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Brain-computer interface based attention and social cognition training programme for children with ASD and co-occurring ADHD: A feasibility trial

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ABSTRACT

Background: Current treatment practices for comorbid conditions of autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) remain limited. This study examined the feasibility of an EEG brain-computer interface (BCI) programme for children with ASD and co-occurring ADHD.
Method: Twenty children were randomised to the intervention or waitlist-control group. Intervention consisted of thrice-weekly sessions of BCI-based training over 8 weeks. Both groups were followed up 4 weeks later. The BCI-based programme comprised of a series of attention and gaze-modulated games aimed to train social cognitive skills.
Results: All participants completed at least 20 training sessions and none dropped out of the study. No severe adverse events were reported. Side effects included mild headaches, fatigue, irritability and self-injurious behaviours. All were addressed within the same session. Feedback from therapists indicated that participants' interest and motivation could be sustained with appropriate supports. Change scores indicated greater improvement in the intervention group compared to the waitlist-control on ADHD symptoms as measured on the ADHD rating scale; no significant differences were observed on social deficits on the Social Responsiveness Scale (SRS). Pooled data suggests that pre-post improvements could be maintained.
Conclusions: Findings indicate the BCI-based program is tolerable for most participants. Positive effects were also reported for ADHD symptoms. A future large clinical trial will incorporate appropriate controls to ascertain the efficacy of our training programme.

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1. Introduction

Autism spectrum disorder (ASD) and Attention Deficit/ Hyperactivity Disorder (ADHD) are neurodevelopmental disorders with long-term psychosocial implications. ASD is characterized by significant impairment in social communication and restricted, repetitive behaviours and interest, while ADHD is characterized by functionally-impairing hyperactivity and inattention (American Psychiatric Association, 2013).

Studies have shown that children and adolescents with ASD present with relatively high rates of ADHD symptoms, ranging from 16 to 85% (Gjevik, Eldevik, Fjæran-Granum, & Sponheim, 2011; Hanson et al., 2013; Murray, 2010). Compared to children with singular disorders, children with co-occurring ADHD in ASD have been found to exhibit poorer executive control (Yerys et al., 2009), adaptive functioning and health-related quality of life (Sikora, Vora, Coury, & Rosenberg, 2012), show more severe autistic symptoms and social impairment (Sprenger et al., 2013), and have increased risk of psychiatric comorbidity (Gordon-Lipkin, Marvin, Law, & Lipkin, 2018).

Current treatment practices for comorbid conditions of ASD and ADHD, which include pharmacological (e.g. stimulants) and/or non-pharmacological (e.g. behavioural intervention) therapies to target core symptoms of inattention, hyperactive-impulsivity and social deficits, remain limited. With stimulant medication, children with comorbid conditions exhibited lower response rates and more adverse effects compared to children with only ADHD, with no positive effects observed for ASD symptoms (e.g. stereotypy) (Harfterkamp et al., 2012; Pearson et al., 2013; RUPP, 2005; Scahill et al., 2015). Behavioural interventions are intensive and require access to trained professionals (White et al., 2015). Patients with ASD have also been shown to require significantly more sessions of behavioral intervention to attain comparable symptomatic improvements, as well as show reduced adherence compared to non-ASD patients, likely due to the developmental nature of ASD as well as increased complexities with comorbidities (McFayden et al., 2021).

The presence of comorbid ADHD may thus further limit the efficacy of ASD-formulated interventions aimed at improving social skills. Comorbid ADHD has been found to negatively moderate social skills training outcomes for children with ASD (Antshel et al., 2011), with poor impulse control and inattention hindering the implementation of learnt social skills. Inattention can result in missed social cues while hyperactivity and impulsivity may discourage peer interactions, reducing social opportunities crucial for skills acquisition (Hoza, 2007). Amongst children with ASD, those with ADHD symptoms were found to exhibit greater deficits in specific domains of social awareness and communication, with no significant differences in social motivation and cognition (Factor, Ryan, Farley, Ollendick, & Scarpa, 2017). Poor attention may thus impede appropriate social behaviours, regardless of the child's knowledge of social rules or motivation to engage in social interactions.

Self-regulation and socio-communicative processes are functions of the attentional system (Rothbart, Posner, & Boylan, 1990). In ASD, abnormalities in visual attention have been suggested to underlie core social deficits (Sacrey, Armstrong, Bryson, & Zwaigenbaum, 2014), with attention disengagement and orienting identified as emerging features (Elsabbagh et al., 2013; Landry & Bryson, 2004). Impairments in areas of executive function such as inhibition, working memory, planning and cognitive flexibility are also commonly reported in ASD (see review by Demetriou et al., 2018), with ADHD symptoms exacerbating impairments (Craig et al., 2016; Sinzig, Vinzelberg, Evers, & Lehmkuhl, 2014; Tye et al., 2014; Yerys et al., 2009). As executive processes facilitate self-regulatory behaviours crucial for social competence (Diamond, 2013), impairments have been found to predict social deficits in ASD (Leung, Vogan, Powell, Anagnostou, & Taylor, 2016). These impairments are also associated with socio-cognitive deficits such as impaired theory of mind, wherein children with ASD are unable to infer the mental states of others based on physical contextual information (Miranda, Berenguer, Roselló, Baixauli, & Colomer, 2017). Given that visual attention is critical in supporting the development of socio-communication abilities, and functions as a gateway for higher-order executive processes key for social competence, it may be an important target for intervention in children with ASD and co-occurring ADHD.

Attention may be improved with neurofeedback therapy, an alternative treatment widely-researched in children with only ADHD

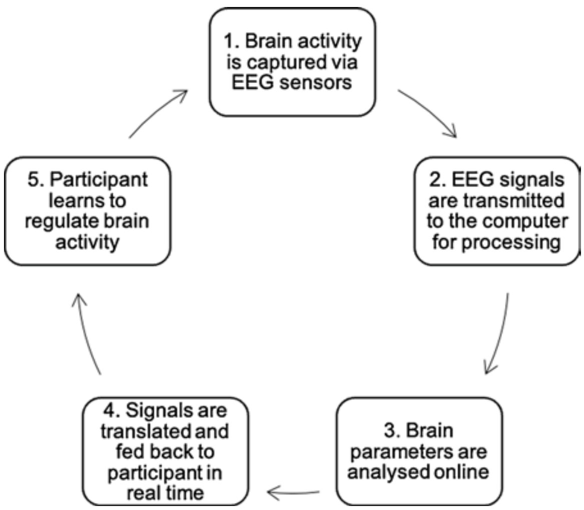

Fig. 1. Illustration of a biofeedback mechanism.

