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Pilot study of a mobile application-based intervention to induce changes in neural activity in the frontal region and behaviors in children with attention deficit hyperactivity disorder and/or intellectual disability

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ABSTRACT

Children with neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD) and intellectual disability (ID), need early intervention and continuous treatment. We aimed to investigate the feasibility and acceptability of mobile application-based interventions in children with ADHD and ID in supporting attention and cognitive function. Twenty-six children with ADHD and/or ID with attention and cognition difficulties were recruited. Participants completed a 12-week mobile application-based intervention. To assess whether digital intervention improved attention and cognitive function, we used the Comprehensive Attention Test (CAT), Cambridge Neuropsychological Tests Automated Battery (CANTAB), and electroencephalography (EEG) to examine direct changes in children's behavior and neural activity. Clinicians and parents assessed changes using the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2), Korean version of the ADHD Rating Scale (K-ARS), Clinical Global Impression-Improvement Scale, and parental questionnaires. The intervention induced changes in neural activities on EEG and behavior but there were no significant changes in CAT and CANTAB results. Relative theta and alpha power were significantly lower post-intervention in the eyes-open (EO) condition of EEG recording and these changes were mainly observed in the frontal regions of the brain. Parental reports using the BRIEF-2 and K-ARS noted significant improvements in executive function, attention, and hyperactivity-impulsivity. In addition, the clinical impression improved in 60% of participants. These results provide evidence that a mobile application-based intervention has the benefit of supporting children with ADHD and/or ID. Digital intervention could change neural activity and improve children's attention and cognitive function. Given our findings, we suggested that mobile application-based digital therapeutics may have great potential for helping children with neurodevelopmental disorders who need continuous treatment.

1. Introduction

Neurodevelopmental disorders are a group of conditions with early onset deficits that produce impairments in personal, social, academic, and/or occupational function (APA, 2013). Although these disorders typically manifest early in development, they can be lifelong conditions (Thapar et al., 2017). Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by persistent and age-inappropriate levels of inattention, hyperactivity, and impulsivity that interfere with function or development (APA, 2013). Recent studies have revealed reduced subcortical brain volume and decreased neural activity in patients with ADHD, resulting in impairments of

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Table 1
Demographic data of participants.

	Total (n = 21)	ADHD (n = 12)	ID (n = 9)	*p*-value
Age	7.11 (1.19)	6.69(0.72)	7.66 (1.50)	0.065
Full scale IQ	72.33 (21.49)	84.75(17.83)	52.33 (15.38)	**0.001*****
Gender ratio (M: F)	11:10	8:4	3:6	–

Mean and S.D. presented. ADHD: attention-deficit hyperactivity disorder, ID: intellectual disability, IQ: intelligence quotient. ***$p < 0.005$.

neurocognitive function, including executive functions (EFs), motivation, and rewards (Tripp and Wickens, 2009). Medications are recommended as a first-line therapy for ADHD; however, evidence for their long-term efficacy is unclear. Along with pharmacological treatment, non-pharmacological interventions such as behavioral therapy are also recommended as an evidence-based treatment for ADHD (Caye et al., 2019).

Intellectual disability (ID) is another neurodevelopmental disorder characterized by both intellectual and adaptive function deficits in conceptual, social, and practical domains, which become obvious during childhood (APA, 2013). People with ID have lifelong deficits in cognitive and adaptive function that affect a variety of everyday activities. There are many different etiologies for ID including genetic, acquired (congenital and developmental), environmental, and sociocultural (Katz and Lazcano-Ponce, 2008). Even if ID is not curable, it is known that some areas of cognitive function can be improved through training. Studies have shown that early interventions have long-term beneficial effects on cognition, language, academic outcomes, and childhood behavior (Purugganan, 2018).

Although ADHD and ID are different disorders, individuals with ID are at heightened risk of being diagnosed with ADHD (Neece et al., 2011, 2013). The prevalence of concurrent ADHD and ID is 14%, which is much higher than the 1% prevalence of ID in the general population. They share neurodevelopmental defects based on their etiology and have common symptoms, such as inattention and hyperactivity/impulsivity (McClain et al., 2017).

It is required to provide early intervention for supporting children with ADHD and ID in their attention, behavioral problems, and cognitive function to maximize their developmental outcomes. However, there are many children who cannot receive therapeutic interventions for various reasons such as time, financial expense, long waiting lists, and lack of well-trained professionals. Therefore, a new therapeutic approach is needed to overcome these difficulties.

The development and adoption of digital technologies in the management of mental healthcare has generated much attention. Digital interventions include the use of technology to provide practical assistance (e.g., short message service medication and appointment reminders), monitoring symptoms and giving notifications, providing information or consultations online, and novel therapies built with technology, such as virtual reality and serious games (Sheehan and Hassiotis, 2017). Smartphones are becoming increasingly popular worldwide. In 2019, the rate of smartphone usage was 76% in developed countries and 45% in developing countries. In particular, the penetration rate of mobile phones in South Korea was 100%, of which smartphone users accounted for 95%, the highest smartphone penetration rate among the countries surveyed (SILVER, 2019).

A mobile application (app)-based platform allows patients to access treatment easily, regardless of their location or time constraints. In particular, in a situation where social distancing is required in a pandemic, such as that of coronavirus disease 2019 (COVID-19), the necessity for this platform has been emphasized more (Wright and Caudill, 2020). For this reason, various treatment methods using mobile apps have been reported. For example, Weisman et al. showed that smartphone apps could promote adherence to medication among youth with ADHD (Weisman et al., 2018). Arean et al. showed the effectiveness of mobile apps in treating depression, especially in people with moderate levels of depression (Arean et al., 2016). Akili Interactive proved that their video game-like digital intervention reduced the severity of pediatric ADHD symptoms and received permission for marketing digital therapeutic devices from the U.S. Food and Drug Administration (FDA) for the first time (2020; Kollins et al., 2020). Therefore, it is expected that the development and application of interventions through digital therapeutics will become more active in the near future.

DoBrain, a type of serious game based on mobile apps, was developed for children to train their attention and cognitive skills, including memory, discrimination, numeracy, and reasoning, through short stories and games. The advantage of using stories and games is that children can use them easily and enjoyably, regardless of the time or place.

This study aimed to assess whether mobile app-based interventions, such as *DoBrain*, are feasible and can benefit children with neurodevelopmental disorders by improving their attention and cognitive function. Our primary goal was to explore the acceptability of mobile app-based interventions at home. The second goal was to evaluate whether mobile app-based intervention leads to improvement in attention, EFs, and cognitive functions. For these goals, tasks were selected to confirm objective changes in children's behavior, and the evaluation of clinicians and parents were also conducted.

2. Methods

2.1. Participants

Participants were recruited from Severance Hospital, Yonsei University College of Medicine, where this study was performed. After the screening, a total of 26 children were enrolled, and 21 of them completed the study. Participants included 12 children with a confirmed diagnosis of ADHD (mean age = 6.69 years) and 9 children with a confirmed diagnosis of ID (mean age = 7.66 years) (Table 1). Five participants in ADHD group had mild ID (<76 total intelligence quotient (IQ)), and there was a significant difference in full scale IQ within ADHD group. Three participants were taking medication for ADHD (Supplementary Table 1). All participants were asked not to change the schedule of treatment and education including medications during the study period. Eligibility criteria for ADHD group included the following: 1) between the ages of 5–7 years; 2) confirmed DSM-5 diagnosis of ADHD; and 3) not accompanied by other neurological disorders. Eligibility criteria for ID group included the following: 1) between the ages of 5–12 years with a developmental age of 5–7 years; 2) confirmed DSM-5 diagnosis of ID; and 3) not accompanied by other neurological disorders. This study was approved by the applicable Institutional Review Boards (IRB) at Severance Hospital, Yonsei University College of Medicine (4-2019-0079). Written informed consent was obtained from all participants and their parents prior to starting study.

