($F(1,34) = 9.35$, $p = 0.004$, $\eta p^2 = 0.22$) was found, in that significantly more omission errors were made during DP ($M = 2.02$; 95% CI [1.11, 2.92]) compared to NDP ($M = 1.67$; 95% CI [0.90, 2.44]). Likewise, at least descriptively ($F(1,34) = 3.74$, $p = 0.061$, $\eta p^2 = 0.10$) more commission errors were observed during DP ($M = 1.19$, 95% CI [0.58, 1.80]) than NDP ($M = 1.00$, 95% CI [0.51, 1.49]).

Patients with ADHD and HC differed in omission errors ($F(1,34) = 5.57$, $p = 0.024$, $\eta p^2 = 0.14$) and reaction times ($F(1,34) = 4.37$, $p = 0.044$, $\eta p^2 = 0.11$). Across phases and feedback conditions, the ADHD group committed more omission errors ($M_{OE} = 2.81$, 95% CI [1.63, 3.99]) and had slower reaction times ($M_{RT} = 471.46$ ms, 95% CI [446.85, 496.07]) than the HC group ($M_{OE} = 0.88$, 95% CI [-0.30, 2.05]; $M_{RT} = 435.64$ ms; 95% CI [411.03, 460.26]).

Gaze behavior

To evaluate the participants' gaze behavior during CPT performance, four gaze direction parameters were

Table 1 Demographic and clinical characteristics

Characteristic	No. (%)		*p*-value[c]
	ADHD ($n=18$)	HC ($n=18$)	Group comparisons
Age, y (SD)	36.1 (10.7)	25.9 (3.1)	.001
Female	6 (33.3)	7 (38.9)	.73
Right handed	17 (94.4)	15 (83.3)	.60
Education			.027
≤ Intermediate certificate	6 (33.3)	0	
Higher education entrance qualifications	6 (33.3)	9 (50.0)	
Higher education degrees	6 (33.3)	9 (50.0)	
Full- or part-time employment	9 (50.0)	15 (83.3)	.075
Married or living with a partner	8 (44.4)	12 (66.7)	.32
IDA-R ADHD symptom severity, mean (SD)	33.6 (7.3)	7.4 (5.5)	< .001
Inattention	18.8 (3.1)	4.8 (3.6)	< .001
Hyperactivity	7.8 (3.6)	1.3 (1.8)	< .001
Impulsivity	6.9 (2.6)	1.2 (1.8)	< .001
ADHD presentations			
Predominantly inattentive	7 (38.9)		
Predominantly hyperactive-impulsive	0		
Combined presentation	11 (61.1)		
Current psychopharmacological treatments			
Methylphenidate/Amphetamine	11 (61.1)	0	< .001
Antidepressant	2 (11.1)	1 (5.6)	.55
Current comorbid psychiatric disorders[a]			
Affective disorders	0	0	
Anxiety disorders	8 (44.4)	2 (11.1)	.060
Other disorders	2 (11.1)	0	.49
Comorbid psychiatric disorders in remission[a]			
Affective disorders	12 (66.7)	2 (11.1)	.002
Anxiety disorders	4 (22.2)	0	.10
Other disorders	1 (5.6)	1 (5.6)	1.00
DASS depression score, mean (SD)	10.1 (1.7)	8.8 (4.2)	.24
DASS anxiety score, mean (SD)	10.6 (2.7)	8.6 (2.5)	.030
WHOQOL quality of life total score, mean (SD)[b]	59.6 (11.8)	80.6 (13.6)	< .001

DASS Depression Anxiety Stress Scales, *IDA-R* Integrated Diagnosis of ADHD in adulthood—Revised, *WHOQOL* World Health Organization Quality Of Life

[a] Assessed on the diagnostic short interview for mental disorders [48]. Note that current severe affective disorders were an exclusion criterion for study participation

[b] Total score calculated as the mean of the four subscales, transformed to range 0–100, with higher values indicating a higher subjective quality of life

[c] Results of independent-samples t-tests, respectively chi-squared tests, are reported

analyzed (cf. Fig. 3D - G): time of task focus, time of distractor focus, time of gaze wandering, and a composite distractibility score. For none of the four gaze direction parameters, a significant main effect of Feedback Condition or an interaction between Feedback Condition and Group was shown.

Instead, a significant group difference was found regarding the time of distractor focus ($F(1,34)=9.40$, $p=0.004$, $\eta p^2=0.22$), in that patients with ADHD spent more time (M = 1.86%; 95% CI [1.38%, 2.34%]) gazing at distractors than HC ($M=0.84\%$; 95% CI [0.36%, 1.32%]). Comparing the time of attending the canvas between the ADHD group ($M=86.35\%$; 95% CI [82.14%, 90.56%]) and HC ($M=91.81\%$; 95% CI [87.60%, 96.01%]), healthy individuals showed only descriptively a higher percentage ($F(1,34)=3.48$, $p=0.071$, $\eta p^2=0.09$). In line with these indications, there was also a trend for a higher distractibility composite score in patients compared with HC ($F(1,34)=3.68$, $p=0.064$, $\eta p^2=0.10$).

