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ORIGINAL CONTRIBUTION

Effects of game-based digital therapeutics on attention deficit hyperactivity disorder in children and adolescents as assessed by parents or teachers: a systematic review and meta-analysis

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset disorder characterized by pharmacological and non-pharmacological interventions. Despite the available treatment options and prevention measures, conventional treatments have several limitations. Digital therapeutics (DTx) like EndeavorRx® is an emerging alternative to overcome these limitations. EndeavorRx® is the first FDA-approved, game-based DTx approved for the treatment of pediatric ADHD. We investigated the effects of game-based DTx in randomised controlled trials (RCTs) on children and adolescents with ADHD. In this systematic review and meta-analysis, we searched PubMed, Embase, and PsycINFO databases up to January 2022. The protocol was registered (CRD42022299866). The assessor was defined as parents and teachers. The primary outcome was differences in inattention reported by the assessor, and the secondary outcome was differences in hyperactivity and hyperactivity/impulsivity reported by the assessor and the relative comparisons between game-based DTx, medicine, and control with indirect meta-analysis. Game-based DTx improved inattention more than the control upon assessment by assessors (standard mean difference (SMD) 0.28, 95% confidence interval (CI) 0.14–0.41; SMD 0.21, 95% CI 0.03–0.39, respectively), while medication improved inattention more than game-based DTx (SMD − 0·62, 95% CI − 1·04 to − 0·20) upon assessment by the teacher. Game-based DTx improved hyperactivity/impulsivity than the control upon assessment by assessors (SMD 0.28, 95% CI 0.03–0.53; SMD 0.30, 95% CI 0.05–0.55, respectively), and medication improved hyperactivity/impulsivity significantly than game-based DTx upon assessment by the teacher. Hyperactivity has not been reported extensively. As a result, game-based DTx had a more significant effect than the control, however medication was more effective.

Keywords Digital therapeutics (DTx) · ADHD · DTx · Meta-analysis · Inattention

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common disorder and affects approximately four million children and adolescents. ADHD symptoms include difficulty staying focused and paying attention, difficulty controlling behaviour, very high activity levels [1].

Front-line interventions for ADHD include pharmacological and non-pharmacological interventions, which have shown short-term efficacy [2]. Existing treatments have side effects that limit their acceptability [3]. They are only effective when administered and may not be very effective for reducing daily impairments [4]. Furthermore, pharmacotherapy may be ineffective for some patients because of caregiver preferences or concerns about abuse, misuse, and diversion [5]. In fact, research from the UK and the USA has revealed that the majority of kids with pediatric mental

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health issues do not have enough access to care [6, 7]. To address these issues, the need for alternative approaches, such as the application of new technologies to the management of ADHD, is emerging [8]. In this circumstance, digital therapy could be an alternative.

According to epidemiologic research, up to 50% of referrals to child mental health clinics are for the diagnosis and management of ADHD [9]. To meet this demand, numerous tests have been developed to evaluate different parts of the three symptoms of ADHD—inattention, hyperactivity, and impulsivity. Most frequently, these symptoms are evaluated using subjective criteria that focus on the disorder's behavioral manifestations. These criteria might vary depending on the stage of development and can include self-report scales for adults and parent- and teacher-rating scales for children [10, 11]. The diagnosis of ADHD includes reviewing symptoms present in home and school settings from parent, teacher because clinical symptoms must be observed in several settings [1]. It is widely acknowledged that parent and teacher rating scales are reliable and valid parts of ADHD evaluations [12].

Recently, EndeavorRx®, a prescription-only game-based digital therapeutics (DTx) [13], was licensed by the FDA in 2020 for pediatric patients with predominantly inattentive or complex ADHD who present with attention problems. In addition, the group with digital health interventions showed no serious side effects in a study, suggesting it could be safely added to the standard of care and could be used in places with poor mental health services [14]. Therefore, game-based DTx can address the limitations of pharmacotherapy with improved accessibility, minimal side effects, and low abuse potential. In addition, targeted digital interventions are being evaluated as treatments to alter brain function in ADHD [15]. In NeuroRacer, a study based on EndeavorRx®, electroencephalography (EEG) improvement was confirmed by game-based treatment during evaluation, and the effect of the treatment was explained as the change observed [16]. Although the recently approved EndeavorRx® did not measure changes in EEG in children with ADHD in its pivotal study [2], it can be inferred that EndeavorRx® also had a positive effect on EEG in children with ADHD when considering the effect of NeuroRacer on elderly patients. Although included in exclusion criteria and not used in our analysis, it was confirmed that EndeavorRx® also improved ADHD symptoms using EEG. EndeavorRx® was enhanced that midline frontal theta (MFT), a well-established EEG-based measure of attentional control [17].

Several systematic reviews and meta-analyses have discussed the effects of non-pharmacological interventions in ADHD [8, 18, 19]. The non-pharmacological intervention includes all forms of digital therapy, rather than game-based DTx alone [20]. Non-randomized studies are typically more susceptible to systematic and confounding biases than RCTs, making it more challenging to draw conclusions [21, 22]. Also, previous studies have lower statistical power than randomized control trials (RCTs) due to including non-randomized clinical trials [18, 23–25]. To the best of our knowledge, there has been no comparison meta-analysis in RCT on whether game-based DTx are effective.

Therefore, we conducted a systematic review and meta-analysis of game-based DTx efficacy by assessors—parents and teachers for children and adolescents diagnosed with ADHD in RCT. First, we conducted a direct meta-analysis to identify the difference between game-based DTx and medicine, or control. Then, an indirect meta-analysis was performed to confirm the relative difference between game-based DTx, medicine, and control.

Methods

The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Table S1) [26]. The protocol was registered in the PROSPERO database (registration number: CRD42022299866).