2.2. Procedures

When all the pre-evaluations were completed, the researcher installed the *DoBrain* app on the participant's device (tablet or mobile phone) and guided how to use it. According to user's cognitive age, the level was divided into A to C (A: 30–43 months, B: 44–57 months, C: 58–72 months). In this study, we determined level based on the participant's full scale IQ and asked parents not to change the level during the research. The program was provided through the app on every Tuesday, Thursday and Saturday. The participants asked to complete 108 sessions (three times a week for 12 weeks). The programs a child needs to complete per day consisted of 2 story sessions and 1 game session (three sessions a day). The story sessions consist of a simple fairy tale and tasks related to the story which are presented in the middle. The tasks were developed to train diverse cognitive skills such as memory, discrimination, mathematical thinking and logical reasoning. The game

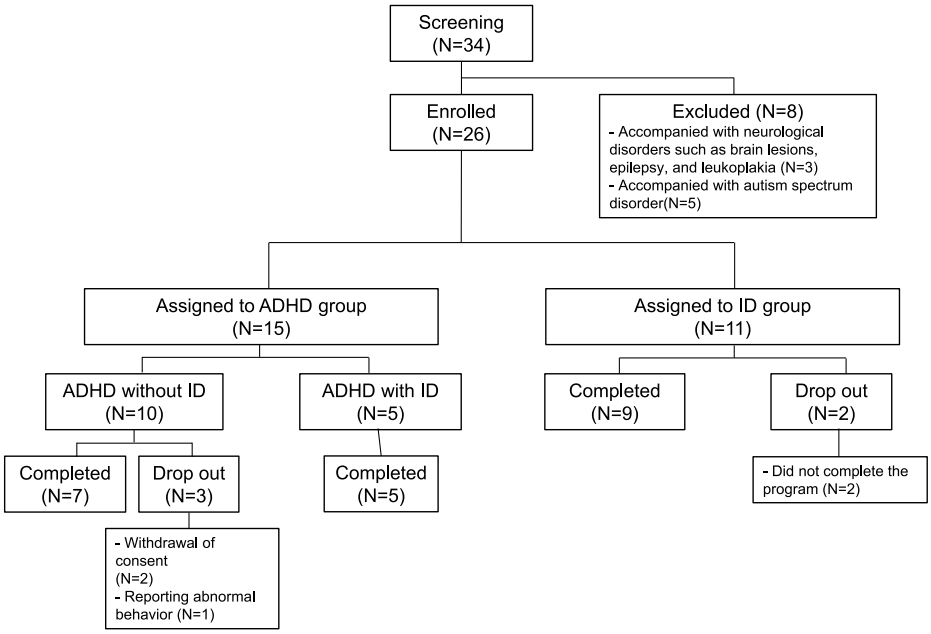

Fig. 1. Flow diagram for study participants.

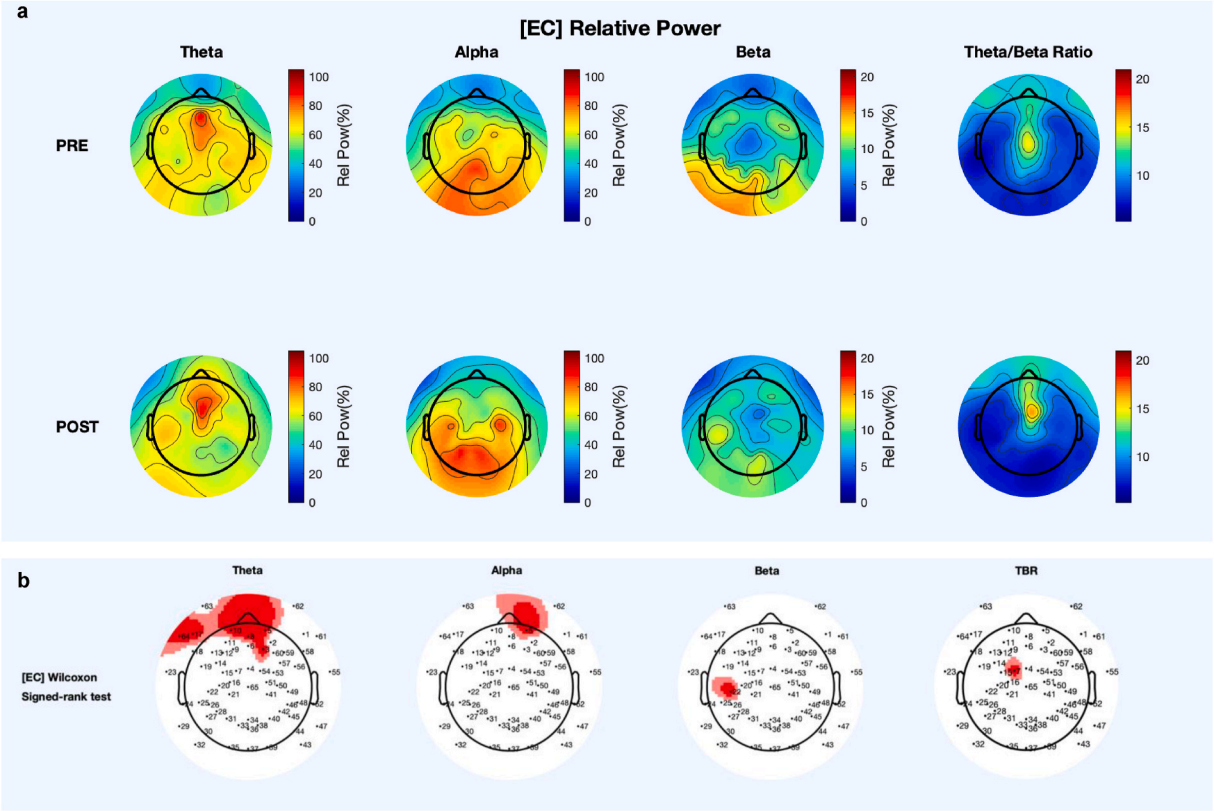

Fig. 2. Topographic maps and significant maps: Eyes Closed (EC) condition. **a.** Topographic maps of relative powers in theta, alpha, and beta bands and TBR in both pre- and post-intervention. **b.** Significance maps (By Wilcoxon signed-rank test) of relative powers in theta, alpha, and beta bands and TBR in both pre- and post-intervention. The red indicates regions with statistically significant differences ($p < 0.05$). Data from 3 children in ADHD group and 5 children in ID group (n = 8), TBR: Theta-to-beta ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

sessions were developed to repeatedly train one cognitive domain (Supplementary Fig. 1). Every level starts with easy tasks and the difficulty gets higher as the session continues. Post-evaluation was conducted after 108 sessions were completed. If the schedule was delayed, participation was encouraged by researcher through text message or phone call.

Table 2
Wilcoxon signed-rank test results for channels with significant differences ($p < 0.05$) between pre- and post-*DoBrain* EEG powers and TBR in Eyes Closed (EC) condition.