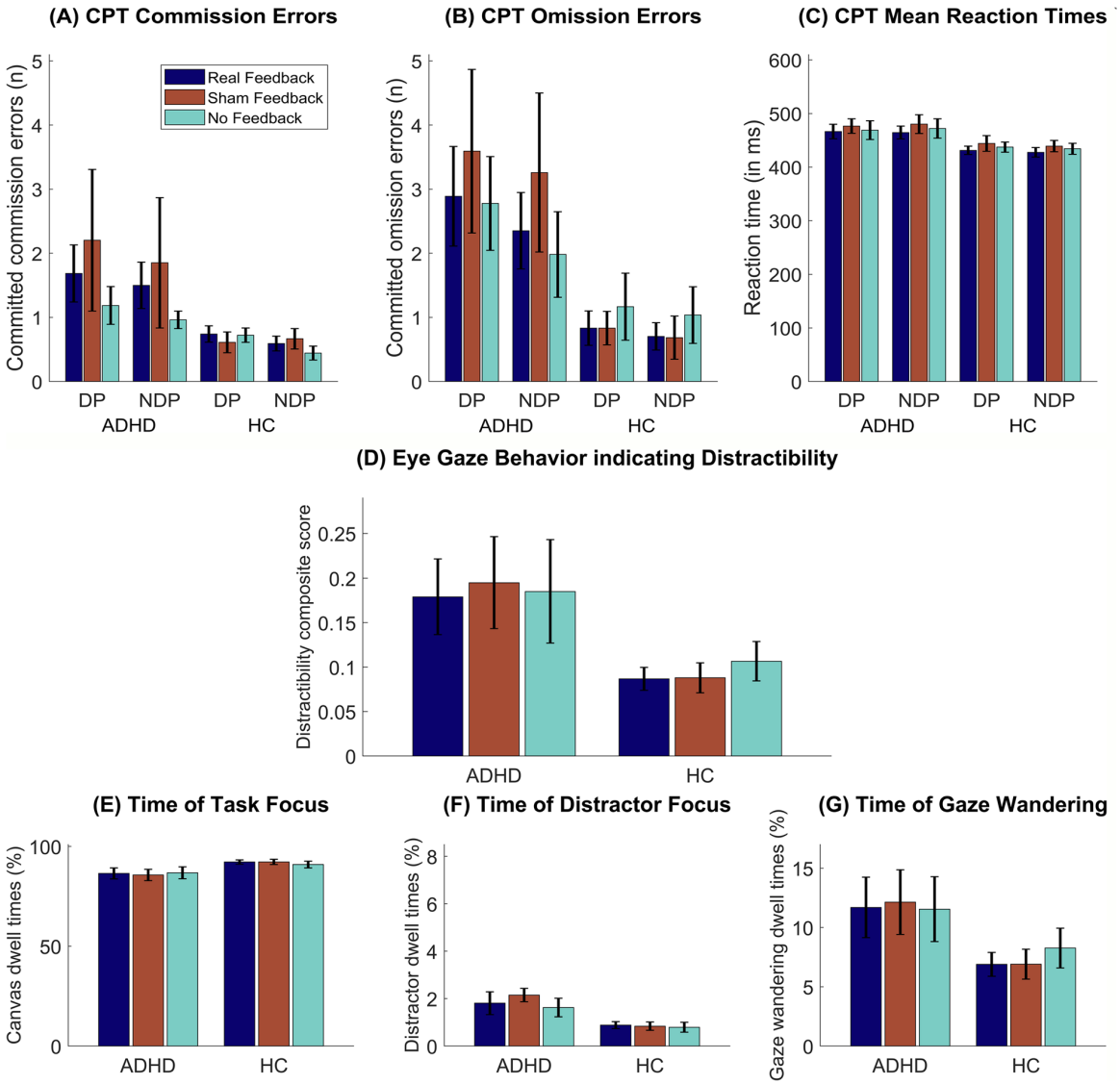

Fig. 3 Results of the continuous performance task (**A**—**C**) and gaze behavior analysis (**D**—**G**). The number of (**A**) commission errors, (**B**) omission errors and (**C**) mean reaction times are depicted for each feedback condition and both distractor phase types. **D** A composite distractibility score of the participants' gaze behavior is depicted. The score reflects the sum of (**F**) the time spent gazing on distractors and (**G**) gaze wandering, divided by (**E**) the amount of time participants were looking onto the canvas on which the continuous performance task was presented. **E** to **G** show relative times for each of the three derived gaze parameters. Bars represent feedback conditions and are grouped by patients with ADHD and HC. Error bars indicate the SEM. *Abbreviations:* ADHD: Attention-deficit/hyperactivity disorder, CPT: Continuous performance task, DP: Distractor phase, HC: Healthy control, NDP: Non-distractor phase

Saccade behavior

For the average duration and the number of saccades, the ANOVAs revealed no interactions, but showed longer ($F(1,34) = 11.73$, $p = 0.002$, $\eta p^2 = 0.26$) and a higher number of saccades ($F(1,34) = 13.87$, $p = 0.001$, $\eta p^2 = 0.29$) during DP than NDP. In addition, we found a higher number of saccades ($F(1,34) = 4.90$, $p = 0.034$, $\eta p^2 = 0.13$) but only descriptively longer saccade durations ($F(1,34) = 3.90$, $p = 0.057$, $\eta p^2 = 0.10$) in ADHD than in HC.

EEG

EEG analyses focused on spectral differences concerning the participants' TBR. Time–frequency power spectra of the conducted wavelet analyses are presented in

Fig. 4A and B, whereas the TBRs are depicted Fig. 4C. We found no significant main or interaction effects for Feedback Condition or Group, but a main effect of Phase ($F(1,34) = 18.02$, $p < 0.001$, $\eta p^2 = 0.35$), in that the TBR was higher during DP ($M = 1.07$; 95% CI [0.97, 1.18]) than NDP ($M = 1.05$; 95% CI [0.95, 1.16]).

Actigraphy

Actigraphy analyses focused on differences in head movements. While the ANOVA indicated a significant main effect of Feedback Condition ($F(2,68) = 3.58$, $p = 0.033$, $\eta p^2 = 0.10$), Bonferroni-adjusted post-hoc comparisons only yielded a trend ($p = 0.053$) toward more head movements during sham feedback compared to no feedback ($M_{Diff} = 0.20$; 95% CI [-0.002, 0.40]). We further found a significant main effect of Group ($F(1,34) = 16.06$, $p < 0.001$, $\eta p^2 = 0.32$), in that patients with ADHD exhibited more head movements ($M = 1.75$; 95% CI [1.41, 2.09]) than HC ($M = 0.80$; 95% CI [0.46, 1.14]).

Experience sampling

To determine the subjective experience of momentary ADHD symptomatology, a short experience sampling was conducted after each CPT block, in which the participants rated their levels of inattention, impulsivity and hyperactivity. For none of the three parameters, any significant main effect of Feedback Condition or interaction effect emerged. Nonetheless, we found significant group differences for symptoms of inattention ($F(1,34) = 19.57$, $p < 0.001$, $\eta p^2 = 0.37$), hyperactivity ($F(1,34) = 16.96$, $p < 0.001$, $\eta p^2 = 0.33$), and impulsivity ($F(1,34) = 8.76$, $p = 0.006$, $\eta p^2 = 0.21$), in that for all three ADHD symptoms higher ratings were observed in patients with ADHD than in HC.