Data sources and searches

Two independent researchers searched PubMed, EMBASE, and PsycINFO from the inception of each database to December 2022. The search terms are listed in Table S2.

The search strategy targeted published articles that evaluated the effects of game-based DTx on ADHD and were restricted to studies in English. References to the collected articles and systematic reviews were manually searched to identify additional studies. Disagreements between the investigators were resolved through a discussion.

Study selection

We selected only randomized control trials (RCTs) of children (under the age of 18 years) or adolescents (age 10–19 years) with ADHD who received treatment with game-based DTx [27]. Studies that used adults with ADHD as participants were excluded from this systematic review. We selected participants' age groups for children and adolescents in this study to specifically analyse the adherence to game-based DTx for these age groups, so as not to generalise the results to other age groups, especially adults. Participants were diagnosed with ADHD symptoms, not other mental or psychological disorders. Many studies concluded that ADHD is more commonly diagnosed in boys than in girls; therefore, a different male-to-female participants ratio could be understood if it was not the same as the initial recruitment assumption [28]. The included studies consisted

of pre- and post- data with one or more inattention, hyperactivity, and hyperactivity/impulsivity outcomes. Studies such as reviews, letters, commentaries, case reports, single-arm studies, conference abstracts, and preclinical studies were excluded. Studies in which assessors were not parents or teachers were excluded.

Data extraction and quality assessment

Data were collected from studies that included characteristics such as publication year, first author, registration number, patient's age and intelligence quotients, disease, intervention name, sample size, mean age, male percentage, ADHD type, assessment instrument, medication dosage, study design, and medication usage percentage. We included the ADHD types as classified and defined in the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth edition (DSM-5) [29]. ADHD type has the following characteristics. Inattention is difficulty staying on task, sustaining focus, and staying organized, and these problems are not due to defiance or lack of comprehension. Hyperactivity constantly moving about, including when it is inappropriate or excessively fidgeting, tapping, or talking. Impulsivity is acting without thinking or having difficulty with self-control. Impulsivity could also include a desire for immediate rewards or the inability to delay gratification [30]. In the DSM guideline, ADHD types were classified into inattention and hyperactivity/impulsivity, but some individual studies reported hyperactivity as a single type, so we classified ADHD types into three. We also extracted pre- and post-data from the retrieved articles, including inattention, hyperactivity, and hyperactivity/impulsivity, according to the assessor. Two investigators independently extracted the data. In the case of discrepancies, the study was re-evaluated, and a consensus was reached.

The risk of bias (ROB) assessment tool, version 2.0, developed by the Cochrane Collaboration was used to assess RCT quality [31]. We used the Grading of Recommendations, Assessment, Development, and Evaluations profiler (GRADEpro) approach to assess evidence quality based on the individual study limitations, inconsistency, indirectness, imprecision, and publication bias. GRADEpro was evaluated as high, moderate, low, or very low [32]. Publication bias was assessed using funnel plots and Egger's test [33].

Data synthesis and analysis

The primary outcome was the difference in inattention, according to the assessor. Treatment types were divided into game-based DTx, control groups, and medicine. The control group was defined as a game of ineffectiveness or a placebo. The secondary outcomes included the evaluation of differences in hyperactivity and hyperactivity/impulsivity according to the assessor. In addition, the rank of the efficacy of inattention, hyperactivity, and impulsivity was measured with an indirect meta-analysis between game-based DTx, medicine, and control.

Direct comparison meta-analysis of the overall effect size for the studies, expressed as the standardised mean difference (SMD) and 95% confidence interval (CI), were calculated using R studio (version 4.1.2) software. Statistical significance was set at $p < 0.05$. We evaluated the parents or teachers as assessors separately. We performed subgroup analyses for assessment instruments and overall ROB by the assessors—parents, and teachers. In addition, we reported a sensitivity analysis of the excluded studies with the most participants. I^2 statistics were applied to determine the significance of heterogeneity among studies classified as 25%, 50%, and 75%, suggesting low, medium, and high heterogeneity, respectively [34].

For our indirect meta-analysis, the evidence network plot was created using R studio (version 4.1.2) in Fig. 1. We used the Bayesian fixed-effects model to incorporate the estimates of direct and indirect treatment comparisons and ranked the interventions in order. The deviance information criterion was also used to select between a fixed-effects or random-effects model (Table S10–11) [35, 36]. The Markov chain Monte Carlo method was used to obtain the results from the aggregate data. We calculated the relative ranking of interventions for efficacy as their surface under the cumulative ranking (SUCRA), which had higher SUCRA scores corresponding to a higher ranking for efficacy. SUCRA was based solely on the point estimates and standard errors of the network estimates. It measured the mean extent of the network estimates and the mean extent of certainty that one intervention was superior to another and was averaged over

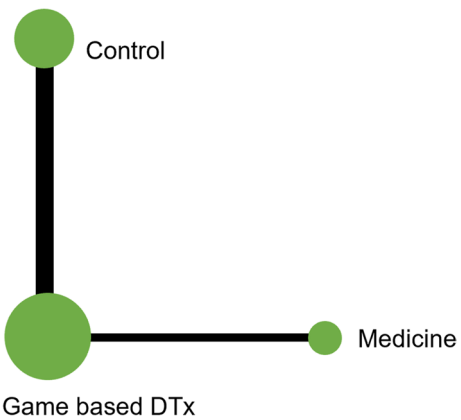

Fig. 1 Network plot. Network of included studies with the available direct comparisons for efficacy participants with ADHD. The size of the nodes and the thickness of the edges were weighted according to the number of studies evaluating each treatment and direct comparison, respectively

all competing interventions [37]. Furthermore, we measured the heterogeneity of indirect meta-analysis.