(e.g. Enriquez-Geppert, Smit, Pimenta, & Arns, 2019; Riesco-Matías, Yela-Bernabé, Crego, & Sánchez-Zaballos, 2021). Neurofeedback is a form of biofeedback (Fig. 1), wherein neural activity is captured as EEG signals via sensors (step 1), which are then transmitted to the computer to be processed (step 2). Pre-selected brain parameters of interest are analysed (step 3) and then translated into signals which are fed back to the participant as perceptible stimuli (e.g. visual, audio) in real time (step 4). Most neurofeedback systems include a brain-computer interface (BCI), which serves as a communication pathway between the brain and an external device. With consistent feedback, participants learn to self-regulate neural activity via these external devices, facilitating neural changes underlying target behaviours (step 5). Neurofeedback therapy thus purports to normalize atypical electroencephalogram (EEG) patterns, thereby improving attention regulation in children with ADHD receiving treatment (Sitaram et al., 2017).

Findings suggest that neurofeedback therapy may be efficacious (Arns et al., 2020) and sustainable (Steiner, Frenette, Rene, Brennan, & Perrin, 2014; Van Doren et al., 2019) in treating ADHD symptoms. However, several placebo-controlled trials did not observe differences between neurofeedback training and a sham control on ADHD symptoms (Arnold et al., 2013; Dongen-Boomsma, Vollebregt, Slaats-Willemse, & Buitelaar, 2013). A review also found neurofeedback to be ineffective when assessed with blinded measures (Sonuga-Barke, Brandeis, Holtmann, & Cortese, 2014). Despite mixed results, many of neurofeedback findings underscores its potential as an effective alternative treatment for ADHD and more recently, for ASD-related symptoms (van Hoogdalem, Feijs, Bramer, Ismail, & van Dongen, 2020). Studies have reported normalization of brain function, as well as significant improvements in areas of executive function and socio-communication in children with only ASD following neurofeedback treatment (Kouijzer, van Schie, de Moor, Gerrits, & Buitelaar, 2010; Coben & Myers, 2010; Datko, Pineda, & Müller, 2018; Kouijzer, de Moor, Gerrits, Buitelaar, & van Schie, 2009; Pineda et al., 2008; Thompson, Thompson, & Reid, 2010), with gains sustained for up to 12 months (Kouijzer et al., 2009).

We had previously developed an attention training program involving a progressive series of games using EEG-based BCI for children with ADHD. This BCI programme identifies and quantifies the attention level of each user by measuring their unique EEG patterns when performing the Stroop Test (Stroop, 1935), allowing users to employ their attention to drive a series of training games. Prior studies have reported significant reductions in ADHD symptoms following training (2012, Lim et al., 2010), and effects were maintained even after a month following treatment (Lim et al., 2019). Additionally, neural evidence indicated that our BCI training reorganised brain functional network and normalized salience network processing (Qian et al., 2018), possibly underlying observed improvements. Our previous trial with ADHD participants recorded low rates of adverse events (6.4 %); none were severe nor required medical attention.

In the present study, we have integrated eye tracking technology with a BCI-based system, aimed at training children with ASD and co-occurring ADHD to modulate their attention with eye gaze to relevant social stimuli (e.g. gaze cues). Participants would undergo our attention training programme, followed by a battery of socio-cognitive games designed to train working memory, selective and sustained attention to social cues, and improve social cognition (e.g. emotional recognition). The programme aimed to attenuate deficits in attention and social cognition that may underlie observed symptomology of inattention and socio-communication deficits in children with ASD and comorbid ADHD.

The present study aimed to ascertain the feasibility of implementing a thrice-weekly 8-week BCI-programme that has been adapted to teach socio-cognitive skills for children with ASD and co-occurring ADHD. No prior study to date has examined the clinical application of BCI-based training in this comorbid population.

Trial feasibility was assessed with intervention completion and retention rates, occurrences of adverse events and qualitative feedback obtained from therapists. The secondary aim of the study is to obtain an estimate of efficacy in improving attention and socio-communication skills. Positive findings will provide preliminary evidence for a future larger scale efficacy study.

We hypothesize that children with ASD and co-occurring ADHD would remain engaged in the BCI-based training programme, shown by moderate treatment completion and retention rates and low rates of reported serious adverse events. As part of our exploratory aim, we expect that the BCI training would result in improvements in attention and socio-communication as measured by the ADHD rating scale and the Social Responsiveness Scale.

2. Methods

A national ethics review board approved this study (reference number 2015/841). Written informed consent from parents and assent from children were obtained prior to study enrollment.

2.1. Study design

The present study used a randomised, controlled waitlist design. It was conducted at a tertiary child psychiatric ambulatory centre in Singapore from 2016 to 2018. The intervention group received the BCI-based attention and social cognition training program for 8 weeks and was followed up 4 weeks later. The control group served as untreated waitlist-controls for the first 8 weeks, after which they received similar BCI-based training for a duration of 8 weeks, and were subsequently followed up 4 weeks later.

The purpose of utilising the Simon's randomised phase II trial design in our study is to determine if the BCI program is deserving of further evaluation in a large scale trial (Simon, Wittes, & Ellenberg, 1985). A total sample size of 20 participants (10 children per group) offer 80 % probability of correctly selecting the intervention as superior to the control if the intervention was truly superior by an effect size of 0.4 SD.