The participants' VR-related cybersickness was rated significantly lower than "0" (moderate sickness) by means of the VRSQ ($t(35) = -2.76$, $p = 0.009$, $d = -0.46$). Groups did not differ significantly ($t(34) = 1.45$, $p = 0.156$, $d = 0.49$) and, on average, scores of -0.25 (95% CI [-0.88,

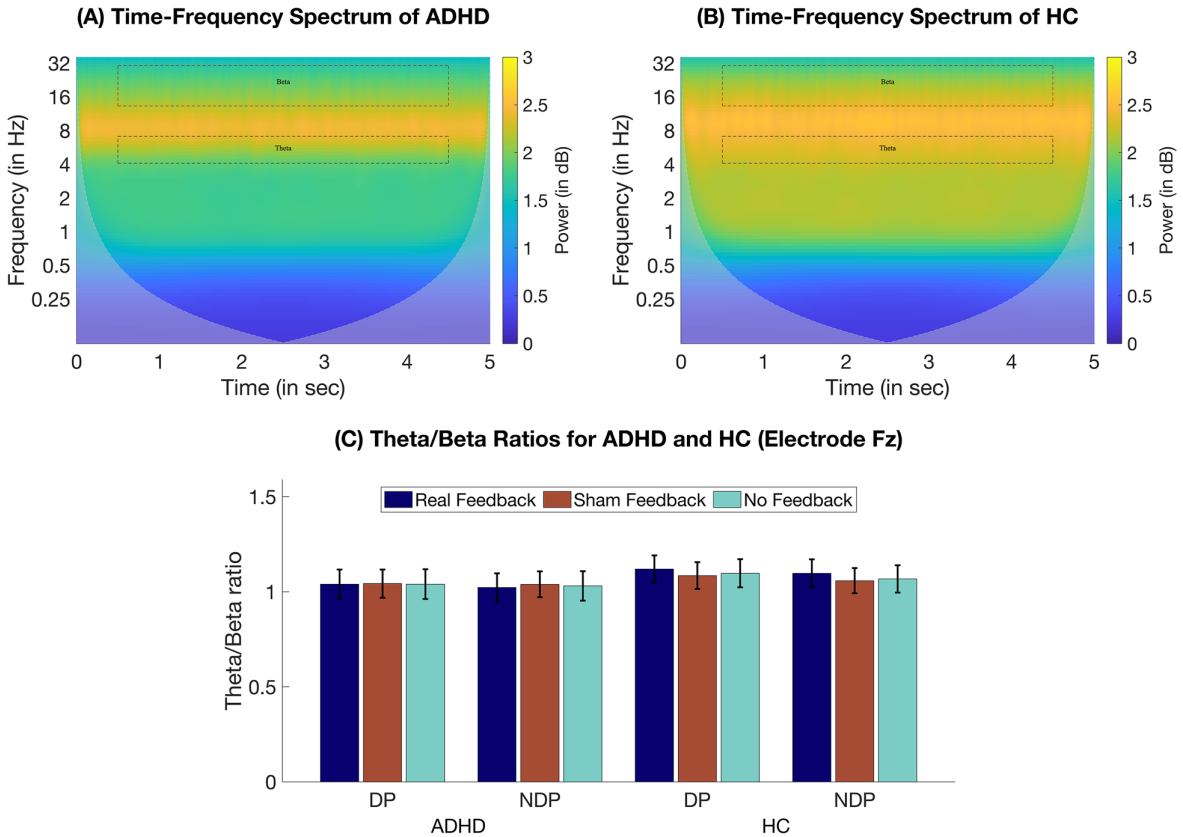

Fig. 4 EEG wavelet analysis. Time–Frequency spectra of the wavelet analysis for (**A**) patients with ADHD and (**B**) HC across feedback conditions and phase types at electrode Fz. Dashed squares indicate analyzed time windows of interest (0.5—4.5 s) and frequency ranges of interest (theta [4 -7 Hz], beta [13—30 Hz]). **C** Comparison of the theta/beta ratio power for each group and between distractor phases and feedback conditions. Error bars indicate the SEM. *Abbreviations:* ADHD: Attention-deficit/hyperactivity disorder, DP: Distractor phase, HC: Healthy control, NDP: Non-distractor phase

0.38]) in the ADHD group and -0.78 (95% CI [-1.25, -0.32]) in the HC group were obtained. In line with this, no adverse events were reported with respect to the VR experiment.

Additionally, the participants' satisfaction with the developed GART was reported to be significantly higher than "0" (moderate satisfaction) after the experiment ($t(35) = 3.62$, $p = 0.001$, $d = 0.60$). Patients with ADHD ($M = 1.56$, 95% CI [0.79, 2.32]) and HC ($M = 0.61$ (95% CI [-0.36, 1.58]) were similarly satisfied with their VR experience ($t(34) = 1.61$, $p = 0.116$, $d = 0.55$).

Recognition task

Of the 60 potential distractors shown to participants after the experiment as a recognition test, only 50% actually represented GART-implemented distractors. Patients with ADHD ($M = 70.46\%$; 95% CI [65.76%, 75.17%]) and HC ($M = 72.71\%$; 95% CI [68.96%, 76.46%]) classified the presented distractors with similar recognition accuracies ($t(32) = -0.78$, $p = 0.443$, $d = -0.27$).

Correlation analyses

Correlation matrices for several primary and secondary outcome parameters are depicted separately for groups and feedback conditions in Fig. 5. Correlation analyses across all feedback conditions revealed clusters of strong correlations within measurement domains (e.g. between time of task focus and time of gaze wandering). In ADHD but not in HC, saccade durations appeared to correlate positively with other physiological measures of inattention, such as CPT omission errors and gaze wandering, and negatively with times of task focus under various feedback conditions. Regarding EEG, the theta and beta power were positively correlated across feedback conditions and groups. Of note, participant age and education were included as the only demographic parameters and, besides a negative correlation between education and time of distractor focus in HC during sham feedback (Spearman's rank correlation, $r(34) = -0.76$, $p = 0.005$) and of education and number of saccades during real feedback ($r(34) = -0.68$, $p = 0.031$), no significant correlations with any parameter presented were observed.

Discussion

In the present study, we developed a new gaze-based attention refocusing training (GART) within a virtual seminar room (VSR) in which participants automatically receive immediate feedback whenever their eye gaze behavior indicates that their visual attention has shifted away from a continuous performance task (CPT). To evaluate the general feasibility and effectiveness of the GART, 18 adult outpatients with ADHD and 18 HC performed a CPT under three different feedback conditions (real feedback, sham feedback and no feedback) and under alternating phases of high (DP) and low distraction (NDP), while they simultaneously underwent a comprehensive multimodal assessment (neuropsychological performances, eye-tracking, EEG, head actigraphy, experience sampling).

Considering the potential of VR experiments to elicit cybersickness, the here presented GART showed promising results. More specifically, all participants completed the experiment without any interruptions caused by discomfort and no adverse events were reported. Consistent with this, there was substantial satisfaction with the VR experience, particularly in the ADHD group. Overall, we observed high tolerability and feasibility of this multimodal VSR evaluation concerning the application in healthy individuals and in patients with ADHD, with overall good data quality and little data loss.