Results

A comprehensive search identified 453 records, from which 98 duplicates were removed. After screening, 175 studies that did not meet the inclusion criteria were excluded. After assessing the full text of the 180 articles, we included 20 RCTs. The included studies comprised 1,402 participants with ADHD (Fig. 2). The sample size of the reviewed studies age ranged between 6 and 17. The control group was classified that active control, and placebo. In detail, baseline characteristics of the included studies are presented in Tables 1 and S3. The subgroup analysis of assessment instruments used a total of 6 assessment instruments which involved rating scale assessments conducted by the parents or teacher. (1) The FBB-HKS German ADHD Rating Scale examined the severity and perceived burden of inattention, hyperactivity, and impulsiveness as defined by the ICD-10 and DSM-IV [38]. (2) The ADHD Rating Scale (ADHD-RS) helps determining the disorder subtype (primarily Inattentive, predominantly Hyperactive-Impulsive, or Combined) [39]. (3) The Conners' Rating Scale-Revised (CRS-R) evaluates behavioural problems [40]. (4) The Diagnostic and Statistical Manual of Mental Disorders (DSM-4) is used to diagnose a variety of childhood psychopathologies, including externalizing disorders [41]. (5) The Disruptive Behaviour Disorder Rating Scale (DBDRS) is a diagnostic tool adopted for a variety of childhood psychopathologies; most notably, externalising disorders [42]. (6) The Conners' Rating Scales are used to detect problem behaviours and ADHD