Participants were randomly assigned to a treatment group using the opaque sealed envelope method. Upon receiving the participant's consent, the envelope was opened and the participant offered the allocated treatment regimen. The randomized permuted blocks method was used to generate an allocation sequence to randomise the participants to either the intervention of the waitlist-control group at 1:1 ratio, with block size determined by an independent statistician. Participants, their parents and study investigators were aware of the treatment allocation. Clinicians who conducted outcome assessments were kept blinded to the treatment allocation. Participants and their parents were regularly advised not to inform the clinicians about their group allocation.

The Gantt schedule (Fig. 2) illustrates the study timeline and respective intervention period for both groups.

2.2. Participants

We recruited 20 participants aged 8–12 years (M = 9.55, SD = 1.43) diagnosed with comorbid conditions of ASD and ADHD. Diagnoses of ASD was determined via the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2012) and Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994), and/or confirmed by clinical consensus (registered allied health professionals and psychiatrists), using the the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR), (American Psychiatric Association, 2000) or 5th edition (DSM-5) (American Psychiatric Association, 2013). Participants met criteria for ADHD with significant inattentive symptoms based on the Computerised Diagnostic Interview Schedule for Children (C-DISC) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), and obtained a score within the clinical range (12 and above) on the Inattentive subscale of the ADHD rating scale (ADHD-RS) (DuPaul, Power, Anastopoulos, & Reid, 1998), which were rated by a parent. If the child was on medication prior to enrolment, the dosage was maintained for at least for 3 months preceding enrolment into the trial, and throughout their participation in the study. To minimize potential risk, they could continue to receive treatment-as-usual medication and supplements throughout the course of the intervention. Children did not undergo any therapy targeting attention or social skills while they were on the trial. We excluded children with intellectual disability (i.e. IQ 70 and below), epilepsy, severe sensorineural deficits or any co-existing psychiatric disorder which would interfere with their ability to complete the computer-based activities.

2.3. Intervention

The first 8 weeks consisted of thrice-weekly sessions of *CogoLand*™ and *BusyEyes,* graphic games designed to train attention and social cognition. Participants received training sessions at the clinic, each lasting between 30−45 min. In case of fatigue, participants were informed they could request for breaks when needed. Each session was administered by a trained study administrator.

2.3.1. Apparatus

The BCI system consisted of a computer, a BCI headband with 2 dry EEG lead sensors and an eye gaze tracker. A machine learning based classifier was trained using multi-band EEG signals (theta, alpha, low beta, high beta, and gamma bands). EEG training data was collected via a calibration task, wherein participants performed two classes of tasks, attentive and inattentive. The color Stroop test was used as an attentive task. This classifier then generated a score (normalized to be between 0 and 100) which indicates the subject's level of attention, as derived from their EEG signals. The classifier was then used online to predict the level of attention every 200 ms using the past 4 s of data. The attention score is then used to control the avatar's speed in the attention training game.

Two-channel EEG signals were recorded from the frontal positions (Fp1, Fp2). These EEG signals first pass through a filter bank to be broken down into various frequency sub-bands covering the range from 4 Hz to 36 Hz (i.e. covering theta, alpha, beta 1, and beta 2 waves). These filtered signals are then sent to the respective spatial filters corresponding to each frequency band, which enhance the detection of information from the brain's electrical rhythm (Lim et al., 2019).

Eye gaze was monitored via an eye-tracker (Tobii Pro X2; Tobii Technology, Stockholm, Sweden) mounted below a monitor screen

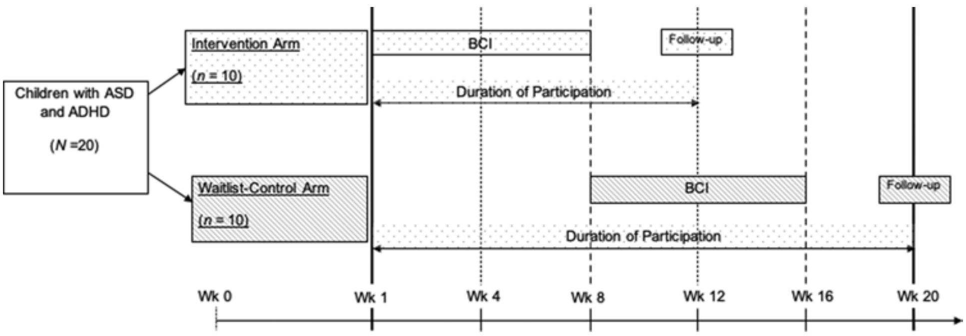

Fig. 2. Gantt schedule illustrating the respective intervention and assessments conducted for both groups, and the time points (Week 1 and Week 8) for preliminary efficacy analyses.

Note: The primary outcome was the clinician-rated ADHD-RS (Inattentive subscale) at Week 8. Secondary outcomes included clinician-rated ADHD-RS (Hyperactive and Total subscales), parent-rated SRS-2 at Week 8, as well as pooled change scores at pre- (Week 1 for BCI-intervention arm and Week 8 for waitlist-control arm), post- intervention (Week8/9 for BCI-intervention arm and Week 16 for waitlist-control group) as well as follow-up (Week 12 for BCI-intervention and Week 20 for waitlist-control arm).

(Height: 47.65 cm x Width: 44.37 cm). Infrared light is projected and reflection patterns on the participant's corneas are detected by image sensors in the Tobii Pro X2 eye tracker, allowing gaze points to be tracked.

Each participant underwent the following tasks during the BCI-based training sessions.

2.3.2. Calibration

Prior to playing the video games (*CogoLand*™ and *Busy Eyes*) at pre-BCI intervention (Week 1 for intervention group, and Week 8 for waitlist-control) and upon completion of the program at post-BCI intervention (Week 8 for intervention group, and Week 16 for waitlist-control), each participant underwent individual calibration using a colour Stroop task on the BCI-based attention training game system. During the Stroop task, participants are instructed to name the colour of the font of the letters that spell a different colour, for instance the font colour that is red for the word GREEN. Participants respond with a button press as quickly as they could. This paradigm tests for a participant's ability to inhibit automatic responses, which necessitates attention (Stroop, 1935). Critical EEG parameters during the correct attempts were analyzed and compared to the participants' resting state, deriving an individualized EEG profile representing the child's most attentive state.