However, we did not find clear evidence of a direct effect of our training on any outcome measure. For CPT performance as the primary outcome of this study, we found comparable error rates and reaction times under our newly-developed gaze-based attention training (real feedback) and under our two implemented control conditions (sham feedback, no feedback). One reason for this might be that in this study, each feedback condition was tested only within a single CPT block of 18 min. This duration was presumably too short to effectively practice the metacognitive and refocusing strategies anticipated by our GART. As with neurofeedback, the current feedback system may also build upon learning processes that commonly involve a series of slow consolidation processes over several weeks and sessions, and which only gradually lead to improvements in cognitive performance [65].

Another unexpected finding was observed in the ADHD group, in that commission and omission errors were descriptively highest during the sham condition, followed by the real feedback condition. This might be considered to indicate additional distraction caused by the feedback stimulus itself, especially if it occurs unexpectedly, and is also reflected in the evaluation of head actigraphy, which suggests a tendency for more head movements during sham feedback. Higher levels of distraction caused by the feedback stimuli, which may even exacerbate ADHD-related symptoms, would be consistent with the present findings demonstrating an increase in omission errors and a tendency toward more commission errors during DP. Additionally, although not statistically significant and of moderate effect size, yet of potential interest for future investigations of such a gaze-based feedback procedure, the fastest reaction times were found while applying the real feedback across groups and distraction phases. This might be consistent

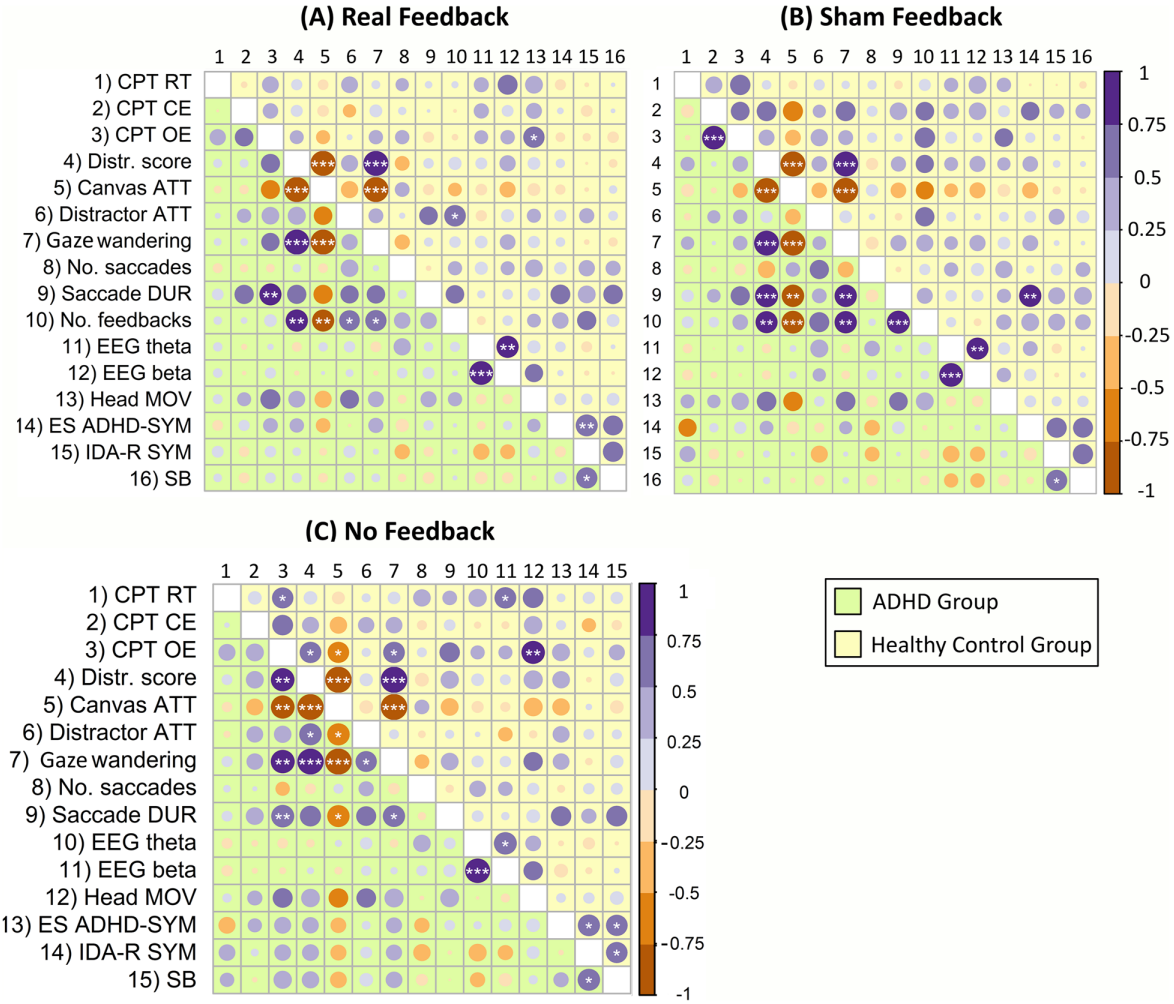

Fig. 5 Exploratory correlation analysis. Correlation matrices including indications of statistical significance based on Benjamini–Hochberg corrected p-values are separately reported for both groups, the ADHD group (left of and below the diagonal) and HC (right of and above the diagonal). Correlations were calculated separately for the (**A**) real feedback, (**B**) sham feedback and (**C**) no feedback condition. Accordingly, correlations with the number of triggered feedback are not presented for the latter condition. The color coding of the strength of the Pearson correlations is shown on the right. Higher contrasts and greater circle seizes indicate stronger correlations. *Abbreviations*: Canvas ATT: Time of task focus indicated by attended canvas dwell times, CE: Commission errors, CPT: Continuous performance task, Distractor ATT: Attended distractors percentage dwell times, Distr. Score: Distractibility score, ES ADHD-SYM: Experience sampling self-rated ADHD symptoms, Head MOV: Head movements, IDA-R SYM: ADHD symptoms observer-rated via the IDA-R, No. feedbacks: Total number of feedback triggered, No. saccades: Total number of saccades, OE: Omission errors, RT: Reaction times, Saccade DUR: Average saccade durations, SB: ADHD symptoms self-rated via the ADHS-SB. *$p < .05$, **$p < .01$, ***$p < .001$

with previous findings related to the state regulation hypothesis, according to which motivational factors, for instance, can be used to improve reaction time performance, especially in ADHD [66, 67].