Chan.	Relative power: Theta			
	Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
E3	Frontal	61.06 (54.38, 74.22)	72.52 (68.52, 93.84)	0.016
E5	Frontal	44.89 (35.79, 56.9)	63.86 (57.17, 81.55)	**0.008****
E8	Frontal	60.39 (45.5, 66.17)	68.87 (54.28, 95.89)	**0.008****
E10	Frontal	56.59 (38.2, 62.97)	57.62 (50.38, 80.88)	0.023
E17	Lt. Frontal	42.61 (34.94, 59.24)	36.6 (29.7, 47.11)	0.039
E64	Lt. Frontal	36.78 (30.71, 53.65)	34.19 (27.1, 39.84)	0.039
Chan.	**Relative power: Alpha**			
	Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
E5	Frontal	19.34 (12.31, 59.07)	36.23 (18.56, 71.72)	0.016
Chan.	**Relative power: Beta**			
	Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
E22	Lt. Temporal	6.17 (5.31, 11.3)	11.08 (7.94, 14.89)	0.0391
Chan.	**TBR**			
	Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
E7	Central	12 (10.67, 14.08)	9.65 (6.56, 12.19)	0.023

Data from 3 children in ADHD group and 5 children in ID group (n = 8). Median, Lower Quartile (Q1) and Upper Quartile (Q3) are presented (Median (Q1, Q3)). Chan.: channel number, Lt: left, TBR: Theta-to-beta ratio. **$p < 0.01$.

2.3. Outcome measures

2.3.1. Comprehensive Attention Test (CAT)

CAT is a kind of continuous performance test designed to comprehensively evaluate the attention of children and adolescents in Korea. The clinical reliability and validity of CAT were previously confirmed (Yoo HK, 2009). Depending on the participant's age, the composition of subtest is different. In the present study, we used simple selective attention (visual and auditory), inhibition-sustained attention and interference-selective attention. The results are calculated as attention quotient (AQ) score, a value calculated based on standardized data by gender and age. It is expressed as "normal" when the AQ score is 85 or higher, "borderline" when it is between 76 and 84, and "low" when it is less than 76.

2.3.2. Cambridge Neuropsychological Tests Automated Battery (CANTAB)

CANTAB is a computer-based assessment tools for measuring the cognitive function correlated to neural networks (Fray PJ, 1996). It has been used for understanding the specific brain functions in diverse disorders and syndromes and also used to evaluate the effects of interventions designed to improve brain function (Davis et al., 2018; Fray PJ, 1996). The following tests were selected in this study to assess the participants' attention and cognitive functions; Motor Screening Task, Reaction Time, Pattern Recognition Memory, Spatial Working Memory, and Spatial Span.

2.3.3. Electroencephalogram (EEG)

Of 26 children who enrolled in the study, 24 children and their parents gave consents to participate in the EEG recording. For these 24 children, baseline EEG was acquired prior to starting the 12-week *DoBrain* program. Of these 24 children, 17 children completed the study and underwent post- EEG recording. Because of poor cooperation in Eyes Closed (EC) condition, Eyes Open (EO) condition was excluded in one child at the pre-evaluation. This child was recorded only under EC condition at the post-evaluation (Supplementary Fig. 2).

Recording for EC and EO conditions each lasted for 5 min. During EEG recording, children sat on a comfortable chair in front of a white paper with a fixation cross, accompanied by an experimenter. For EC condition, children were instructed to sit still with eyes closed for 5 min. For EO condition, they were instructed to sit still while looking at the fixation cross with minimal blinking. Children were given a few seconds to blink and move around whenever they seemed impatient or irritable during the 5-min recording sessions.

An Electrical Geodesics Inc. Net Station system (EGI-Philips, Eugene, OR, USA) was used for EEG acquisition. EEG was recorded from 65-channel HydroCel Geodesic Sensor Net, and Net Station v5.4 software, with reference to Cz electrode. Signals were filtered with a 0.01 Hz–400 Hz band-pass filter, and digitized with a sampling rate of 1000 Hz. The impedance for each electrode was maintained below 30 kΩ. Channels were grouped into scalp regions as following: Frontal - E2, E3, E5, E8, E9, E10, E11, E12; Central - E4, E7, E16, E21, E41, E51, E54, E65; Parieto-Occipital - E31, E33, E34, E35, E36, E37, E38, E39, E40; Left Temporal - E14, E15, E19, E20, E22, E25, E26, E27, E28; Right Temporal - E42, E45, E46, E48, E49, E50, E53, E56, E57 (Supplementary Fig. 3).

MATLAB 9.5.0 (MathWorks, USA) with EEGLAB toolbox v2019.0 was used for data preprocessing and analysis (Delorme and Makeig, 2004). Data was re-referenced to common average reference, and filtered using a high pass filter of 0.1 Hz and a 50 Hz notch filter. Continuous EEG data were segmented into 2-s epochs and subjected to an artifact rejection procedure. Using an EEGLAB function for artifact detection, any data with signal amplitude above 100 μV were marked as artifacts. Artifactual data were then rejected through a multi-step process. First, epochs were rejected if more than 13 channels (20% of all channels) within a single epoch were marked as artifacts. If the number of remaining epochs was smaller than 30 after epoch rejection, thus yielding less than 60 s of data, the dataset was removed. Second, channels were rejected if marked as artifacts in more than 50% of all epochs. If more than 20% of all channels (13 channels) were rejected, the dataset was considered as inadequate and likewise removed from further processing and analysis. Bad channels that had been marked were then interpolated on an epoch-by-epoch basis, using TBT plugin (Ben-Shachar, 2018).

This pipeline yielded a minimum of 60 s of artifact-free data for each remaining dataset. After preprocessing, 8 participants with clean EEG datasets for both pre- and post- EEG in the EC condition, and 9 participants in the EO condition were included in further analysis. Summary of acquired and preprocessed data is provided in Supplementary Fig. 1. Preprocessed data were then subjected to power computation. For each dataset, 30 epochs (60 s of data) were randomly extracted, and Fourier transformed for spectral analysis of five frequency bands (delta, 1–3 Hz; theta, 3.5–7.5 Hz; alpha, 7.5–12.5 Hz; beta, 13–21 Hz). Relative power was computed as the percentage of the amplitude in each band, relative to the total amplitude across all frequency bands. Theta-to-beta ratio (TBR) was calculated as power of theta divided by power of beta.

2.3.4. Behavior Rating Inventory of Executive Function, second edition (BRIEF-2)-parent form

BRIER-2 is a second edition of BRIEF and a 63-item questionnaire about executive functioning behaviors shown by children over the past 6 months in everyday life. Each question is scored from 1 to 3 points based on frequency (Gerard A. Gioia, 2015). The nine subscales (inhibit, self-monitor, shift, emotional control, initiate, working memory, plan/organize, task-monitor and organization of materials) are aggregated into three domains (Behavior Regulation Index (BRI), Emotion Regulation Index (ERI) and Cognitive Regulation Index (CRI)) and yield one overall score, Global Executive Composite (GEC). In each scale and index, a raw score was converted to a T-score (M = 50, SD = 10). A higher score indicates greater impairment.