2.3.3. CogoLand™

This 3-D computerized graphic game was developed to train attention (Lim et al., 2019). When playing these games, participants wore a BCI headset that detected their neural oscillations using dry EEG electrodes (Fig. 3). Participants controlled an avatar via the signals detected by the EEG electrodes. EEG data was transmitted to the computer via Bluetooth technology and analysed using an algorithm, which drove the game interface, providing real-time feedback to participants about the attention level using a score ranging from 0 (minimum attention) to 100 (maximum attention), which was reflected on the computer screen. The participant hence needed to 'concentrate' in order to move the avatar, which moved at a speed proportional to the participant's attention level as measured by the BCI-based attention training game, i.e. the 'higher' the concentration score, the greater the speed of the avatar's movement.

2.3.4. BusyEyes

The computer-based training activities included 6 games, each targeting domains of attention, working memory, facial and emotion recognition and joint attention, designed based on the same attentional algorithm as that of CogoLand™. For example, in *Eye Gazer* (Fig. 4), participants were instructed to focus eye gaze and attention on the character in the centre of the screen (Step 1). An array of objects would subsequently appear on the periphery of the character (Step 2) and participants had to follow the gaze of the character to select the target. The character disappears thereafter, and participants select the previous target item again (Step 3). The target item may be in a different location and participants will have to recall targets based on memory. *Eye Gazer* was thus designed to train attention, working memory and joint attention, modulated by gaze.

Participants underwent and completed an eye-calibration exercise prior to starting this game suite at each session. Eye gaze was monitored via an eye-tracker mounted below the computer screen. Participants were required to orient their eye gaze to select a target on the screen. The position of their gaze was represented by a magnifying glass, which also served as a cursor. Participants were required to concentrate on the target to "lock in" the answer, by maintaining an attention score above threshold for at least 2–3 seconds. The 'higher' the concentration level of the participant, the faster the answer was selected and the more game levels they could complete within the given time.

An eye gaze tracker connected to the computer detects the location of participant's eye gaze on the computer screen during the Busy Eyes games. The game progresses according to how well the participant can focus their eye gaze on correct objects whilst sustaining their attention.

2.3.5. Behavioural supports

All participants were provided with a standardized set of behavioural supports, which included a visual schedule to inform them of task demands at the start of every session (Fig. 5a), a reward chart to encourage game completion (Fig. 5b), and a set of visual rules to

Fig. 3. The Brain-Computer Interface (BCI) attention training apparatus. A model wearing the EEG headband across her forehead. The eyetracker is mounted on the bottom of the monitor to detect eyegaze at the same time.

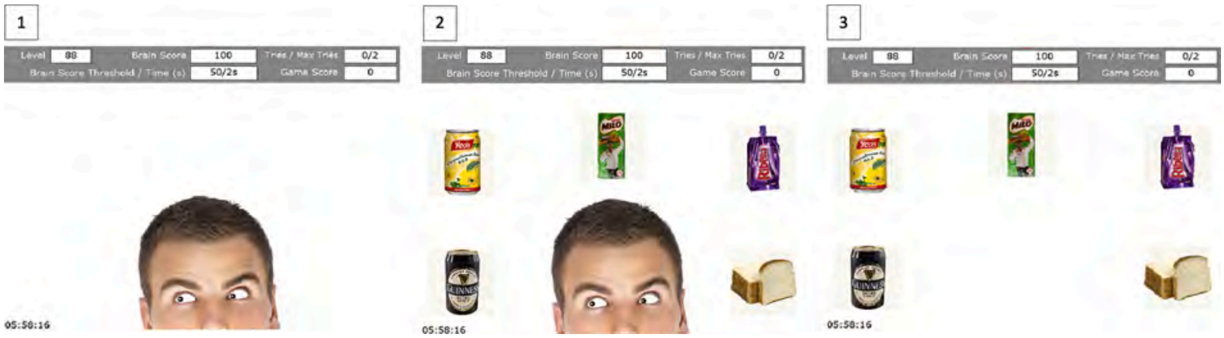

Fig. 4. An example of a socio-cognitive game (Eye Gazer) from BusyEyes.

remind and reinforce task-appropriate behaviours (Fig. 5c). When participants completed a session, they were awarded a sticker following which they could exchange them for a reward based on a token economy system. Behavioural supports were administered by trained therapists during the training sessions.

2.4. Outcome measures

Primary outcome measures were treatment completion and adherence rates, adverse events and feedback obtained from therapists of the BCI programme that were recorded at the end of each session.

Secondary outcomes of potential efficacy were assessed using the ADHD Rating Scale (ADHD-RS) and the Social Responsiveness Scale (SRS). The ADHD-RS (DuPaul et al., 1998) is an 18-item rating scale used to rate the frequency of ADHD symptoms based on the DSM-IV TR. Frequency of each symptom is rated on a 4-point scale; higher scores indicate greater severity. One of two blinded clinicians on the study team interviewed a parent and completed the ADHD-RS at each time point. The same clinician followed up with the same parent at subsequent time points. The SRS (Constantino, 2002) is a 65-item rating scale used to rate the severity of social difficulties in autism. Scores are summarized into 5 domains: Social Awareness, Social Cognition, Social Communication, Social Motivation, Autistic Mannerisms and a total score. Higher scores indicate more impairment. A total score of 75 and above indicate clinically significant deficits in social behaviours. The same parent completed the SRS at each time point.

Assessments were administered at the following time points: Weeks 1 and 8 for both groups; Week 12 for the intervention group; Weeks 16 and 20 for the waitlist-control group (Fig. 2). Secondary outcomes included: change in inattention, hyperactive-impulsive and total scores on the ADHD-RS (clinician-rated), change in SRS scores (parent-rated) at Week 8 from Week 1; change in pre-post and post-follow up scores on the ADHD-RS and SRS pooled across groups.