In the group comparison of patients with ADHD and HC, on the other hand, we found promising evidence that our multimodal symptom assessment can discriminate well between both populations based on the findings within several measurement domains. Such a more holistic evaluation system could be of particular value in treatment outcome evaluations and the clinical assessment of ADHD, especially considering the large heterogeneity that patients with ADHD exhibit. Specifically, comparing CPT performances of the two groups across feedback conditions and distractor phases, patients with ADHD made more omission errors and reacted more slowly than HC. Previous research comparing children and healthy controls in a virtual CPT

further indicated specifically increased distractor-induced performance deficits in ADHD [68]. However, while our implementation of phases of additional distraction also led to reduced CPT performances compared to phases without such additional distractors, no group interactions were observed. In the interpretation of group effects of this study, the presence of demographic differences between the groups should further be taken into consideration. The average age was higher and the average education level was lower in patients with ADHD. Older individuals, for instance, might adapt less quickly to the use of new technology compared to younger individuals. Regarding the participants' gaze behavior, patients with ADHD spent more time gazing at presented distractors than healthy individuals. These findings relate well to previous evaluations of gaze behavior in adults with ADHD during a non-virtual CPT [69], with higher dwell times at task-irrelevant areas and distractors impacting eye movements of patients more strongly than those of HC. Notably, in the present study, patients and HC performed similarly accurate in the post-experimental recognition of distractors. This suggests that healthy individuals comparably shift their attention to distracting events, but are able to disengage their attention from those events more quickly.

The present EEG analysis revealed no group differences in the TBR. Previous reviews have provided reasonable evidence of an enhanced TBR in ADHD, although reporting age-dependence and limitations in terms of comorbidities [70]. More recent reviews, however, found smaller effect sizes in adolescents compared to children [71] and no consistent evidence for atypical TBR in adults with ADHD [72]. While this is in line with the present findings, our results should be interpreted under consideration of the higher age of the ADHD group. Notably, similar to CPT omission errors, and the number and duration of saccades, we found higher TBRs during DP than NDP, but no significant group interactions.

Head movements were identified as the only outcome parameter that distinguished ADHD from other clinical patient groups in a recent study on the combined measurement of CPT performance and head actigraphy for the differential diagnosis of ADHD in adults [73]. Our results are consistent with their findings and the general consensus in ADHD research regarding actigraphy measures [40], in that patients with ADHD initiated more head movements than HC across all feedback conditions and distraction phases.

Experience sampling, which was conducted as an in vivo time sampling of self-rated ADHD symptoms at the end of each feedback condition, revealed higher scores of inattention, hyperactivity, and impulsivity in patients with ADHD than in HC. This can be considered an important finding for future evaluations of symptoms and treatment outcome, as the assessment of symptoms in ADHD is commonly based on retrospective reports, which require sufficient metacognitive ability and accurate recognition. The present results are consistent with initial evidence that experience sampling can reflect specific ADHD symptoms in the moment [74].

Our exploratory correlation analyses revealed clusters of strong correlations within measurement domains, such as among EEG or gaze parameters. Additionally, some group-specific associations were found. For instance, only in ADHD, saccade durations were positively correlated with CPT omission errors and gaze wandering, and negatively correlated with on-canvas gaze times. Self-rated ADHD symptoms during experience sampling were more associated with retrospectively self- and observer-rated symptoms in the HC group than in the ADHD group. This possibly suggests some specificity of such in-the-moment assessments of symptoms in adult ADHD that may not be recalled in later retrospective evaluations.

This study has some limitations. First, there were demographic differences between the groups as no matching for age and education was performed, with higher age in the ADHD and a higher education level in the HC group. This may have influenced our results concerning group effects, as, for example, individuals with higher levels of education may have different abilities in processing information than individuals with lower levels of education. Yet, age did not correlate with any of the present measures, and education also did not seem to have a major impact with respect to the correlational results. Therefore, and since the implementation of covariates in smaller samples should be considered carefully, the analyses were performed as planned and as preregistered without including covariates. With respect to ethnicity, the sample is representative of the area in which the study was conducted, but its generalizability may be limited.

Second, while this study was not designed to longitudinally evaluate treatment effects of a multi-session feedback training and instead is an evaluation of the direct impact and feasibility of such a gaze-based attention feedback during a multimodal ADHD symptom assessment, indications of some additional distracting effect of the sham feedback on patients with ADHD were unexpected. This implies that we cannot rule out that confusion generated by randomized feedback stimuli in the sham condition carried over to the feedback condition. As this was a single-session experiment with only small breaks of about two minutes, no sufficient washout

periods between conditions were performed. Future trials should therefore consider incorporating a patient control group that receives sham feedback and implementing a multi-session repeated measures design.

Third, while medication had to be withheld before the intervention, several patients in this sample were generally taking medication for ADHD. Consequently, possible delayed effects of ADHD medication intake, particularly on physiological measurements, need to be taken into account.

Finally, the feedback presented here uses gaze locations unimodally as an input for the feedback, while other parameters, such as periods of increased head movements, ERP components (that were left out of the present analysis due to length constraints), or specific eye movement characteristics, might be of interest for future studies as well. However, there are also technical limitations to advanced eye-tracking analysis, as VR-based eye-tracking is currently still limited to sampling rates below 300 Hz, which is, for example, considered the minimum for evaluating microsaccades [75]. Also, the feedback stimulus itself could be adapted, for instance, by providing a more ecologically valid feedback based on an avatar briefly guiding the participant, or by providing audio-only feedback that is less intrusive.

Conclusions

We demonstrate the feasibility of gaze-based attention training using VR and multimodal assessments in adults with ADHD. However, we did not find a direct effect of gaze-based feedback on attentional performance. There were indications that sham feedback elicited particularly negative responses in patients with ADHD. We propose future longitudinal, multi-session trials to determine the prerequisites for potential initiations of learning processes similar to neurofeedback procedures to derive a therapeutic potential for adult ADHD. The differentiation of patients with ADHD from healthy individuals yielded promising results in this virtual seminar room study: patients made more omission errors and showed higher CPT reaction times, had higher distractor-related dwell times, moved their heads more, and self-reported higher ADHD symptoms during task engagement. A more holistic, multimodal assessment, such as the one proposed here, might adequately grasp the heterogeneity of ADHD symptomatology and potentially provide an exploratory set of biomarkers, thereby taking another step toward precision medicine in ADHD.

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
CPT	Continuous performance task
CCT	Computerized cognitive training
VR	Virtual reality
TBR	Theta/beta ratio
GART	Gaze-based attention refocusing training in virtual reality
VSR	Virtual seminar room
HC	Healthy control
DP	Distractor phases
NDP	Non-distractor phases
IDA-R	Integrated Diagnosis of ADHD in Adulthood
MINI-DIPS	Brief Diagnostic Interview for Mental Disorders
ADP-IV	Assessment of DSM-IV Personality Disorders
ADHS-SB	Self-rating behavior questionnaire
WHOQOL	World Health Organization Quality Of Life questionnaire
DASS	Depression, Anxiety and Stress Scales
HMD	Head-mounted display
VRSQ	Virtual Reality Sickness Questionnaire
LSL	Lab Streaming Layer
ICA	Independent component analysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-023-04551-z.