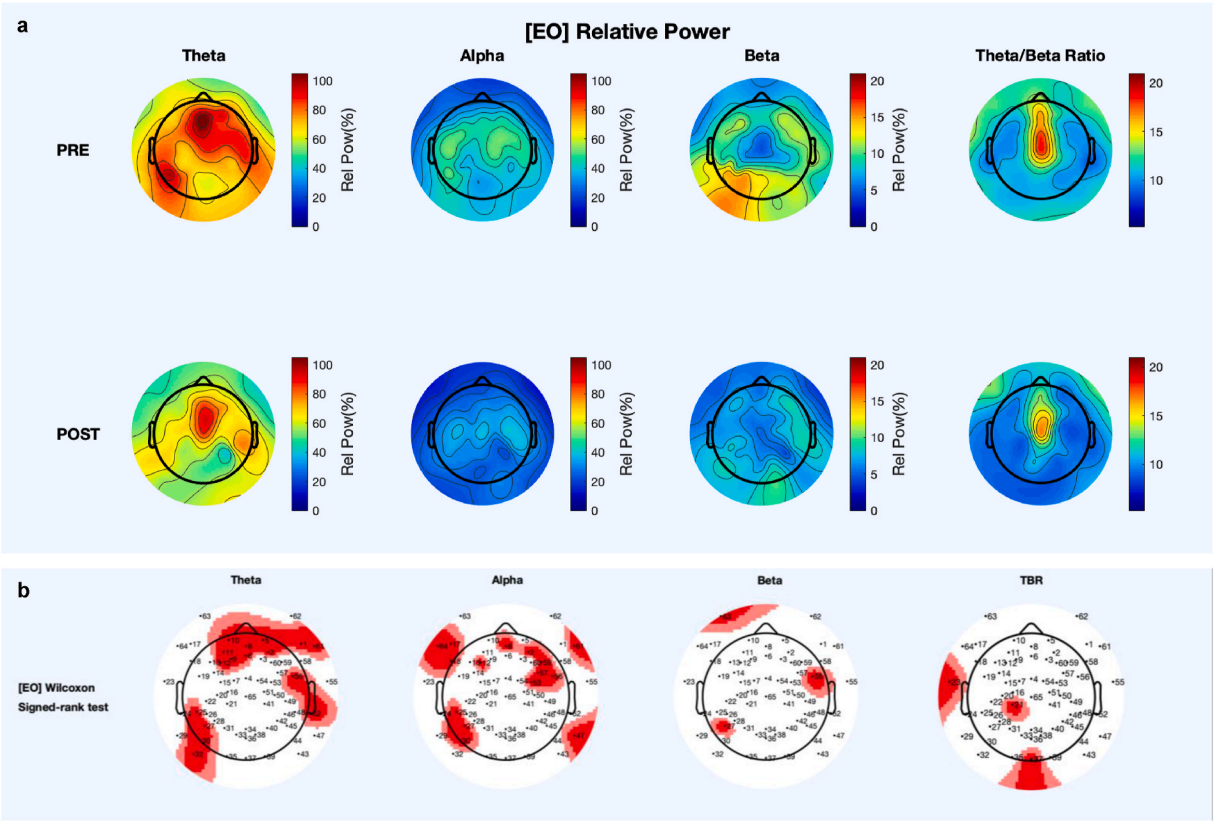

Fig. 3. Topographic maps and significant maps: Eyes Open (EO) condition. **a.** Topographic maps of relative powers in theta, alpha, and beta bands and TBR in both pre- and post-intervention. **b.** Significance maps (By Wilcoxon signed-rank test) of relative powers in theta, alpha, and beta bands and TBR in both pre- and post-intervention. The red indicates regions with statistically significant differences ($p < 0.05$). Data from 4 children in ADHD group and 5 children in ID group (n = 9). TBR: Theta-to-beta ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.3.5. Korean version of ADHD rating scale (K-ARS)

K-ARS is a Korean version of ARS, ADHD symptom severity scale developed by DuPaul et al. (DuPaul GJ, 1998). It is an 18-item inventory and consists of two subscales, inattention and hyperactivity-impulsivity. Either the parents or teacher can give a score from 0 to 3 for each item according to the frequency of the child's behavior. The reliability and validity of K-ARS has been confirmed (So YK, 2002). A higher score indicates greater impairment and the cut off score was 19.

2.3.6. Clinical Global Impression-Improvement Scale (CGI-I)

To provide an objective clinical impression of a single individual, CGI scale has been used in clinical studies (Guy, 1976). Especially, CGI-I measures a change of individual's change compared to baseline. Before and after the study, it was evaluated through an interview with a specialized child and adolescent psychiatrist. CGI-I is rated on a seven-point scale: 1 = very much improved since the initiation of treatment; 2 = much improved; 3 = minimally improved; 4 = no change from baseline; 5 = minimally worse; 6 = much worse; and 7 = very much worse since the initiation of treatment (Busner and Targum, 2007).

2.4. Statistical analysis

Analyses were performed using the Statistical Package for the Social Sciences software (version 25.0; SPSS Inc., Chicago, IL, USA), SAS (version 9.4, SAS Inc., Cary, NC, USA) and R software version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). We used independent *t*-test to compare the mean between groups. Considering the small sample sizes and the lack of data normality, non-parametric statistical methods were used for analysis within group. Wilcoxon Signed Ranks test was used to examine the effect of intervention within group. Statistical significance was defined at $p < 0.05$.

3. Results

3.1. Participant flow

A total of 34 children were screened for this study; a total of eight children were excluded after screening. All excluded children had neurological disorders, such as brain lesions, leukomalacia, and epilepsy (n = 3) or other neurodevelopmental disorders, such as autism spectrum disorder (ASD) (n = 5). In the ADHD group, three participants were excluded from the study for withdrawal of consent (n = 2) and reporting abnormal behaviors (n = 1). Two participants in the ID group were excluded from the study because they did not complete the program as scheduled. A total of 12 children with ADHD and 9 with ID completed the study, as shown in Fig. 1.

3.2. Neurocognitive outcomes

3.2.1. Electroencephalography (EEG)

EEG analysis was conducted only in children with clean EEG datasets for both pre- and post-intervention (8 children in the EC condition (ADHD: 3, ID: 5) and 9 children in the EO condition (ADHD: 4, ID: 5)). For the EC condition, the relative theta power was significantly higher after the *DoBrain* intervention compared to that at baseline in channels located in the frontal region ($p < 0.05$ at E3 and E10; $p < 0.01$ at E5 and E8). In left frontal channels, on the other hand, theta activity was significantly reduced after the intervention ($p < 0.05$ at E17 and E64). An increase in alpha power was found in one frontal channel (E5, $p =$

Table 3
Wilcoxon signed-rank test results for channels with significant differences ($p < 0.05$) between pre- and post-*DoBrain* EEG powers and TBR in Eyes Open (EO) condition.