2.5. Data analysis

Treatment completion rates were calculated as the percentage of participants who had completed a minimum of 20 sessions in 8-weeks as per protocol, based on literature that have suggested a minimum of 20 sessions to elicit positive change (Arns et al., 2020; Vernon, Frick, & Gruzelier, 2004), Retention rate was defined as the proportion of participants who remained at post-intervention and follow-up time points. Outcome measures were compared between arms using the Mann-Whitney *U* test Given the present study's small sample size ($n = 20$), non-parametric tests were applied. Median change scores in ADHD-RS and SRS scores at week 8 from week 1 were summarized and differences in the distribution of change scores between the two groups were compared using the Mann-Whitney *U* test The change scores between pre, post BCI and follow-up for the domain scores for the ADHD-RS and SRS were pooled across groups and tested using the Wilcoxon signed rank test.

All statistical significance tests and confidence intervals were two-sided. All confidence intervals (CI) were calculated at the 95 % level. All statistical analyses were conducted using SPSS version 23 (Statistical Package for Social Sciences, IBM Corporation, New York, USA).

3. Results

3.1. Study participation

Twenty participants were recruited in the study, including 17 males (85 %) and 3 females (15 %). The CONSORT flowchart (Suppl. 1) provides details about the participant flow throughout the study. Table 1 summarises demographic and baseline characteristics of participants. Both arms appeared comparable on baseline features. Medication included methylphenidate whereas supplements included fish oil supplements (e.g. omega-3 fatty acids).

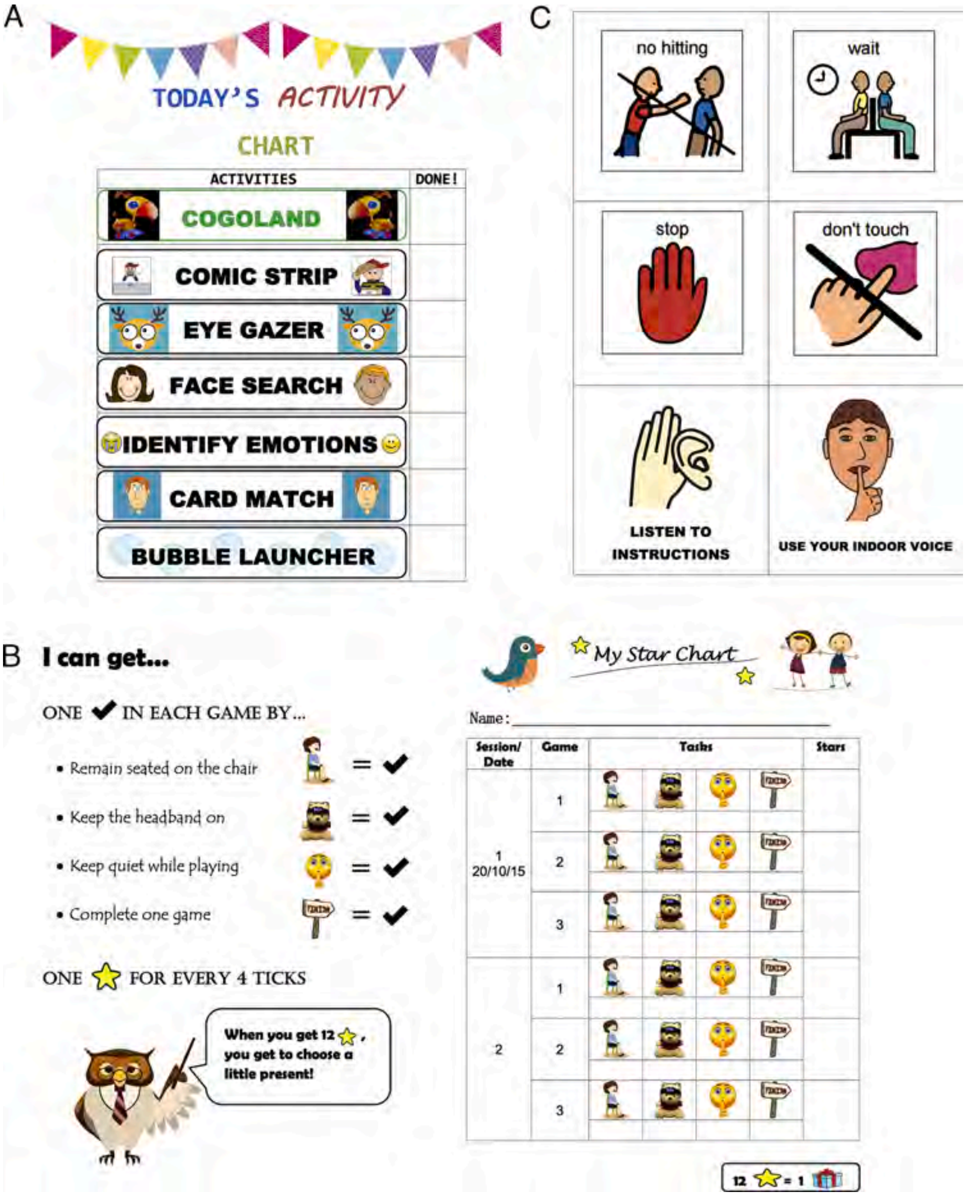

Fig. 5. a) Visual activity schedule to inform participants of task demand prior to each session. Participants would tick the box next to each task upon completion. b) Rewards chart focused on facilitating session completion, upon which participants could collect stickers in exchange for a reward. c) Visual rules to aid behavioural regulation.

3.2. Outcomes

The primary outcome measures of feasibility are displayed in Table 2, with a summary of outcomes described below.

3.2.1. Completion and retention rates

All participants completed a minimum of 20 BCI sessions within 8 weeks; 13 participants (65 %) completed all 24 sessions. Remaining participants had missed sessions (17 sessions in total) due to scheduling difficulties and/or delay caused by ASD-related behaviours such as persistent emotional dysregulation (7 sessions), fatigue (2 sessions) and technical difficulties (8 sessions). No significant group differences in number of sessions completed were found (*Mdn* = 24 for each arm, $p = 0.56$). All participants attended assessment visits at baseline, pre-, post- and follow up.

3.2.2. Adverse events

Adverse events were recorded at the end of each session. For participants who reported at least one incidence of an adverse event,

Table 1
Baseline demographic and outcome variables.