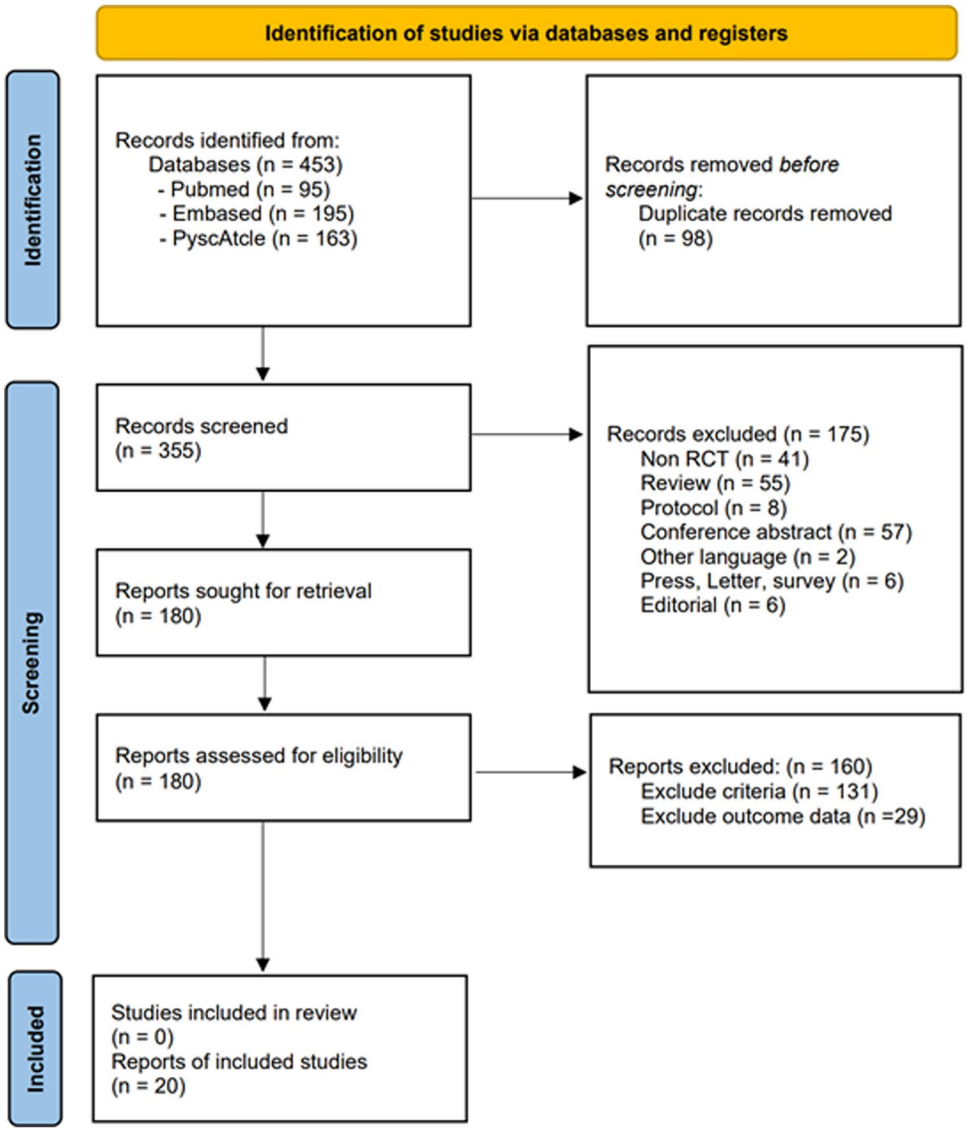

Fig. 2 Flow diagram of the study selection process

Table 1 Baseline characteristic

Study	Register number	Design	Inclusion patients age	Inclusion IQ	Patients	Intervention (Game name)	Sample size	Mean age	Male %	ADHD type	Medication usage	Control (Game name)	Sample size	Mean age	Male %	ADHD type	Medication usage
Bikc 2017[45]	NCT02728011	RCT	14–17	≥80	ADHD	Scientific Brain Training (SBT)	9	ND	ND	ICD-10 (F90.0): 80%	ND	Active control (Terimino)	9	ND	ND	ICD-10 (F90.0): 79.2%	ND
Bikc 2018[46]	NCT01752530	RCT	6–13	≥80	ADHD	ACTIVATE	35	9.77	83%	Inattentive: 34% Combined: 57% Hyper/impulsive: 9%	57%	Active control (Tetris)	35	10.14	86%	Inattentive: 53% Combined: 44% Hyper/impulsive: 3%	57%
Kollins 2020[7]	NCT02674633	RCT	8–12	≥80	ADHD	AKL-T01	180	9.7	69%	ND	Not available	Active control (AKL-T09)	168	9.6	73%	ND	ND
Weerdmeester 2016[47]	NTR5083	RCT	6–13	ND	ADHD	Dragon	37	9.84	41%	AVL Combined: 17.56% Hyperactivity: 6.93% Impulsivity: 6.9% Inattention: 5.95%	33%	Active control (Angry Birds Trilogy)	36	9.69	38%	AVL Combined: 16.98% Hyperactivity: 6.79% Impulsivity: 6.43% Inattention: 5.95%	30%
Dovis 2015[48]	NTR2728	RCT	8–12	≥80	ADHD	Brain game Brian	31	10.6	76%	ND	65%	Active control (Braingame Brain placebo condition)	30	10.5	75%	ND	73%
Klingberg 2005[49]	ND	RCT	7–12	≥80	ADHD	RoboMemo	24	9.7	83%	ND	Not available	Active control (RoboMemo)	20	9.8	80%	ND	ND
Lee 2017[50]	ND	RCT	6–12	≥80	ADHD	Airplane game	18	8.72	88.90%	Combined: 50% Inattentive: 38.9% hyper/impulsive: 11.1%	ND	Medication	18	8.78	61.10%	Combined: 38.9% Inattentive: 44.4% hyper/impulsive: 16.7%	ND
Lim 2019[51]	NCT01344044	RCT	6–12	ND	ADHD	Cogoland	81	8.7	85.20%	CDISC-type of ADHD Combined: 50.6% Inattentive: 49.4%	Not available	Placebo (Wait list control)	82	8.6	84.10%	CDISC-type of ADHD Combined: 65.9% Inattentive: 34.1%	Not available
Meisel 2013[52]	ND	RCT	7–14	≥80	ADHD	Puzzles, Races, Pacman	12	9.53	50%	Combined: 75% Inattentive: 25%	ND	Medication	11	8.9	54.55%	Combined: 81.82% Inattentive: 18.18%	ND

Table 1 (continued)

Study	Register number	Design	Inclusion patients age	Inclusion IQ	Patients	Intervention (Game name)	Sample size	Mean age	Male %	ADHD type	Medication usage	Control (Game name)	Sample size	Mean age	Male %	ADHD type	Medication usage
Rajabi 2020[53]	ND	RCT	6–12	≥85	ADHD	SmartMind	16	10.2	100%	Combined: 62.5% Inattentive: 18.8% Hyper/impulsive: 18.8%	ND	Placebo (Wait list control)	16	10.5	100%	Combined: 56.3% Inattentive: 12.5% Hyper/impulsive: 31.3%	ND
Steiner 2011[54]	ND	RCT	11–14	ND	ADHD	Airplaine game	13	ND	ND	ND	ND	Placebo (Wait list control)	15	ND	ND	ND	ND
Steiner 2013[55]	NCT01583829	RCT	7–8, 9–10	≥80	ADHD	Dolphins game	34	8.4	67%	ND	44%	Placebo (Wait list control)	36	8.4	69%	ND	56%
Sudnawa 2018[56]	TCTR20160512001	RCT	6–12	≥70	ADHD	Rocket ship Picture memory Paper airplane cooking basketball shooting	20	8.4	90%	Combined: 40% Inattentive: 60%	ND	Medication	20	9	90%	Combined: 45% Inattentive: 55%	ND
Bakhshayesh 2011[57]	ND	RCT	6–14	≥80	ADHD	Neurofeedback	18	9.6	72%	ICD-10 (F90.0): 78%	22%	Active control (EMG Biofeedback)	17	9.1	76%	ICD-10 (F90.0): 88%	18%
Benzing 2019[58]	DRKS00010171	RCT	8–12	ND	ADHD	Shape UP	28	10.46	86%	ND	71%	Placebo (Wait list control)	23	10.39	82%	ND	74%
Gevensleben 2009[59]	ISRCTN87071503	RCT	8–12	ND	ADHD	SCP training	59	9.1	86%	Combined: 66.1% Inattentive: 33.9%	9%	Active control (Skillies)	35	9.4	74%	Combined: 77.1% Inattentive: 22.9%	3%
Eugene 2020[60]	NCT02251743	RCT	7–10	≥80	ADHD	EEGer	84	8.51	77%	Combined: 65.5% Inattentive: 34.8%	31%	Placebo	58	8.67	79%	Combined: 63.1% Inattentive: 36.9%	27%
Maurizio 2014[61]	ISRCTN82524080	RCT	8.5–13	≥80	ADHD	Neurofeedback	13	10.6	85%	ND	8%	Active control (EMG Biofeedback)	12	10	92%	ND	8%
Beauregard 2006[62]	ND	RCT	8–12	≥85	ADHD	Lexicor NRS	15	10.2	73%	ND	ND	Placebo	5	10.2	100%	ND	ND
Ogrim 2013[63]	ND	RCT	7–16	ND	ADHD	Neurofeedback (Brain Tuner)	14	10.6	57.14%	Combined: 79% Inattentive: 21%	ND	Medication	15	11.2	66.67%	Combined: 73% Inattentive: 27%	ND

symptoms [43]. The risk of bias (ROB) for RCTs provided a framework for scoring the quality of the included studies by addressing different aspects of the research, such as randomization, allocation concealment, blinding, missing data, and selection bias. The methodological quality of included studies was felt to be high risk, mostly because of trials providing insufficient details or being unclear in their reporting (Figure S1). Table S9 illustrates the quality of evidence using the GRADEpro method for the effects of game-based DTx compared to the control and medicine in the outcome. A funnel plot of included studies did not show any asymmetry, an indication that significant publication bias was unlikely (Figure S2). We have presented a funnel plot in Figure S2.