Additional file 1. A short video presentation of the virtual scenario in first person perspective. A user performs the continuous performance task in the developed VSR. Two exemplary distractors are presented and audiovisual feedback is played based on the gaze behavior.

Additional file 2. Detailed results of all conducted ANOVA procedures (Supplementary Tables 1 – 5).

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Not applicable.

Authors' contributions

Conceptualization: BS, AP, NB; Methodology: BS, UE, SL, NB; Formal Analysis: BS, LMA, AW, KK, TMG, DS, NB; Investigation: BS, LMA, BA, MK; Writing—Original Draft Preparation: BS, LMA, NB; Writing—Review & Editing: AW, KK, BA, TMG, DS, UE, MK, SL, AP; Visualization: BS, LMA, NB; Supervision: AP, NB. All authors read the final manuscript, approved its submission and agreed to take responsibility for the integrity and veracity of the work.

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Availability of data and materials

The dataset and analysis code supporting the conclusions of this article are available in the Open Science Framework (OSF) repository, https://osf.io/6a23b (https://doi.org/10.17605/OSF.IO/6A23B).

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Helsinki Declaration as revised in 2013, and approved by the local medical ethics committee of the University of Bonn (protocol number: 297/20). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

BS, NB received funding from BONFOR and the German Federal Ministry of Education and Research. AW received funding from Medice. Within the past three years, UE has acted as a consultant for Eleusis Ltd. AP is an editorial board member of BMC Psychiatry and, over the past three years, she received funding by the German Federal Ministry of Education and Research, Horizon2020, and DFG; she reports serving on advisory boards for Takeda, Medice, and Boehringer; and delivering lectures sponsored by Medice, Takeda; and being the author of books and articles on psychotherapy. All other authors declare no conflicts of interest.

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Publisher's Note

4. Discussion

In this PhD project, three separate clinical intervention studies were conducted to investigate the potential of mHealth apps and VR for the treatment of ADHD in adults. The results of two psychoeducation studies suggest that digital psychoeducation using a smartphone app as a support for clinical groups (Selaskowski et al., 2022), and using either a modular smartphone app or a chatbot for a self-guided psychoeducation approach (Selaskowski et al., 2023b), is safe and can improve symptoms of adult ADHD. The VR-based GART, on the other hand, showed no immediate improvements in a single-session design (Selaskowski et al., 2023a). Notably, however, the application of a VR environment to assess ADHD-related symptoms appears to be promising.

4.1 Digital psychoeducation for adult ADHD

Regarding the two psychoeducation studies, the first study (Selaskowski et al., 2022) compared the effects of a smartphone-assisted psychoeducation (SAP) and traditional pen-and-paper brochure-assisted psychoeducation (BAP) after eight weeks of attending a psychoeducation group. Results from a total of 43 patients who completed the study indicated that both interventions significantly reduced ADHD symptoms, but the SAP group showed greater symptom decrease than the BAP group. While we found improvements in all ADHD core symptoms in both groups, SAP was particularly superior in decreasing symptoms of inattention and impulsivity. There were no differences in content learning outcomes between the two groups, suggesting that the superiority in symptom reduction may be related to app-specific features, such as flexibility of use and less effortful integration into daily life. Possibly for similar underlying factors, homework compliance was higher in the SAP group.

In the second study (Selaskowski et al., 2023b), 34 patients with ADHD completed a three-week self-guided psychoeducation using either a chatbot or the conventional app used in the first study. While both forms of digital psychoeducation showed strong effects in the improvement of ADHD symptoms, neither intervention demonstrated superior efficacy. Likewise, no differences in learning outcomes for psychoeducation content emerged. Although clinical improvements of both self-guided interventions descriptively exceeded those of the brochure-assisted psychoeducation group from the first study, the results should be interpreted in consideration of the lack of an established treatment comparison,

so that effects independent of the interventions may also have contributed. However, given that medication was held constant and no contact with clinical experts or any type of emotional support was offered as part of the interventions, it seems plausible that the effects were related to the interventions themselves.

While there is only limited research on psychoeducation for adult ADHD and the here presented studies are among the first to evaluate digital approaches, the findings are broadly consistent with previous research suggesting that psychoeducation is effective in reducing ADHD core symptoms (Bachmann et al., 2018; Hoxhaj et al., 2018; Vidal et al., 2013). Moreover, there are indications from further research that digital psychoeducation appears to be at least as effective and equally safe as traditional psychoeducation (Jang et al., 2021; Knouse et al., 2022). With regard to secondary outcomes, contrary to previous psychoeducation trials (Hoxhaj et al., 2018; Vidal et al., 2013), no improvements in depression symptoms and functional impairments were demonstrated in the present studies. Although this finding may be related to the more restrictive study eligibility criteria, it is of clinical relevance and should be investigated in future research. More specifically, patients presenting with severe symptoms of affective disorders were not eligible to participate in both psychoeducation studies (Selaskowski et al., 2022, 2023b). Previous studies that found improvements in depressive symptoms were less restrictive in this regard (Hirvikoski et al., 2015; Hoxhaj et al., 2018). Similarly, although improvements in quality of life and functional impairment were expected based on previous non-digital psychoeducation studies (Hoxhaj et al., 2018; Vidal et al., 2013), no enhancements were found following any intervention in the present studies. This could be partly explained by the use of less health-related and more global measurement instruments such as the WHO Quality of Life questionnaire (THE WHOQOL Group, 1998) and the Weiss Functional Impairment Scale (Weiss, 2000). However, the extent to which this might be an effect of digital versus non-digital psychoeducation requires further investigation.

Specific app usage patterns are an additional aspect that should be explored in more detail, as this was not technically feasible within the scope of this project. Nevertheless, while we do not have data to evaluate the exact amount of time spent using the psychoeducation app or chatbot compared to traditional paper-based formats, the finding of a higher homework compliance in an app-supported format is of particular interest. This

result from the first study may have contributed to the greater reduction in symptoms in the app-assisted group, especially in light of a previous meta-analysis suggesting that higher homework compliance is associated with more favorable therapy outcomes (Mausbach et al., 2010). In general, the larger symptom reduction of app-based psychoeducation seems plausible given the general benefits of smartphone apps, such as flexible availability at the time a patient is motivated to engage with psychoeducation content or is in need of a literature source to review a technique on a particular coping strategy. In addition, clinical experience shows that organizational difficulties, such as misplacing paper documents, can be a concern with ADHD that may be largely resolved through the use of a smartphone app.