	Intervention (n = 10)	Waitlist-Control (n = 10)	*p*-value
Demographics			
Age[a]	9.5 (1.65)	9.6 (1.27)	0.88
Gender (Male/Female)	9/1	8/2	0.53
Race (Chinese/Malay)	9/1	9/1	–
ADHD subtype (Inattentive/Combined)	3/7	5/5	0.36
Medication type (Stimulants/Supplements/Both)	1/4/3	1/4/3	–
Stimulants dosage (mg/day)	10–20	10–36	–
Supplements dosage range (tabs/day)	2–4	1–3	–
Outcome Measures[b]			
ADHD-RS			
Inattention	19 (13–25)	20.5 (9–27)	0.63
Hyperactive-impulsive	17 (11–25)	14 (3–24)	0.32
Total	36.5 (25–50)	36 (16–51)	0.63
SRS			
Social Awareness	12.5 (9–15)	13 (8–19)	0.48
Social Cognition	16.5 (7–28)	18.5 (16–33)	0.28
Social Communication	30 (20–48)	36.5 (18–47)	0.17
Social Motivation	11 (7–25)	14 (11–26)	0.19
Autistic Mannerisms	17 (7–26)	19 (9–33)	0.39
Total	90 (53–138)	103 (66–149)	0.22

[a] Mean (s.d.).
[b] Median (range).

Table 2
Feasibility outcomes.

	% (n/n)
Completion and retention	
Treatment completion (at least 20 sessions)	100 % (20/20)
Treatment completion (all 24 sessions)	65 % (13/20)
Retention (post-intervention)	100 % (20/20)
Retention (follow-up)	100 % (20/20)
Adverse events	
Serious adverse events	0
Complaints of headaches and/or fatigue	65 % (13/20)
Behavioural and emotional dysregulation	45 % (9/20)
Anger outbursts (shouting, hitting items, devices and self, crying)	
Oppositional behaviours (non-compliance)	
Other difficulties	
Orienting eye gaze towards target stimuli	50 % (10/20)
Technical issues	60 % (12/20)
Headband disconnectivity	
System errors (hanging)	
Low sensitivity of eye tracker	

parents were informed to monitor the participant's wellbeing following the session and to report to the therapists should it persist or recur. Feedback from four therapists, who had received prior training with working with children with ASD and ADHD, were also collated from participant's individual records. Significant events were recorded and common themes were identified.

No significant adverse events warranting medical attention were recorded. Common complaints included mild headaches and fatigue from having to pay prolonged attention to a screen. All participants were able to resume training after short breaks within the same session. No participants were reported to have experienced adverse events that persisted or recurred following the end of the session, and prior to the subsequent session. None of the participants had sensory complaints regarding audio and visual stimuli.

Behavioural difficulties arising from emotional dysregulation were most commonly reported, with a total of nine participants recorded as having exhibited at least one incidence of challenging behaviour. This included anger outbursts and irritability resulting from perceived failure, and wherein participants banged their fists on the table, hit items, displayed verbal outbursts or cried. Of these, three participants exhibited mild self-injurious behaviours. They hit their heads with their hands due to frustration with game performance on several sessions. On all occasions, they calmed down after intermittent breaks, validation of their efforts and visual reminders of appropriate behaviours. All resumed and completed training thereafter within the same session. Three participants exhibited significant oppositional behaviours and were non-compliant during sessions. Two of them directed mildly aggressive behaviours towards therapists on several occasions (e.g. pushing, spitting).

Ten participants exhibited pervasive difficulties with shifting eye gaze to targets located on the periphery of the computer screen during the socio-cognitive games. They displayed compensatory behaviours by making physical movements rather than shifting their gaze. This disrupted headband connectivity and eye tracker sensitivity which further delayed game progress. These participants were also observed to have difficulties maintaining eye gaze on target stimuli, resulting in non-selection or selection of non-target stimuli within the given time limit, causing frustration. Of these ten participants, five frequently exhibited emotional outbursts as a result, and were included in the number of participants who exhibited challenging behaviours from emotional dysregulation. The remaining participants in the sample did not exhibit significant difficulties with gaze control.

Technical difficulties included freezing of the computer program, intermittent disconnection with the headband, and low detectability by the eye-tracking device. This resulted in increased wait time. On several occasions, sessions had to be rescheduled in order to resolve the technical faults.

All participants were provided with a standardized set of behavioural supports, which focused on facilitating session completion. However, therapists indicated they had to make appropriate modifications for eight participants with persistent challenging behaviours. This included breaking tasks down into achievable levels within each game to cater to individual capabilities, or incorporating cool down time for the participants who had hit themselves out of frustration. A combination of positive and negative reinforcements was also implemented to regulate specific oppositional behaviours during sessions (e.g. time-out), with varying success. Participants were often able to resume training within the same session after being given a break. Sessions were discontinued and rescheduled to the following day when challenging behaviours persisted for two participants. Overall, therapists reported improvements such as reduced incidences of outbursts and increased task-appropriate behaviours (i.e. staying seated) with tailored supports. Most participants found the game engaging, and looked forward to the start of training sessions despite aforementioned difficulties.

3.2.3. Changes in ADHD-RS (Inattentive, hyperactive impulsive, total) and SRS subscale scores between arms

Negative change scores indicated improvements on symptoms whereas positive change scores indicated increasing impairment. The description and analysis of change scores in the outcome measures between groups is presented in Table 3. The description and analysis of change scores of the pooled sample is presented in Table 4.

Between Week 8 and Week 1, differences in change scores on the ADHD-RS (Inattentive) between the intervention arm (*Mdn*= -5) and the waitlist-control arm (*Mdn* = .5) were significant, p = .011. Change scores on the ADHD-RS (hyperactive-impulsive) were significantly different between the intervention arm (*Mdn*= -2.5) and the waitlist-control arm (*Mdn* = 2), p = .015. There was a significant difference in Total change scores between the intervention arm (*Mdn*= -8.5) and the waitlist-control arm (*Mdn* = 2), p = .009. Total change scores were obtained by summarizing the differences between Total scores (sum of Inattentive and Hyperactive-Impulsive scores) at week 8 from week 1.

Differences in change scores between groups on the subscales on the SRS were not significant (Table 3).