Results of assessor: parents

Inattention

The analysis of 14 RCTs including 1,183 participants with inattention showed an attention improvement after intervention (SMD 0·28, 95% CI 0·14–0·41, $I^2 = 0\%$, $p < 0·01$) (Fig. 3a). A comparison of medication versus game-based

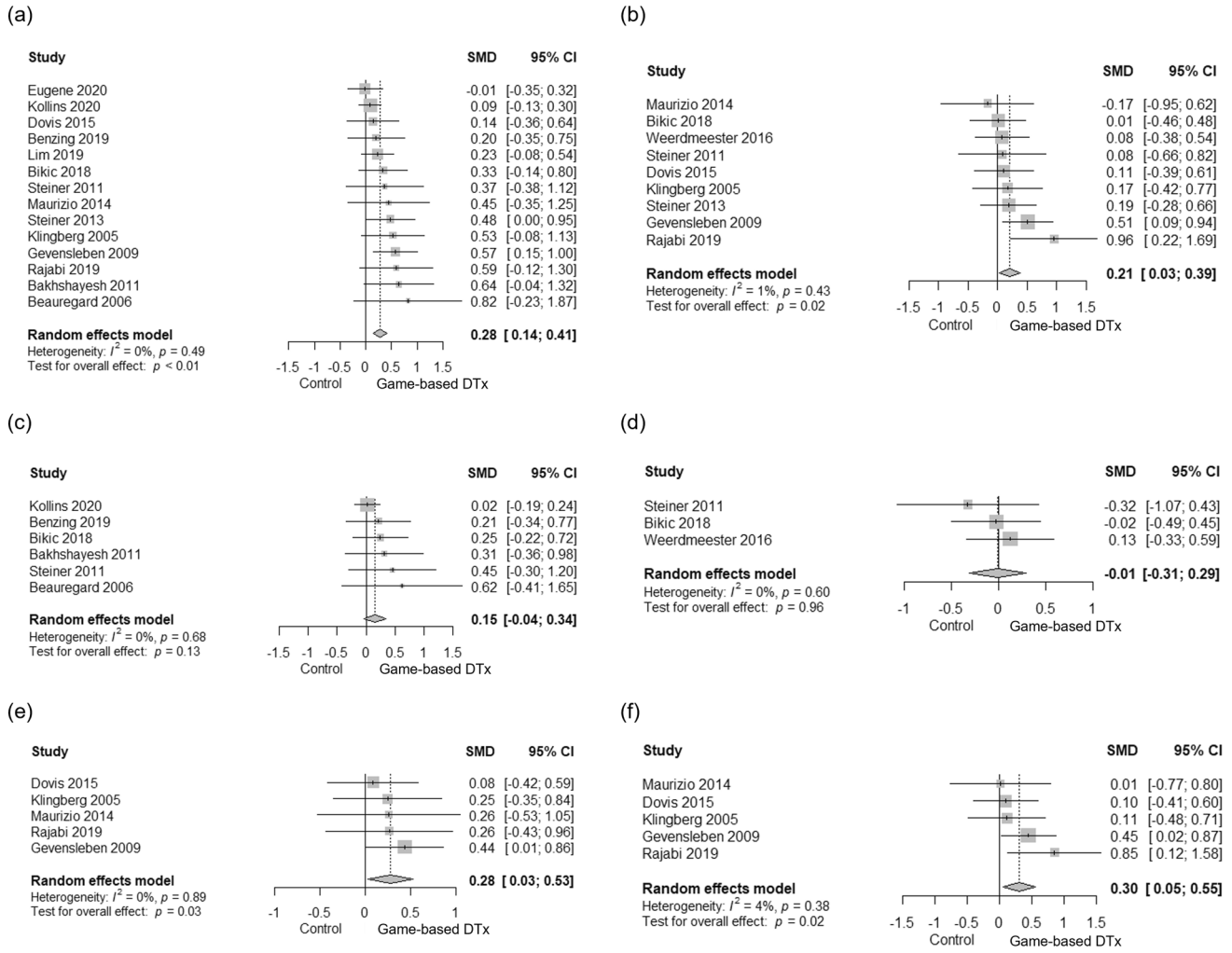

Fig. 3 Forest plot of the effect of game-based DTx compared to the control group using direct meta-analysis. **a** Inattention with the assessment of parents; **b** Inattention with the assessment of the teacher; **c** Hyperactivity with the assessment of parents; **d** Hyperactivity with the assessment of the teacher; **e** Hyperactivity/impulsivity with the assessment of parents; **f** Hyperactivity/impulsivity with the assessment of the teacher. For parents, the inattention improved after intervention (SMD 0.28, 95% CI 0.14–0.41, $I^2 = 0\%$, $p < 0.01$) (**a**). The game-based DTx improved hyperactivity compared to the control (SMD 0.15, 95% CI – 0.04 to 0.34, $I^2 = 0\%$, $p = 0.13$) (**c**). The game-based DTx showed improved hyperactivity/impulsivity than the control group (SMD 0.28, 95% CI 0.03–0.53, $I^2 = 0\%$, $p = 0.03$) (**e**). For teachers, Game-based DTx improved attention compared to the control group (SMD 0.21, 95% CI 0.03–0·39, $I^2 = 1\%$, $p = 0.02$) (**b**). The control group had improved hyperactivity than the game-based DTx group (SMD – 0.01, 95% CI – 0·31 to 0.29, $I^2 = 0\%$, $p = 0.96$) (**d**). The game-based DTx improved hyperactivity/impulsivity compared to the control (SMD 0·30, 95% CI 0.05–0.55, $I^2 = 4\%$, $p = 0.02$) (**f**)

DTx included 128 participants from four RCTs. The results showed that medication improved attention compared to game-based DTx; however, the difference was insignificant (SMD − 0·30, 95% CI − 0·65–0·05, $I^2 = 0\%$, $p = 0{\cdot}10$) (Fig. 4a). For indirect analysis, medicine (SUCRA, 0·99) was ranked highest, followed by game-based DTx (SUCRA, 0·51) and control (SUCRA, 0·00) for improved attention by parents (Table S18). Detailed indirect efficacy comparison of inattention between the interventions is presented in Table S12.