Chan.	Relative power: Theta			
	Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
E1	Lt. Frontal	55.3 (50.8, 77.5)	42.58 (38.6, 50.29)	0.0391
E2	Frontal	84.94 (69.77, 112.25)	60.17 (57.08, 83.68)	**0.0039*****
E5	Frontal	62.58 (59.33, 88.38)	58.39 (54.53, 64.35)	0.0195
E6	Frontal	116.68 (92.22, 126.43)	79.27 (70.78, 89.98)	**0.0078****
E8	Frontal	86.44 (78.04, 95.73)	59.09 (53.74, 69.44)	**0.0039*****
E9	Frontal	87.71 (72.16, 95.28)	68.6 (60.23, 76.69)	0.0391
E10	Frontal	60.45 (56.69, 87.62)	54.3 (52.78, 61.69)	0.0391
E11	Frontal	75.05 (59.41, 84.23)	54.95 (51.75, 71.27)	0.0273
E12	Frontal	78.48 (74.34, 94.55)	54.7 (45.89, 58.69)	0.0391
E25	Central	85.52 (65.67, 107.28)	64.66 (51.88, 75.06)	0.0391
E27	Central	94.36 (79.04, 113.5)	60.54 (50.16, 70.48)	**0.0039*****
E30	Lt. Parietal	86.39 (60.17, 114.37)	54.81 (48.87, 70.17)	0.0195
E32	Lt. Parietal	83.1 (61.37, 99.42)	52.69 (42.29, 71.11)	0.0273
E52	Rt. Parietal	82.38 (61.68, 113.03)	74.82 (57.45, 85.42)	**0.0078****
E56	Rt. Temporal	81.58 (64.18, 118.61)	66.37 (47.82, 78.72)	**0.0078****
E61	Rt. Frontal	50.18 (47.04, 64.74)	41.29 (39.09, 47.26)	0.0273
Chan.	**Relative power: Alpha**			
	Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
E2	Frontal	33.73 (23.4, 49.05)	26.92 (19.57, 31.73)	0.0195
E8	Frontal	28.97 (18.84, 37.51)	21.32 (16.62, 30.36)	0.0195
E12	Frontal	30.24 (25.3, 68.47)	20.74 (15.77, 29.92)	0.0195
E17	Lt. Frontal	21.63 (18.23, 39.04)	11.25 (7.5, 21.41)	0.0273
E18	Lt. Frontal	32.28 (24.48, 44.05)	21.26 (16.4, 21.87)	0.0391
E25	Lt. Temporal	45.96 (28.81, 53.5)	27.63 (19.76, 36.57)	0.0117
E27	Lt. Temporal	47.31 (33.65, 77.01)	29.76 (21.87, 35.13)	**0.0039*****
E30	Lt. Parietal	29.46 (26.95, 73.93)	28.68 (21.69, 35.3)	0.0273
E47	Rt. Parietal	33.04 (27.73, 41.71)	25.69 (21.87, 29.62)	0.0195
E53	Rt. Temporal	54.55 (33.79, 57.61)	32.26 (23.52, 41.85)	0.0391
E56	Rt. Temporal	49.85 (21.69, 69.54)	31 (25.13, 39.03)	0.0273
E57	Rt. Temporal	49.78 (22.77, 57.74)	28.58 (26.79, 38.16)	0.0391
E59	Rt. Frontal	42.32 (21.65, 56.67)	30.77 (22.4, 35.92)	0.0391
E61	Rt. Frontal	20.19 (11.36, 37.81)	13.06 (10.54, 18.04)	0.0391
E64	Lt. Frontal	20.1 (13.1, 29.28)	16.31 (7.62, 17.85)	0.0391
Chan.	**Relative power: Beta**			
	Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
E22	Lt. Temporal	6.17 (5.31, 11.3)	11.08 (7.94, 14.89)	0.0391
Chan.	**TBR**			
	Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
E21	Central	8.66 (8.11, 11.57)	6.64 (5.49, 9.86)	0.0195
E23	Lt. Temporal	8.51 (6.79, 9.67)	7.69 (6.46, 7.83)	0.0391
E37	Occipital	5.32 (4.12, 5.78)	3.23 (2.83, 5.67)	0.0391

Data from 4 children in ADHD group and 5 children in ID group (n = 9). Median, Lower Quartile (Q1) and Upper Quartile (Q3) are presented (Median (Q1, Q3)). Chan.: channel number, Lt: left, Rt: right, TBR: Theta-to-beta ratio. **p < 0.01, ***p < 0.005.

0.05). TBR was significantly reduced after the *DoBrain* program in one central channel (E7, $p = 0.023$) (Fig. 2, Table 2).

For the EO condition, lower theta power than that at baseline was found in several frontal channels ($p < 0.05$ at E2, E5, E6, E8, E9, E10, E11, E12, and E61), left frontal (E1, $p < 0.05$), right frontal (E61, $p < 0.05$), central channels (E25 and E27, $p < 0.05$), and left and right parietal channels ($p < 0.05$ at E30, E32, E52, and E56) (Fig. 3). The relative alpha power was significantly decreased after the *DoBrain* intervention in frontal channels (E2, E8 and E12, $p < 0.05$), left frontal channels (E17, E64 and E18, $p < 0.05$), right frontal channels (E59 and E61, $p < 0.05$), left and right temporal parietal channels (E30 and E47, $p < 0.05$), as well as in left and right temporal channels (E25, E27, E53, E56 and E57, $p < 0.05$). Increased beta power after the intervention was observed in one left temporal channel (E22, $p < 0.05$). A significant reduction in TBR was found in central channel, E21 ($p = 0.027$); left temporal channel, E23 ($p = 0.039$); and an occipital channel, E37 ($p = 0.039$) (Fig. 3, Table 3).

To determine the brain where the greatest change was observed, we divided 64 channels into five regions and analyzed them (Supplementary Fig. 3). Regional analysis revealed a significant reduction after the *DoBrain* intervention in the relative powers of theta and alpha in the frontal region ($p < 0.05$) in the EO condition. (Fig. 4 and Table 4). In the EC condition, no differences were observed in any frequency (Fig. 4 and Supplementary Table 2).

3.2.2. *Behavior Rating Inventory of Executive Function, second edition (BRIEF-2)*

Parents of children in the ADHD group reported a significant improvement from pre-to post-intervention in EFs. Fig. 5 and Table 5 show reductions in the BRIEF-2 summary index, GEC, and BRI. For the ADHD group, the median GEC score significantly decreased from 64.92 to 59.75 ($p = 0.031$). Among the three subdomains, the median BRI score, including inhibition and self-monitoring, decreased from 65 to 57.75 ($p = 0.007$) and this change was significantly observed even after correction using Bonferroni method (Bonferroni adjusted $p = 0.020$). No significant changes were found in the ERI or CRI. A score of 60 or higher can be interpreted as having a problem with executive function, and a score of less than 60 is considered normal. There was no significant change in any of the subdomains in the ID group (Table 5).

3.2.3. *Korean version of the ADHD Rating Scale (K-ARS)*

Parents of all participants reported changes in their child's inattention and hyperactivity-impulsivity. As shown in Fig. 6 and Table 5, the median total K-ARS score significantly decreased from 28 to 22.10 ($p = 0.003$) in all groups and this change remained significant even after correction using Bonferroni method (Bonferroni adjusted $p = 0.017$) (Fig. 6a). As a result of analyzing the total score for each group, there was a significant decrease in the ADHD group. For the ADHD group, the median total K-ARS score decreased from 30 to 23.67 ($p = 0.018$) (Fig. 6b). The ID group showed a non-significant reduction in total score ($p > 0.05$) (Table 5).

3.2.4. *Clinical Global Impression-Improvement Scale (CGI-I)*

A specialized child and adolescent psychiatrist rated clinical improvement from pre-to post-intervention of each participant. A child in the ADHD group was excluded from the post-intervention interview because his parents refused to visit the hospital due to COVID-19. For 55% of all groups, clinical symptoms were slightly improved compared to pre-intervention, and a child (5%) showed much improvement in clinical symptoms (Table 6). No significant change was observed in 40% of the participants. Compared to the ADHD group (54.55%), a higher rate of clinical improvement (66.67%) was observed in the ID group (Table 6).

3.2.5. *Parental report*

Measures of children's interest in and concentration during the intervention revealed that most parents believed their child was