In summary, psychoeducation may be well suited for digital presentation and, moreover, may be superior to traditional formats for many patients. However, the studies presented here are initial exploratory investigations and have some limitations. Subgroups, such as based on age or symptom presentation, for whom digital formats are potentially less appropriate could not be identified because of the relatively small sample sizes. In addition, the study designs were based on only two time points, with no follow-up to determine the duration of effects. Beyond that, no intention-to-treat analyses were performed in these exploratory studies. Therefore, a detailed drop-out evaluation should be part of prospective, well-powered confirmatory studies. In the future, based on the promising present results related to digital presentation, content may further not be limited to psychoeducation, but could incorporate therapeutic techniques that have been shown to be beneficial for adult ADHD (Fullen et al., 2020; Nimmo-Smith et al., 2020). Yet, the type of content and techniques, such as those based on cognitive or dialectical-behavioral approaches, that are effective and applicable to the format remain to be explored (Liu et al., 2023; Philipsen et al., 2015; Scholz et al., 2023). Finally, digital platforms also offer great potential in terms of personalization. Mobile sensing (i.e., the collection of data via smartphone sensors or wearables) can be used to determine digital phenotypes of users, for instance, based on their activities and sleep behavior (Koch et al., 2021). These context parameters can then provide direct indications of which factors exacerbate symptoms and offer relevant therapeutic recommendations, such as on the basis of the content that has been implemented digitally within this project.

4.2 VR for the treatment of adult ADHD

VR as a tool for the treatment of adult ADHD was investigated in the third study of this PhD project. Specifically, we developed an attention training based on gaze behavior in a virtual seminar room to evaluate its feasibility and efficacy for patients with ADHD. For the detailed characterization of symptoms and to assess the specificity of the attention training, 18 healthy controls completed the study besides 18 adults with ADHD. Within the VR scenario, participants performed a CPT and received feedback whenever their gaze behavior indicated signs of inattention. Phases of additional virtual distraction were implemented and alternated with phases in which no further distraction occurred. Task performance and eye movements, as well as EEG, head actigraphy and experience sampling of ADHD symptoms were evaluated during three conditions: receiving GART feedback, receiving sham feedback, or not receiving any feedback. Although we found that the GART was feasible and well-tolerated, there was no evidence of a direct effect on any outcome measure. Aside from the possibility that the feedback may have no effect, it is also conceivable that the relatively short presentation time of approximately 20 minutes for each condition without significant washout periods in between may have contributed to the results. Notably, some parameters indicated that the unexpected feedback stimulus of the sham feedback may have led to a worsening of performance, especially in patients with ADHD in terms of head movements and CPT errors.

The present results provide suggestions for adjustments to the feedback system that could increase its efficacy. A recent meta-analysis showed that computer-based cognitive training can improve individual cognitive functions within the specific training setting (Westwood et al., 2023), but had little effect on clinical symptoms of ADHD. In light of this finding, VR may already address limitations of traditional computer-based cognitive training by providing an environment that is closer to real-life situations. However, the CPT itself was still presented as a task on a virtual screen in the current study, similar to traditional neuropsychological assignments and cognitive trainings. Therefore, refinements could include not only implementing a realistic environment, but also a task as it can occur in everyday life, such as being immersed into a virtual office room and sorting and processing emails while typical distractions of an open-plan office are simulated. In addition, in line with neurofeedback principles of operant conditioning, a scoring system could be introduced to reward good performance. Considering that the

task presented here was specifically designed to induce monotony, it would be particularly interesting to examine the effects of an attention task in patients with ADHD in which motivational processes are promoted. Apart from that, the feedback stimulus itself might also be perceived as too distracting and rather interrupt attention. Consequently, the feedback could be adapted and only be presented auditorily, or the visual component could be displayed in a less intrusive manner.

Beyond that, an improvement of the specificity of the system could be achieved based on the results of the multimodal symptom assessment which showed that patients with ADHD made more omission errors, reacted more slowly, exhibited longer dwell times on presented distractors and moved their heads more. While VR-based assessment approaches are still rare for adults (Wiebe et al., 2022), our findings are broadly in line with previous research regarding decreased distractor-related task performance of children with ADHD in a virtual classroom scenario (Neguț et al., 2017), as well as increased task-irrelevant dwell times (Elbaum et al., 2020), and more head movements (Brunkhorst-Kanaan et al., 2020) in adults with ADHD. Moreover, our research group recently replicated the present findings by showing that unmedicated adults with ADHD made more CPT errors, showed more head movements, and engaged in more dysfunctional gaze behavior than healthy individuals (Wiebe et al., 2023). As a result, the feedback could be given not only based on explicitly looking away from the task area, but also incorporating parameters such as specific head and eye movement features. Eye movements in particular could have great potential for further refinement, as several deviations have previously been reported for ADHD (for a meta-analysis on oculomotor inhibition in ADHD, see Chamorro et al., 2021). However, the rather low and, in combination with VR, often inconsistent sampling rate complicates in-depth eye-tracking offline analyses; an accurate online feedback system based on immediate saccade and fixation classification would require even higher capabilities. Currently, technical limitations of eye-trackers installed in VR systems still provide limited possibilities for the detailed evaluation of eye movement parameters.

Building on the findings of this exploratory study, we recommend a future longitudinal multisession study based on a larger sample to rigorously investigate the extent to which such a feedback system can address clinical symptoms of ADHD beyond changes in

neuropsychological attention scores. Regarding the design of a prospective study, the inclusion of a measurement of the real-life effect of the GART would be of substantial interest. For instance, a recent trial investigating driver inattention in adolescents with ADHD applied a multi-session VR intervention in a driving simulator (Epstein et al., 2022). Positive intervention effects beyond in-lab measures were demonstrated by recording real-life driving behavior for up to one year following the intervention. This is one of the few studies in the field to demonstrate the translation of improvements to real life, an important clinical research objective for which VR may offer the greatest potential to date.