The subgroup analysis of the assessment instruments was not significantly different from any within-group analysis. The assessment instruments of a total of six were reported game-based DTx versus control, and three assessment instruments were conducted game-based DTx versus medication (Table S4). The overall ROB analysis results were not generally significant within groups, except for game-based DTx compared to the control ($p = 0{\cdot}02$) (Table S5).

Hyperactivity

Hyperactivity was reported for game-based DTx and control data. In 552 participants of six RCTs, game-based DTx improved hyperactivity compared to the control (SMD 0·15, 95% CI − 0·04, 0·34, $I^2 = 0\%$, $p = 0{\cdot}13$) (Fig. 3c). Indirect analysis of hyperactivity could not be conducted because medical data were unavailable.

The subgroup analysis of the four assessment instruments was included, and the results were not significant (Table S4). To analyze the overall ROB, low- and high-level ROB were evaluated; however, no significant subgroup difference was observed (Table S5).

Hyperactivity/impulsivity

Five RCTs with 256 participants reported the effect of game-based DTx versus control. The game-based DTx group showed improved hyperactivity/impulsivity than the control group (SMD 0·28, 95% CI 0·03–0·53, $I^2 = 0\%$, $p = 0{\cdot}03$) (Fig. 3e). The medication group showed enhanced hyperactivity/impulsivity than the control group (SMD − 0·24, 95% CI − 0·65 to 0·17, $I^2 = 0\%$, $p = 0{\cdot}25$) (Fig. 4c). Medicine (SUCRA, 0·94) was the highest, followed by game-based DTx (SUCRA, 0·55) and control (SUCRA, 0·02) for improving hyperactivity/impulsivity assessed by parents (Table S16). Detailed indirect efficacy comparison of hyperactivity/impulsivity between game-based DTx is shown in Table S13.

For subgroup analysis, no differences were observed between the assessment instruments. The assessment instruments of a total of four were reported as game-based DTx versus control (Table S4). The analysis of both game-based DTx versus control and game-based DTx versus medication showed that some concerns and high-level ROB were not significantly associated with subgroup differences (Table S5).

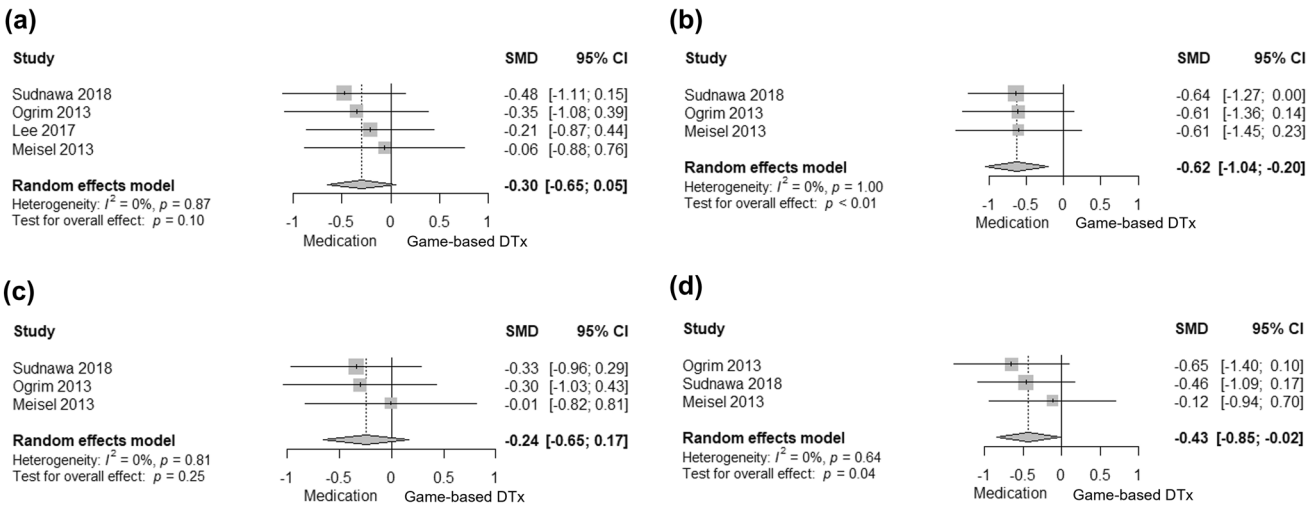

Fig. 4 Forest plot of the effect of game-based DTx compared to the medicine group using direct meta-analysis. **a** Inattention with the assessment of parents; **b**) Inattention with the assessment of the teacher; **c** Hyperactivity/impulsivity with the assessment of parents; **d** Hyperactivity/impulsivity with the assessment of the teacher. For parents, the medication improved attention compared to game-based DTx; however, the difference was insignificant (SMD – 0.30, 95% CI – 0.65 to 0.05, $I^2 = 0\%$, $p = 0.10$) (**a**). The medication group showed enhanced hyperactivity/impulsivity than the control group (SMD – 0.24, 95% CI – 0.65 to 0.17, $I^2 = 0\%$, $p = 0.25$) (**c**). For teacher, the game-based DTx versus medication (SMD – 0.62, 95% CI – 1.04 to – 0.20; $I^2 = 0\%$; $p < 0.01$) (**b**). The medication group showed enhanced hyperactivity/impulsivity compared to the control group (SMD: − 0.43, 95% CI – 0.85 to – 0.02, $I^2 = 0\%$, $p = 0.04$) (**d**)