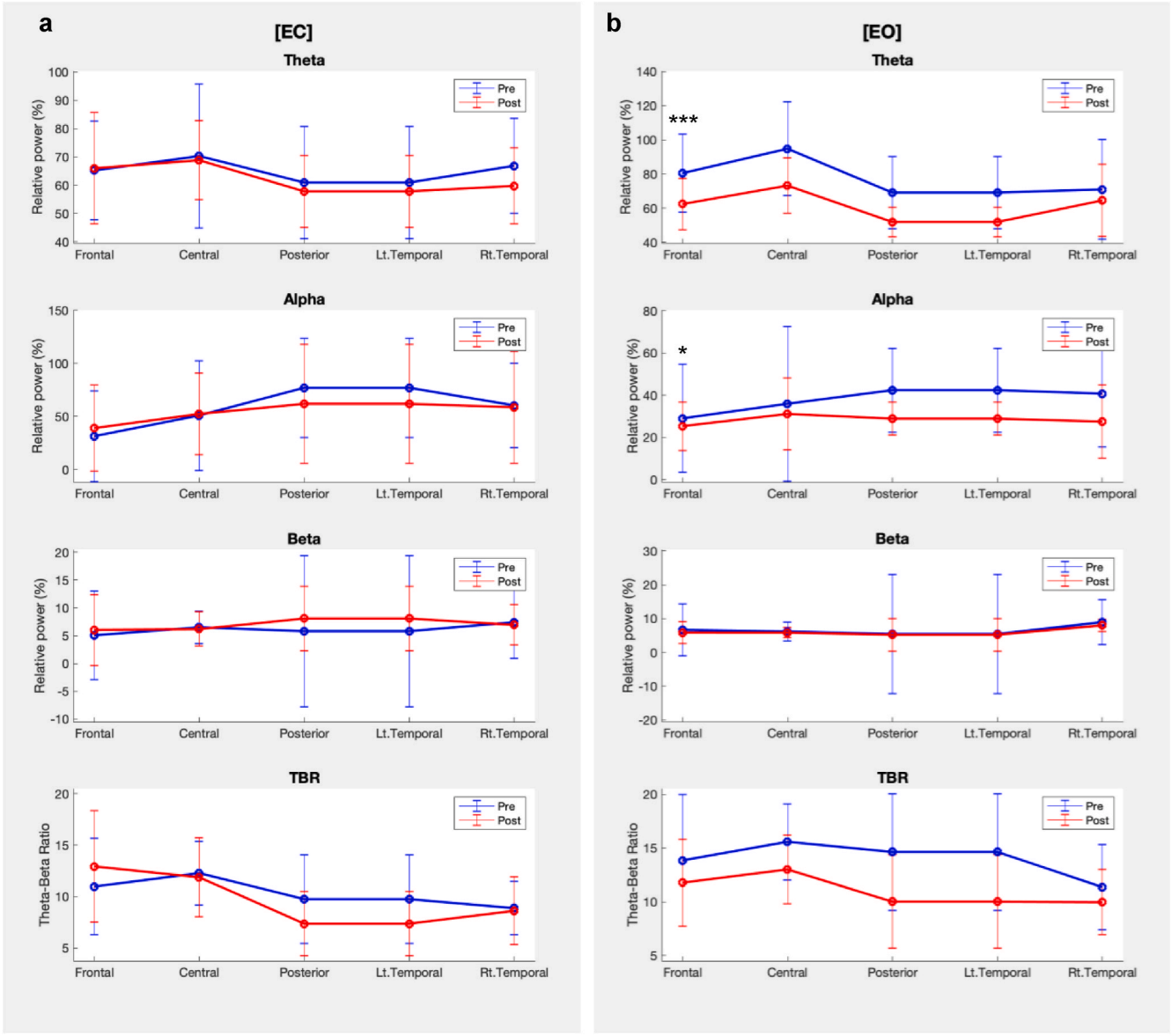

Fig. 4. Relative powers of theta, alpha, and beta bands and TBR in 5 brain regions. **a.** Eyes Closed (EC) condition. Data from 3 children in ADHD group and 5 children in ID group (n = 8); **b.** Eyes Open (EO) condition. Data from 4 children in ADHD group and 5 children in ID group (n = 9). TBR: Theta-to-beta ratio, LT: Left, RT: Right, *p < 0.05, ***p < 0.005.

interested in *DoBrain*'s story session (strongly agree = 77.3%, agree = 18.2%, neutral = 4.5%, disagree = 0% and strongly disagree = 0%). They also believed that their children were concentrated while solving the problems associated with the story session (strongly agree = 63.6%, agree = 31.8%, neutral = 4.5%, disagree = 0%, and strongly disagree = 0%) (Supplementary Table 3). According to the responses to the parental questionnaire, the ability to categorize various objects and identify similarities between various cognitive domains showed the greatest agreement (strongly agree = 45.5%). Additionally, the ability to understand quantity, identify differences, and solve puzzles were reportedly improved after the intervention (strongly agree = 40.9%) (Fig. 7).

DoBrain did not lead to significant improvements in CAT or CANTAB scores (data not shown). There was large variability in performance, with some participants showing little progress after the intervention.

4. Discussion

The current study was performed to examine the possibility and acceptability of digital therapeutics in children with ADHD and/or ID. Here, we present pilot data on a mobile app-based digital intervention targeting attention and neurocognitive function in children with ADHD and/or ID. Our EEG results showed that *DoBrain* intervention induced changes in neural activity, especially in the frontal lobe region in all groups. According to BRIEF-2 and K-ARS results based on parental reports, there were significant reductions in some scores associated with EF-related problems, inattention, and hyperactivity-impulsivity. For 60% of all participants, clinical impressions also improved compared to those before the intervention. These results suggest that mobile app-based digital intervention has value for improving children's attention and other cognitive functions. These behavioral changes were observed more markedly in the ADHD group than in the ID group.

EEG has been widely used in studies to uncover neural underpinnings of developmental disorders. In particular, EEG studies of children with ADHD have consistently found increased theta band activities (typically 3.5–7.5 Hz) and decreased activities in the alpha (7.5–12.5 Hz) and beta (13–21 Hz) bands compared to those in children without ADHD (Barry et al., 2003; Chabot and Serfontein, 1996; Fernandez et al., 2002; Janzen et al., 1995; Lazzaro et al., 1998). The EEG of children with educational

Table 4
Wilcoxon signed-rank test results from regional analysis: Eyes-Open (EO) condition.

Relative power: Theta			
Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
FR	80.48 (75.2, 91.04)	62.39 (57.87, 72.89)	**0.0039*****
CT	94.79 (58.95, 102.14)	73.17 (62.73, 81.3)	0.0977
PO	69.1 (64.31, 79.27)	51.86 (45.11, 62.32)	0.1289
LT	87.31 (57.09, 103.34)	61.16 (46.84, 75.83)	0.0977
RT	70.95 (52.23, 106.03)	64.49 (42.41, 78.26)	0.0742
Relative power: Alpha			
Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
FR	29.06 (24.13, 43.7)	25.37 (20.6, 28.34)	**0.0273***
CT	35.97 (28.85, 43.06)	31.14 (23.19, 34.97)	0.3008
PO	42.41 (22.37, 49.04)	28.91 (20.83, 32.74)	0.2031
LT	47.64 (28.71, 57.51)	30.41 (20.12, 37.72)	0.0547
RT	40.79 (32.89, 55.2)	27.52 (20.76, 40.52)	0.1641
Relative power: Beta			
Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
FR	6.66 (5.39, 8.26)	5.87 (4.98, 7.26)	0.1641
CT	6.17 (5.35, 6.9)	5.84 (5.18, 6.24)	>.9999
PO	5.43 (4.81, 8)	5.23 (4.5, 8.53)	0.3008
LT	7.96 (7.31, 8.34)	7.08 (5.6, 7.48)	0.4258
RT	8.96 (6.33, 9.89)	7.99 (6.89, 8.45)	0.25
TBR			
Region	Pre-intervention Median (Q1, Q3)	Post-intervention Median (Q1, Q3)	*p* value
FR	13.85 (11.29, 15.32)	11.78 (10.28, 13.39)	0.25
CT	15.59 (13.59, 17.49)	13.01 (10.58, 15)	0.1289
PO	14.64 (8.03, 14.85)	10.02 (6.45, 13.79)	0.25
LT	12.28 (6.86, 13.03)	9 (8.44, 11.36)	0.25
RT	11.37 (7.41, 12.95)	9.96 (8.04, 11.36)	0.3008