4.3 Future direction and application in clinical practice

The results of this PhD project have shown that both digital psychoeducation and VR could have potential for the future treatment of adult ADHD, with digital psychoeducation being significantly closer to implementation in clinical practice. However, further confirmatory research is needed to determine the specific effects of digital psychoeducation on ADHD symptom reduction, and in particular the lack of effects on quality-of-life measures. The findings also need to be interpreted in light of the overall limited amount of research on psychoeducation for ADHD in adults. Although the few non-digital psychoeducation studies have found symptom improvements over time and psychoeducation is generally recommended (Kooij et al., 2019), comparisons with active control groups have not shown superiority (Bachmann et al., 2018). Of note, these studies themselves present methodological challenges, such as the use of comparisons with mindfulness-based therapies, for which there are also indications for improvement of adult ADHD symptoms (for a meta-analysis, see Cairncross and Miller, 2020). Nevertheless, the present results warrant the conduct of a larger-scaled, well-controlled confirmatory trial that might also elucidate the present evidence of higher homework compliance and descriptively lower attrition with app-supported than with brochure-supported psychoeducation. Given that adherence is a particular concern in ADHD, these factors are of great value to clinical practice.

The prospect of future adoption of digital psychoeducation would offer some significant benefits to current routine care. For example, the number of in-person psychoeducation groups commonly offered in clinics could be reduced or possibly even conducted entirely online without the constant involvement of clinical experts. Aside from cost-effectiveness

benefits, long waiting times before treatment initiation could be shortened through the provision of clinician-independent digital psychoeducation shortly after diagnosis. Given the rapidly growing potential of chatbots, basic conversational interaction could be combined with psychotherapeutic elements in the future (Knouse et al., 2017; Philipsen et al., 2015). However, much remains to be considered before a sufficient regulatory framework for the clinical use of chatbots and AI is established that addresses the many ethical concerns, such as those arising from the potential to cause harm, particularly to vulnerable individuals including patients with mental disorders (Fiske et al., 2019).

The presented VR study has a higher degree of exploratory character compared to the digital psychoeducation studies. Here, we developed the first GART in VR for adults with ADHD. Since the present study was also the first in which the virtual seminar room was used as a treatment approach, some valuable insights for further advancements could be gained as described above. Given the recent replication of several findings on the virtual seminar room when comparing healthy individuals and adults with ADHD (Wiebe et al., 2023), there is potential for this system to at least contribute to the assessment of ADHD symptoms and monitoring of treatment outcomes. Building on this potential in symptom detection, we propose a multi-session study to gain further insight into the extent to which a revised GART might be suitable for clinical use. Although a therapeutic application is not an option at this stage, the system has demonstrated its basic feasibility and merits further research, especially as effective non-pharmacological alternatives for the treatment of ADHD are still lacking.

Finally, one advantage that digital treatments in particular could offer is the facilitated incorporation of elements of personalized medicine, for example through consideration of different learning styles or mobile sensing. Especially with a heterogeneous disorder such as ADHD, the automatic provision of personally relevant treatment strategies based on individual characteristics and behavioral patterns could be highly valuable. For example, there may be patients who have only recently been diagnosed and therefore prefer a more structured approach to initial psychoeducation, such as that offered by the linear conventional app used in our studies. Patients who have been diagnosed for a longer period of time and who want to refresh their previously acquired knowledge or who have specific questions about a coping strategy, on the other hand, might prefer direct contact

with a chatbot. In this regard, a digital solution can easily change format and adapt to the individual needs of the patient. The VR system can evaluate multiple behavioral and psychophysiological data streams simultaneously and therefore not only has the potential to be useful in diagnostic procedures, but can also track treatment outcomes beyond typical retrospective questionnaires and assessments. The present findings may be of increased interest when considering the conclusions of a recent systematic review that, although there are some promising biological markers, no reliable prediction of treatment outcome in adult ADHD is yet possible (Capellazzi et al., 2022).

4.4 Limitations

Each of the studies had limitations that were discussed in detail. For the interpretation of the main results of this project, it is essential to outline some general considerations that can also generate hypotheses for required confirmatory studies. Regarding the samples enrolled, all studies in this project included patients who were already taking medication for ADHD. Although medication was held constant during psychoeducation and was briefly discontinued during the VR experiments, moderation effects may have occurred. In particular, patients taking medication may be more capable of learning psychoeducation strategies and eventually apply them in everyday life. Additionally, several of the included patients had other comorbid diagnoses. Medications and comorbidities may contribute to the heterogeneity of the results of many adult ADHD studies, especially smaller ones, and should therefore be investigated in detail in well-powered follow-up studies.

Regarding digital psychoeducation, although generally appearing safe, the self-guided online format substantially reduces expert supervision. Given the present encouraging results on clinical efficacy, a confirmatory study must particularly examine safety issues in ADHD subgroups. For example, whether digital psychoeducation is still advisable in patients with severe symptomatology, or to what extent comorbid depressive symptoms might present a contraindication.

Regarding the VR study, a prospective follow-up trial examining the efficacy based on multiple sessions over several weeks is needed. As part of this, a carefully considered implementation of the sham condition must also be carried out. Especially in VR, control conditions are often applied without a clear understanding of whether found effects can be attributed to the scenario or simply to the experience with VR as a medium (Garrett et

al., 2018). A sham condition that is too intrusive may have negative outcome effects, while one that is too subtle may cause participants to guess their allocation.

4.5 Concluding remarks

The present results demonstrate the feasibility of all evaluated treatment approaches for adults with ADHD. However, some distinctions between the specific interventions need to be considered. First, digital presentation of psychoeducational content in the form of a smartphone app was found to be more effective in reducing ADHD symptoms than paper-based psychoeducation. Second, although the presentation of content via a chatbot led to similar results as a conventional smartphone app in self-guided psychoeducation, the comparison with an established treatment is lacking. The technical implementation of a chatbot appears to represent a more challenging aspect, especially as ethical considerations such as automated interaction with vulnerable groups, for example including patients with suicidal ideation, must be taken into account. In the context of self-guided psychoeducation, however, both a conventional app and a chatbot have proven to be safe. Self-guided digital psychoeducation may offer potential for a first intervention early in the treatment process of adult ADHD. Finally, contrary to the psychoeducational interventions, the GART in a virtual seminar room did not show immediate improvements in adult patients with ADHD. Yet, the successful differentiation of patients from healthy participants based on CPT performance, gaze behavior, and head movements, as well as indications of performance deterioration in the presence of unexpected sham feedback, provide reason for further refinement and investigation of its clinical efficacy in the context of a multi-session trial.

Overall, digital psychoeducation is approaching clinical application in adult ADHD, although a well-powered multicenter confirmatory study is needed as a next step to further specify responder subgroups and individual user behavior. The potential to cost-effectively target large numbers of patients early in the treatment process, as well as the many other opportunities offered by digital technology, particularly in the area of precision psychiatry, should encourage research to rigorously address the gaps in existing evidence. The capability for largely effortless personalization of treatments that these technological developments can provide is set to significantly impact the future of the field, beyond adult ADHD.

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