Results of assessor: teacher

Inattention

Game-based DTx improved attention compared to the control group, with 424 participants in nine studies (SMD 0·21, 95% CI 0·03–0·39, $I^2 = 1\%$, $p = 0·02$) (Fig. 3b). The three RCTs with 92 participants included game-based DTx versus medication (SMD − 0·62, 95% CI − 1·04 to − 0·20; $I^2 = 0\%$; $p < 0·01$) (Fig. 4b). For indirect analysis, medicine (SUCRA, 1·00) had the highest rank, followed by game-based DTx (SUCRA, 0·49) and control (SUCRA, 0·01) (Table S16). Detailed indirect efficacy comparison of inattention by the teacher between the interventions is presented in Table S14.

For subgroup analysis, no differences were observed between the game-based DTx and control groups based on the assessment instruments. The assessment instruments of a total of six were reported as game-based DTx versus control (Table S6). No low level was observed for the overall ROB results, and the results were insignificant (Table S7).

Hyperactivity

In 171 participants of three RCTs, the control group had improved hyperactivity than the game-based DTx group (SMD − 0·01, 95% CI − 0·31 to 0·29, $I^2 = 0\%$, $p = 0·96$) (Fig. 3d). However, only game-based DTx versus control data have been reported. Indirect analysis of hyperactivity could not be conducted because medical data were unavailable.

Hyperactivity/impulsivity

In 256 participants from five studies, game-based DTx improved hyperactivity/impulsivity than the control (SMD 0·30, 95% CI 0·05–0·55, $I^2 = 4\%$, $p = 0·02$) (Fig. 3f). In game-based DTx versus medication, the medication group showed enhanced hyperactivity/impulsivity than the control group (SMD: − 0·43, 95% CI − 0·85 to − 0·02, $I^2 = 0\%$, $p = 0·04$) (Fig. 4d). Overall, medicine (SUCRA, 0·93) was ranked highest, followed by game-based DTx (SUCRA, 0·55) and control (SUCRA, 0·02) for improving hyperactivity/impulsivity by parents (Table S16). Detailed indirect efficacy comparison of hyperactivity/impulsivity in game-based DTx is presented in Table S15.

In the subgroup analysis of game-based DTx versus the control, no difference was observed between the assessment instruments. The assessment instruments of a total of five were reported as game-based DTx versus control (Table S6). The game-based DTx versus control groups showed that some concerns and high-level ROB were insignificant with subgroup differences (Table S7).

Sensitivity analysis

Sensitivity analyses were based on the exclusion of studies with the most participants. There were no main analyses or changes in most studies except for three outcomes. We attempted to perform a sensitivity analysis using ROB; however, the sample size of each study was too small to conduct. The details of the analysis are presented in Table S8.

Discussion Although the treatment method for ADHD differs according to age, non-pharmaceutical treatment is implemented as the first-line treatment for children and adolescents [44, 45]. However, pharmaceutical treatment is used in children from 6 years or older based on the symptoms [44, 46, 47]. Currently, in the treatment of children with ADHD, existing drug treatment is effective for a short period; however, considering the severity of ADHD symptoms, it is ineffective in reducing daily living disorders or has the risk of side effects, misuse, and abuse [48, 49]. In this scenario, game-based DTx is expected to be a new turning point, and the role of DTx in ADHD treatment is emerging as EndeavorRx® was recently approved by the FDA for treating ADHD. In this study, we performed a systematic review and meta-analysis based on the assessor—parents and teachers for ADHD-related interventions to investigate the effect of game-based DTx on each specific ADHD symptom.

In our study, 20 studies including 1,402 patients with ADHD were divided into inattention, hyperactivity, and hyperactivity/impulsivity groups, which are the main types of ADHD, and each group was evaluated. From our direct and indirect results in all assessors, game-based DTx significantly improved attention, a key outcome in children and adolescents with ADHD, compared to the controls. ADHD has numerous well-characterised but heterogeneous neurobiological substrates underlying cognitive impairments, making it a target for intervention development [14]. For instance, lower frontal, frontoparietal, and ventral attention network activation is linked to deficiencies in attention and cognitive control [50]. Game-based DTx improves attention because it treats diseases with related cognitive impairments by activating specific nervous systems in the brain [14]. From the analysis, we observed that medication treatment increased attention more than game-based DTx in teacher assessment; however, no significant difference was observed when the assessor was a parent. Given that this is a subjective, observer-based assessment, the parents of children with ADHD spend more time with them than their teachers on average; hence, they may have judged the child's attention more accurately [51].

Regarding hyperactivity, we observed no difference between the game-based DTx and control groups, regardless of the assessor, and several factors can explain these

results. First, the results reported by parents and teachers may be insensitive to the influence of game-based DTx. In other words, the proven effectiveness of interventions on hyperactivity may be difficult for parents and teachers to easily observe because young children are generally active, and it is difficult to determine deviating activity levels [52]. In addition, most of the studies evaluated both hyperactivity and impulsivity, and the number of individual studies that evaluated only hyperactivity was significantly small; hence, it is worth noting that a significant result may not have been obtained. Finally, certain mechanisms common to game-based DTx and controls may have led to improvements in both groups. Furthermore, both groups required sustained patience and may have required trained coping and reevaluation skills or even increased self-efficacy and mastery [53]. Generally, children and adolescents with ADHD who show hyperactivity symptoms respond well to drug treatment [54]. In a previous meta-study, medicine was evaluated because it significantly reduced hyperactivity [49]. Among therapeutic drugs, stimulants correct a prefrontal dopamine deficit and dopamine excess in the basal ganglia [55]. Although stimulants are very effective in treating ADHD, side effects such as stomach pain, decreased appetite, insomnia, headaches, and restlessness can be observed [56, 57]. Some children may develop tics, and side effects such as rebound hyperactivity and psychosis have been reported [58]. The effects of game-based DTx on ADHD are related to EEG [57]. However, there is still insufficient evidence to present an evaluation on the effect of game-based DTx on hyperactivity in ADHD patients; hence, additional research is required.