Data from 4 children in attention-deficit hyperactivity disorder (ADHD) group and 5 children in intellectual disability (ID) group (n = 9). Median, Lower Quartile (Q1) and Upper Quartile (Q3) are presented (Median (Q1, Q3)). TBR: Theta-to-beta ratio, FR: Frontal region; CT: Central region; PO: Posterior- Occipital region; LT: Left Temporal region; RT: Right Temporal region. *p < 0.05, **p < 0.01, ***p < 0.005.

problems, such as ID and learning disability, is also characterized by increased slow activities particularly in the theta bands, and decreased alpha activities (Gasser et al., 1983, 2003). Consistent with previous studies, we have confirmed that relative theta power, which was increased pre-intervention, was remarkably lower after using *DoBrain* in this study, particularly in the EO condition. In the EC condition, however, the results were mixed, with frontal channels close to the midline showing increased theta activity after the intervention, while left frontal channels showed reduced theta activity after the intervention. This may have to do with possible laterality or asymmetry of theta activity in the frontal region, and may be reflective of the dynamic states of theta band activity depending on the eyes-closed or eyes-open status. While most previous studies have identified a theta-dominant EEG profile in ADHD, some research groups have revealed that distinct subtypes of ADHD have excess alpha power (Byeon et al., 2020; Chabot and Serfontein, 1996; Clarke et al., 2011; Robbie et al., 2016). Chabot et al. found a group with excess alpha power and suggested a possible association with central nervous system arousal abnormalities observed in children with attention problems (Chabot and Serfontein, 1996). Other studies demonstrated that the excess alpha group had fewer frontal region abnormalities and suggested that the high alpha power may be associated with other comorbid conditions, such as ASD and depression (Byeon et al., 2020; Clarke et al., 2011; Robbie et al., 2016). In this study, we excluded children with ASD, but did not consider emotional disorders, such as depression. In future studies, it will be necessary to select and evaluate the participants in consideration of various factors that may affect the participant's EEG results.

In addition, the *DoBrain* intervention led to a decrease in TBR in the central region of the brain. In a meta-analysis of EEG in children with ADHD, Snyder and Hall showed that an increase in TBR was commonly observed in children with ADHD, and suggested that TBR could be used to diagnose ADHD (Snyder and Hall, 2006). The FDA approved the use of TBR to aid the assessment of ADHD in 2013 (2013). However, Arns et al. argued that the effect size of previous studies on TBR was exaggerated and proposed that TBR can be used as a prognostic rather than diagnostic measure (Arns et al., 2013b). Although the implications of TBR are controversial, several studies have shown that TBR is positively correlated with inattentive symptoms in children, and higher frontal TBR was related to poor attentional control and response inhibition (Arns et al., 2013a; Putman et al., 2010). Since we performed EEG analysis in a small number of children in heterogeneous groups, it was difficult to specifically examine EEG characteristics and changes in participants. Nevertheless, we confirmed that digital intervention induced changes in neural activity, and we provided a possible neural mechanism for the behavioral improvements that we found in this study.

EFs control and regulate other cognitive functions and actions. Even though there is little consensus on the definition of EF, it includes three main components: working memory, response inhibition, and mental set shifting (Hofmann et al., 2012; Miyake et al., 2000). In our results, improvements in GEC and BRI scores were observed in the ADHD group as assessed using BRIEF-2. The BRI index consists of items related to inhibition and self-monitoring among EFs. Inhibition refers to the ability to control attention to selectively focus on what we want and to suppress interfering information (Barkley, 1999; Daucourt et al., 2018). In the Go/No-go task, response inhibition has been related to TBR (Loo et al.,

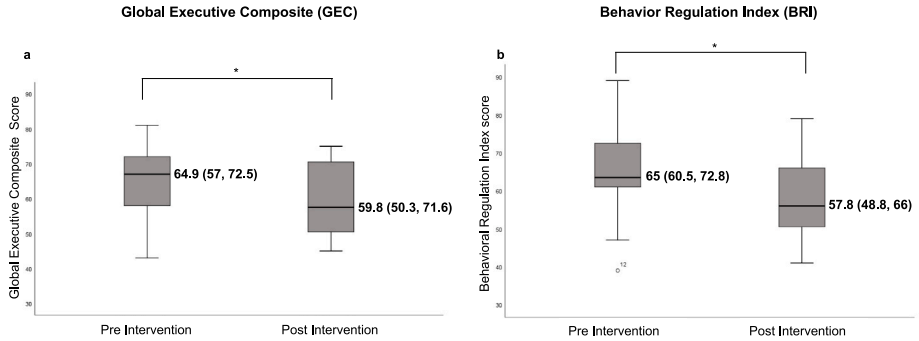

Fig. 5. BRIEF-2 results in ADHD group. **a.** Box plot of Global Executive Composite (GEC) scores in ADHD group. **b.** Box plot of Behavior Regulation Index (BRI)scores in ADHD group. Median, Lower Quartile (Q1) and Upper Quartile (Q3) are presented (Median (Q1, Q3)). BRIEF-2: Behavior Rating Inventory of Executive Function, Second Edition, Parent form, *p < 0.05.

Table 5
Wilcoxon signed-rank test results of BRIEF-2 and K-ARS scores.

	All group (n = 21)			ADHD group (n = 12)			ID group (n = 9)		
	Pre-intervention scores	Post-intervention scores	*p* value	Pre-intervention scores	Post-intervention scores	*p* value	Pre-intervention scores	Post-intervention scores	*p* value
BRIEF-GEC T-score	64.00 (10.32)	62.62 (10.10)	0.525	64.92 (11.37)	59.75 (10.69)	**0.031***	63.00 (8.73)	65.20 (8.78)	0.594
BRIEF-BRI T-score	62.29 (12.56)	59.10 (10.26)	0.204	65.00 (13.41)	57.75 (11.51)	**0.007****	59.10 (10.48)	59.70 (8.97)	0.342
BRIEF-ERI T-score	58.29 (11.91)	56.14 (10.60)	0.384	59.50 (13.28)	54.25 (9.62)	0.065	58.10 (10.75)	58.30 (11.26)	0.15
BRIEF-CRI T-score	62.19 (8.41)	62.43 (9.81)	0.981	61.92 (8.83)	58.67 (8.73)	0.064	62.30 (7.90)	66.10 (9.72)	0.263
K-ARS	28.00 (10.71)	22.10 (11.10)	**0.003*****	30 (11.29)	23.67 (13.08)	**0.018***	25.33 (9.87)	20.00 (8.02)	0.079

Mean and S.D. presented. ADHD: attention-deficit hyperactivity disorder, ID: intellectual disability, BRIEF-2: Behavior Rating Inventory of Executive Function, Second Edition, Parent form, GEC: Global Executive Composite, BRI: Behavior Regulation Index, ERI: Emotion Regulation Index, CRI: Cognitive Regulation Index, K-ARS: Korean version of ADHD rating Scale. *p < 0.05, **p < 0.01, ***p < 0.005.

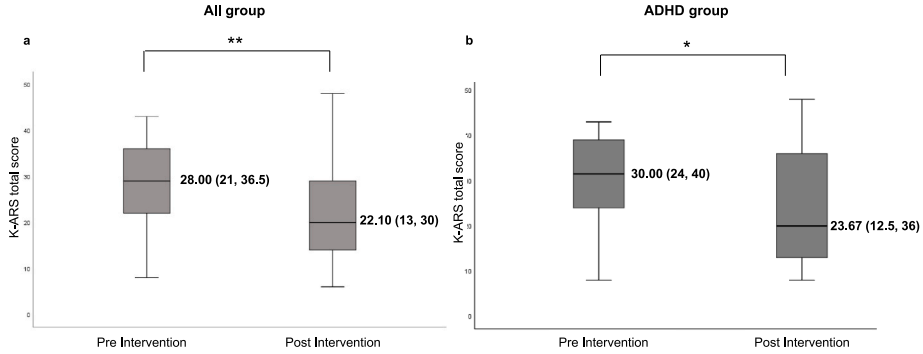

Fig. 6. K-ARS results in all groups and ADHD group. **a** Box plot of K-ARS total scores in all groups(n = 21). **b** Box plot of K-ARS total scores in ADHD group(n = 12). Median, Lower Quartile (Q1) and Upper Quartile (Q3) are presented (Median (Q1, Q3)). K-ARS: Korean version of ADHD rating Scale. *p < 0.05, **p < 0.01.