3.2.4. Pooled analysis

Pooling the pre, post and follow-up (1 month) BCI data from both groups, changes on the subscale scores of the ADHD-RS (inattentive) and ADHD-RS (hyperactive-impulsive) were significant from pre- to post-BCI (*Mdn*= -4.5, $p<0.001$). Changes from post-BCI to follow-up were not significant (*Mdn*= -0.5, $p = 0.793$), suggesting that the pre-post BCI changes were maintained.

Significant improvements were observed for Social Communication ($p = 0.036$), Social Motivation ($p = 0.015$), Autistic Mannerisms ($p = 0.021$) and Total ($p = 0.008$) on change scores from pre to post-BCI (Table 4). Change scores were not significant on the subscale of Social Awareness among pre-, post-BCI and follow-up. For all the subscales, changes in scores from post-BCI to follow-up were not significant.

4. Discussion

The present study aimed to ascertain the feasibility of implementing a novel BCI-programme that has been adapted to teach socio-cognitive skills for children with ASD and co-occurring ADHD. Estimates of efficacy in improving inattention and socio-communication skills were also obtained.

Table 3
A comparison of change in ADHD-RS and SRS scores between Week 1 and Week 8 for Intervention and Waitlist-control arms.

	Intervention			Waitlist-control			
	Min.	Max.	Median	Min.	Max.	Median	*p*-value
ADHD-RS							
Inattentive	−14	0	−5	−8	9	0.5	0.011
Hyperactive-Impulsive	−6	4	−2.5	−8	9	2	0.015
Total	−15	3	−8.5	−16	18	2	0.009
SRS							
Social Awareness	−4	3	0	−4	4	1	0.315
Social Cognition	−6	4	−2.5	−3	10	−1	0.143
Social Communication	−10	5	−2	−9	10	−0.5	0.436
Social Motivation	−3	3	−1.5	−7	5	1.5	0.165
Social Mannerisms	−4	4	−1.5	−8	14	−1	0.739
Total	−19	9	−8	−19	35	−2.5	0.247

Table 4
Changes in ADHD-RS and SRS Scores of Pooled Participants (n = 20) amongst Pre-, Post- and One Month following BCI Training.

	Pre-Post	Post-Follow up
ADHD-RS		
Inattentive		
Median (Range)	−4.5 (-14 to 1)	−0.5 (-9 to 10)
P-value	<0.001	0.793
Hyperactive-impulsive		
Median (Range)	−2.5 (-8 to 4)	−1.5 (-10 to 7)
P-value	0.003	0.2
Total		
Median (Range)	−7.5 (-15 to 4)	0 (-19 to 13)
P-value	<0.001	0.794
SRS		
Social Awareness		
Median (Range)	−0.5 (-5 to 3)	0.5 (-6 to 5)
P-value	0.135	0.420
Social Cognition		
Median (Range)	−2.5 (-10 to 4)	−0.5 (-5 to 5)
P-value	0.055	0.439
Social Communication		
Median (Range)	−2.5 (-17 to 9)	−0.00 (-14 to 10)
P-value	0.036	0.985
Social Motivation		
Median (Range)	−2.0 (-5 to 3)	−0.5 (-7 to 3)
P-value	0.015	0.251
Autistic Mannerisms		
Median (Range)	−1.5 (-15 to 4)	−1 (-11 to 9)
P-value	0.021	0.336
Total		
Median (Range)	−9 (-40 to 14)	−1 (-35 to 26)
P-value	0.008	0.794

All P-values were obtained from the Wilcoxon signed rank test.

High treatment completion and adherence rates suggest that 24 sessions of BCI training, adapted to train socio-cognitive skills over an 8-week period, is acceptable to both parents and participants. However, a considerable proportion of participants (45 %) exhibited significant emotional and behavioural dysregulation during sessions. This necessitated tailored behavioural supports and intermittent breaks that were time-consuming and resulted in significant delays in-session. Of these, three participants also displayed persistent oppositional behaviours, resulting in scheduling delay when they were deemed too dysregulated or uncooperative to continue the given session. For this subgroup of participants, treatment feasibility and acceptability was low.

Although our previous trial with ADHD-only participants showed higher completion rates (94.7 %), the present comorbid sample presented with behavioural challenges that resulted in scheduling delay. Technical difficulties with the inclusion of additional devices (i.e. eye tracker) had also resulted in delay. Importantly, literature has suggested a minimum of 20 sessions to elicit positive change (Arns et al., 2020; Vernon et al., 2004), which all participants fulfilled.

No serious adverse events warranting medical attention were reported. However, side effects such as headaches and/or fatigue, and self-injurious behaviours resulting from frustration were observed. Performance on the socio-cognitive games were contingent on both gaze and attention, requiring effortful control which may have been taxing on participants. Furthermore, a subset of participants exhibited pervasive difficulties with gaze control. Deficits in visual attention have been associated with autism; Symptoms include poorer precision and accuracy in orienting, shifting, difficulties disengaging attention, and limited distribution of spatial attention (Keehn, Nair, Lincoln, Townsend, & Müller, 2016; Forgeot d'Arc et al., 2017; Pantelis & Kennedy, 2017). The socio-cognitive training tasks may thus have been more challenging for this subgroup.

To reduce strain, future iterations may integrate standardised breaks within the programme at timely intervals, reduce overall game duration, or intersperse socio-cognitive games (*Busy Eyes*) with attentional games (*Cogoland*), in order to moderate cognitive load. An introductory session presented in an autism-friendly manner such as comic strips may also be introduced to better prepare participants for anxiety-invoking events such as time limits and technical difficulties. This is especially relevant in an ASD population vulnerable to stress and behavioural escalation in novel or stressful situations.

To facilitate arousal regulation, behavioural supports were provided for all participants and modifications deemed necessary for persistent challenging behaviours. Most participants responded well, and were able to complete the session. Despite frustrations experienced by participants, there were no dropouts and participants continued attending subsequent BCI sessions, indicating that the programme is adequately engaging with supports.