Hyperactivity/impulsivity is pathophysiologically presumed to be a symptom caused by weaker function and structure of prefrontal cortex (PFC) circuits, PFC requires optimal levels of norepinephrine and dopamine for proper functioning [59]. In this study, as in previous studies, game-based DTx significantly improved hyperactivity/impulsivity in children and adolescents with ADHD compared to controls, regardless of the assessor [23, 24]. For pharmacological treatment, when psychostimulants are slowly absorbed into the body through oral administration, they modulate the neurodevelopment of dopaminergic neurons and improve hyperactivity and impulsivity [60]. However, symptoms of hyperactivity and impulsivity become somewhat resistant to psychostimulant treatment [45]. When medication and game-based DTx were compared, medication showed good efficacy; however, this effect of our study was not statistically significant in parental assessment. An existing meta-analysis reported that pharmacological treatment showed better efficacy than non-pharmacological treatment [23]. However, this was not a game-based DTx study, and analysis according to the evaluators was not performed. Also, the teachers view the child in the context of peers with more distractions in school, and parents have the possibility of providing results by observing the participants for a relatively long time [61]. Therefore, it may be the result of differences in the potential disturbance effects of places, groups, peers, etc., and this can be evaluated as an area that requires additional research in the future.

This study had several limitations. First, a significant number of game-based treatment studies were conducted before EndeavorRx® approval; however, small sample size and various outcome endpoints were measured in addition to indirect analysis, and the evaluation indicators were also very diverse, care must be taken in interpretation. Nevertheless, we attempted to statistically verify the differences between the evaluation methods used by conducting thorough selection exclusion criteria and subgroup analysis for each assessment instrument. Second, most of the included studies did not report safety; therefore, it was impossible to analyse them. We recommend that the evaluation part of safety in addition to efficacy be performed for future game-based DTx studies. Third, the control groups included in this study were diverse. The control group was classified as active control and placebo. Since game-based DTx was not approved as a treatment before EndeavorRx® approval; we analyzed all treatments evaluated unrelated to ADHD improvement in each study by classifying them into the control group. Also, the active control did not show improvement in cognitive function, so it had the same properties as the placebo, and therefore, the possibility of bias caused by the diversity of the control group is low in our study. Finally, we have a limitation of outcome assessment tools. Our study used typical tools, parent-rated or teacher-rated. Although these are generally reliable and valid components of the ADHD assessment [12], they are variously organized into classifications and subjective assessments. However, the Test of Variables of Attention measurement tool (TOVA), which is an objective assessment tool, differs from typically used measures. Widely used in both clinical practice and research investigations, TOVA is an FDA-cleared tool for the objective evaluation of attention and inhibitory control as part of the diagnosis of ADHD or for tracking the effectiveness of interventions [62]. The TOVA tests cognitive abilities that are connected with clinically significant outcomes, such as academic conduct, inattention, and social issues, and are pertinent to the clinical presentation of ADHD [63–65]. Additionally, it has been stated that the TOVA environment mimics "one aspect of the classroom context in which students are obliged to remain seated and engaged in a boring, repetitive job," which suggests that the TOVA has ecological validity for settings found in the real-world[66]. Therefore, the diversity and objectification of evaluation methods after treatment intervention, it is necessary to use a standardized outcome measurement tool in future clinical trial studies. Nevertheless, this study is the first meta-analysis study to compare the efficacy of game-based DTx between control

and medication according to the assessor, including only RCT studies.

Successive developments and approvals of digital therapeutics have raised the expectation that digital therapeutics such as EndeavorRx® will play an important role in the treatment and improvement of human diseases. However, the present clinical research agenda for ADHD is lacking, and more well-designed and published randomized studies are required to evaluate the advantages and disadvantages of the many therapies available for the treatment of ADHD. Objective evaluation indicators such as TOVA also should be needed. In the other hand, brain imaging techniques such as functional MRI, which can capture dynamic situations such as oxygen flow in the brain in ADHD patients [67], or diffusion tensor imaging (DTI), which uses the motion of water molecules to image nerve cells in the brain [68], are being increasingly studied. Therefore, research using brain imaging techniques in game-based DTx is also needed. The various treatment studies suitable for children with ADHD, considering the age and individual disease type and clinical trials to confirm the long-term effects and safety of game-based DTx should be conducted. Consequently, it is expected that a new treatment era will emerge for children and parents with ADHD through the successful development of game-based DTx-related scientific and objective results with minimized research bias.

This study is the first direct and indirect meta-analysis to compare the efficacy of game-based DTx between control and medication according to the assessor in an RCT. In conclusion, game-based DTx had a more significant effect than the control. Additionally, between medication treatment versus DTx, medication was more effective. However, the evaluation results may be different in clinical effectiveness depending on the assessor. Our findings can help clinicians, parents, and caregivers make informed decisions about treatment options for managing ADHD, and the uncertainty, benefits, costs, and potential risks of available treatments can be discussed before initiating treatment.

Author contributions EY contributed to the conceptualisation, methodology, project, administration, supervision, and writing (review and editing). SA contributed to the conceptualisation, data curation, methodology, project administration, visualisation, and writing (original draft, review, and editing). JN, DH assessed the study eligibility and quality. All the authors contributed to the interpretation and subsequent editing of the manuscript.

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Data avilability Extracted data are available on request to the corresponding author.

Declarations

Conflict of interest The authors declare they have no conflict/competing of interest.

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