Table 6
Clinical Global Impression-Improvement Scale (CGI-I) results. (Unit: %).

	All (n = 20)	ADHD (n = 11)	ID (n = 9)
No change	40.00	45.45	33.33
Minimally improved	55.00	45.45	66.67
Much improved	5.00	9.09	0.00

ADHD: attention-deficit hyperactivity disorder, ID: intellectual disability.

2013). It is noteworthy that both a reduced inhibition index and decreased TBR were observed in our results. Self-monitoring is the ability to observe one's own behavior and performance (Hofmann et al., 2012). It is associated with attention and academic performance; therefore, self-monitoring interventions are being applied to children with ADHD (Bruhn et al., 2015). According to the parental questionnaire, they reported that their child showed increased concentration on their words and increased bidirectional communication after using *DoBrain*. It is assumed that these positive changes in daily life were caused by the improvement in EFs, especially inhibition and self-monitoring.

The K-ARS was used to confirm behavioral changes related to inattention and hyperactivity-impulsivity of the participants based on parental evaluation. We found that K-ARS scores were lower in all groups after the intervention, indicating that the intervention had a positive effect on inattention and hyperactivity-impulsivity. Although there were no significant changes in EFs in the ID group, the K-ARS scores were significantly lower in both the ADHD and ID groups. In addition, the improvement in clinical impression as judged using the CGI was higher in the ID group than in the ADHD group (66.67% vs. 54.54%). In the case of parental evaluation, the expected effect of research participation can be reflected in some contexts; however, the CGI performed by clinicians shows more reliable results. Given these results, it seems that *DoBrain* can be applied to any children who have difficulty in attention and other cognitive functions, regardless of diagnosis.

To objectively examine changes in EF and cognitive ability, we used the CAT and CANTAB in this study. Although some participants had improvements in several sub-domain scores, we could not find significant differences with these tests. In this study, there were significant differences in full-scale IQ scores between groups and within the ADHD groups. Therefore, it is possible that some children with ID did not fully understand the task due to their cognitive limitations. In other words, the intervention effects may not be observable by these tasks in our study. Kollins et al. used the Test of Variables of Attention and Attention Performance Index (API) scores as a primary outcome in their clinical trial. They found significant improvement in the API score, but did not observe improvements in parental and clinician ratings (Kollins et al., 2020). Therefore, to examine the effects of digital interventions, it is necessary to select appropriate evaluation methods according to the age and intelligence of the participants.

Regarding safety, the researcher kept in contact with parents and monitored their child during the intervention period. After the end of the study, a questionnaire about safety was answered by the parents. No serious side effects were reported but concerns related to vision loss were reported. One child stopped participating in this study due to abnormal behavior at the beginning of the study period. He has shown the same problem due to media exposure in the past, so he had restricted media exposure until he participated in this study. None of the other participants reported similar problems. When applying digital therapeutics to children in the future, content usage time and frequency should be considered carefully, and appropriate guidelines should be provided to the guardians.

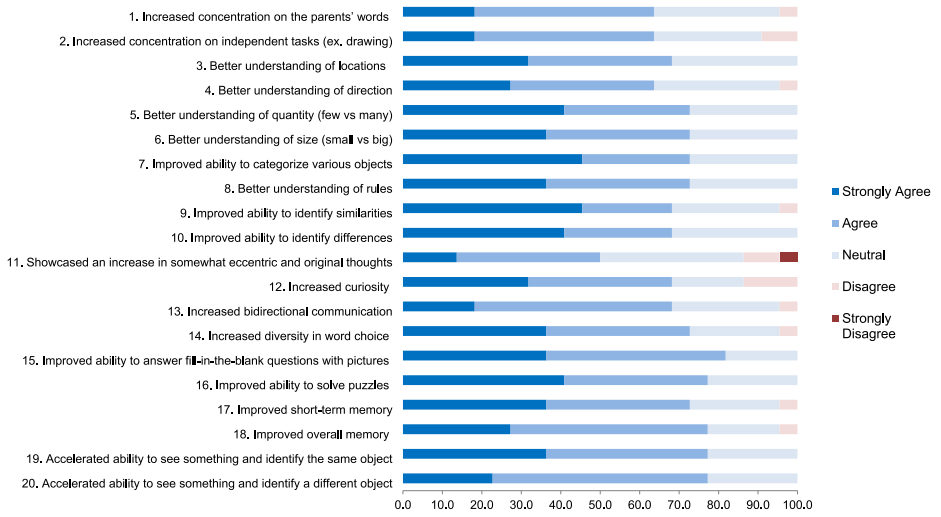

Fig. 7. Parent questionnaire: Assessment of the children's improvement following the use of *DoBrain*. Cognitive domain corresponding to each question: 1,2- Concentration; 3,4- Spatial Perception; 5,6- Numerical Knowledge; 7,8- Logical Reasoning; 9,10- Categorical Discrimination; 11,12- Creativity; 13,14- Language Ability; 15,16- Composition; 17,18- Memory; 19,20- Speed of Perception.

There are several limitations to the current study. First, the study included a modest number of participants. Therefore, there were limitations in the statistical analysis methods and analyses considering various factors (drug effects, etc.). When we performed a Bonferroni correction with our EEG data analysis, no significant results were observed. In the case of behavior data, BRI score in the ADHD group and K-ARS score in all groups showed significant differences after correction. To more reliably verify the effectiveness of the intervention, additional randomized controlled trials with a larger sample size are needed. Second, the cognitive abilities of participants were heterogeneous, so some changes could not be measured in some tasks. Third, only short-term effects were evaluated in this study. Further studies to provide a more formal assessment of efficacy in a homogeneous group, to test possible interactive effects between *DoBrain* and other treatments, and to measure long-term maintenance effects of intervention will be required.

Despite these limitations, this is the first study to explore the acceptability and confirm the effectiveness of mobile app-based digital therapy in Korean children with ADHD and/or ID. This study presented evidence that a digital intervention could induce positive neural and behavioral changes in children. Mobile app-based therapy offers great potential for supporting children with neurodevelopmental disorders who need continuous treatment, especially during pandemics, such as that of COVID-19. Although follow-up studies are needed, our findings suggest that digital therapeutics can be an alternative in situations where face-to-face treatment is not possible.

Authors' contributions

Conceived and designed the experiments: Sungji Ha, Yejin Choi and Keun-Ah Cheon; Participants recruitment and evaluation: Sungji Ha, Jaeun Ahn, Kangto Lee, Yejin Choi and Keun-Ah Cheon; EEG data recording and analysis: Sungji Ha, Jung Hwa Han, Jaeseok Heo and Jin Young Park; Writing-original draft preparation: Sungji Ha and Jung Hwa Han; Writing-review and editing: Sungji Ha, Jung Hwa Han, Jaeun Ahn, Kangto Lee, Jaeseok Heo, Yejin Choi, Jin Young Park and Keun-Ah Cheon; Funding acquisition: Yejin Choi.

Declaration of competing interest

Yejin Choi is a CEO of *DoBrain* Co., Ltd. All other authors have no conflicts of interests to declare that are relevant to the content of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.11.018.

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