In terms of obtaining estimates of preliminary efficacy, the intervention group showed a larger improvement in clinician-rated ADHD symptoms on ADHD-RS scores, between Week 8 and Week 1 compared to the waitlist-control group. Moreover, clinicians were blinded to participants' treatment status. There was also no significant change in scores at one-month follow-up from post-BCI in the pooled sample, suggesting that observed improvements in ADHD behaviours may have been maintained for at least one month after cessation of training. While the results may appear promising, the absence of a sham control group limits conclusions that may be drawn. An active control condition such as the use of computerized training can be included as a plausible alternative (Gevensleben et al., 2014) for the next trial.

Conclusions regarding positive effects in the pooled sample on the SRS subscales are limited as parents were not blinded which could have introduced bias. Blinding was difficult as the intervention was carried out at the clinic, and participants were often accompanied by parents before proceeding to a separate room to complete training. Notably, parents reported improvements in autistic mannerisms and social motivation that were not explicitly targeted in our games. While we cannot attribute causation, we can postulate that improved attention may have contributed to global gains in autism-specific deficits. Researchers have suggested that restricted patterns of interest and behaviours in ASD may be related to deficits in attention, wherein children exhibit difficulties in orienting or selecting attention while ignoring task-irrelevant stimuli (Agam, Joseph, Barton, & Manoach, 2010; Ozonoff et al., 2004; Ravizza, Solomon, Ivry, & Carter, 2013). Our present programme trains participation to orient, and sustain eye gaze *with* attention to task relevant information, which may have improved cognitive control. Additionally, regular one-to-one interactions with a therapist, who administered supports for participants during sessions, may have also created social learning opportunities and facilitated an interest in social interactions. Further research can shed light on the mechanism of action underlying these domains.

Our battery of socio-cognitive games may not have been sufficient to scaffold significant improvements in tenets of social communication over 8 weeks, or 24 sessions. Furthermore, the SRS may not have been a valid instrument to measure change in socio-communication behaviours over a short interval of 8 weeks; the SRS has also been found to demonstrate limited sensitivity to changes in ASD-related social impairments (McConachie et al., 2015). Any observable improvements in ASD symptoms may thus require more time or sessions to become more apparent on parent-reported measures, and is a limitation of our present study. Neurofeedback literature indicates that effect size correlates with the number of sessions, and future research may further shed light on dose-response rates for neurofeedback sessions to elicit observable change in social behaviours in ASD.

The role of non-specific effects remains a limitation. The accompanying behavioural supports may have contributed to reported improvements at post-treatment through teaching appropriate regulation strategies. Improvements on parent-report measures may thus be due to interventions put in place by the therapist rather than the BCI-based games. Modifications to supports also introduced variability in supports provided to participants, whereas frequent challenging behaviours for a subset of participants led to significant delays per session. The feasibility of implementing this programme on a larger scale may thus be low for this subgroup. However, for the majority of the participants, these supports facilitated motivation and adherence to sessions. This reflects the challenges of working with this heterogeneous population, wherein idiosyncrasies in difficulties, interests, as well as underlying rigidity (Leekam, Prior, & Uljarevic, 2011), necessitate individualised supports in order to for them to benefit from intervention. Future studies may include a manualized protocol to standardize responses to common behavioural challenges that have been identified.

The primary aim of pilot studies is to determine the feasibility of trial and assessment procedures (Leon, Davis, & Kraemer, 2011). High adherence rates, treatment completion rates and no drop outs indicate that our training is relatively safe and sustainable despite its high volume and intensity for the majority of the participants. However, feasibility and acceptability remains low for a subgroup of participants with persistent dysregulated behaviours. This programme may thus be feasible for only children with milder symptomatic presentations, without significant emotional dysregulation or oppositional behaviours. Further steps can also be taken to achieve greater standardization in treatment implementation, such as building supports into the programme to reduce reliance and load on therapists, as well as manualizing responses to challenging behaviours. Nevertheless, some variability is expected when working with this population.

On estimates of efficacy, significant improvements on ADHD symptoms were reported, which were maintained at one month follow-up. Positive effects on tenets of social deficits were observed in the pooled sample as well. Conclusions, however, remain limited as we are unable to rule out effects of placebo and varied supports with therapists. A future large clinical trial will incorporate appropriate controls for non-specific effects, to further ascertain the efficacy of our training programme.

5. Implications

In spite of study limitations and challenges of the present study, it is worthwhile to further investigate and develop neurofeedback programmes using brain-computer interfaces. Currently, medication remains a standard treatment for ADHD symptoms in this co-morbid population with side effects and limited efficacy. Given neurofeedback's relatively lower risk of side effects, it may hold promise as a complement to standard treatment. To date, no studies have investigated the effects of neurofeedback training on children with ASD and co-occurring ADHD. Delivered in a game-based format, our BCI programme was able to adequately sustain participants' interest. We are presently refining and further developing the battery of socio-cognitive games to reduce occurrences of side effects, determine performance ceilings and improve transferability of social skills.

With high rates of co-occurrence and greater impairment with comorbidity, our BCI programme may hold the potential to serve as a relatively safe, engaging and complementary intervention children with milder symptomatic presentations with further refinement.

Author statement

Sze-Hui Jane Teo: Formal Analysis, Investigation, Data curation, Writing-Original draft, Writing-Reviewing and editing, Visualization. **Xue Wei Wendy Poh**: Investigation, Data curation, Writing-Original draft. **Tih Shih Lee**: Conceptualization, Methodology, Supervision, Funding acquisition, Project administration. **Cuntai Guan**: Conceptualization, Methodology, Software, Validation, Supervision. **Yin Bun Cheung**: Methodology, Formal Analysis, Writing-Reviewing and editing. **Daniel Shuen Sheng Fung**:

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Declaration of Competing Interest

Intellectual property for the device has been jointly filed under the provisions of the respective institutions, including the Institute of Mental Health, Duke-National University Hospital and Agency for Science, Technology and Research (A*STAR). The study sponsors had no involvement in the study. Ms Jane Teo Sze-Hui wrote the first draft of the manuscript, and no honorarium, grant or any form of payment was given to anyone to produce the manuscript.

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Appendix A. Supplementary data

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