

RUNNING TITLE: EFFECTS OF IBBS ON ERP MEASURES

Effects of an Integrated Brain, Body, and Social (IBBS) intervention on  
ERP measures of attentional control in children with ADHD

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**Key words:** Attention-Deficit/Hyperactivity Disorder (ADHD), Children, Cognitive Training, Physical Exercise, EEG

## Abstract

### Objective

A primary goal of this study was to examine the impact of an Integrated Brain, Body, and Social (IBBS) intervention on event-related potentials (ERPs) of inhibitory (N2) and attentional (P3) control in a sample of young children (5 to 9 years) with ADHD. We also aimed to replicate previous findings of significant group differences between children with and without ADHD on ERP and behavior (i.e., Go/No-Go performance) measures.

### Methodology

A total of thirty-two participants (M age = 7.03 years; 57% male; 42.9% white) recruited from the IBBS efficacy study completed a Go/No-Go task before and after treatment as brain activity was recorded using electroencephalography (EEG). Thirty-six healthy matched controls also completed the same EEG study procedures at one time point.

### Results

As compared to the HC group, the ADHD group were significantly slower and showed greater variability in response times ( $p=.001$ ,  $p=.06$ ). Moreover, the HC group evidenced a No-Go P3 effect ( $p=.003$ ), whereas the ADHD group did not. Following treatment, a No-Go P3 effect and a significantly reduced Go P3 latency was revealed for the IBBS group ( $p=.05$ ,  $p=.04$ ) and not the TAU group. No treatment effects were found on any behavior measures.

### Conclusion

Our study provides initial evidence that attentional control systems in the brain might show changes following treatment with IBBS. However, it is unlikely that IBBS in its present form provides a substantial benefit to children with ADHD, given treatment effects were only found on ERP measures and not on behavior measures.

Clinical trial registration information— Integrated Brain, Body, and Social (IBBS) intervention for Attention-Deficit/Hyperactivity Disorder; <http://clinicaltrials.gov/>; NCT01542528.

## Effects of an Integrated Brain, Body, and Social (IBBS) intervention on neural correlates of inhibitory and attentional control in children with ADHD

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder of childhood, exemplified by age-inappropriate levels of inattention, hyperactivity, and impulsivity causing impaired functioning across multiple environments. These symptoms often persist into adulthood and are associated with poor developmental outcomes including occupational problems, other psychiatric disorders, substance abuse, criminal activity, and higher mortality rates (Cherkasova, Sulla, Dalena, Pondé, & Hechtman, 2013; Dalsgaard, Østergaard, Leckman, Mortensen, & Pedersen, 2015; Knecht, De Alvaro, Martinez-Raga, & Balanza-Martinez, 2015). ADHD symptoms are thought to reflect an underlying executive function (EF) deficit, primarily in the domains of attention, response inhibition, and working memory (Barkley, 1997; Castellanos & Tannock, 2002; Hervey, Epstein, & Curry, 2004; Schachar et al., 2000). Substantial empirical evidence supports an EF deficit model, primarily from studies showing significant group differences between children with ADHD and healthy controls on EF measures (e.g., Frazier, Demaree, & Youngstrom, 2004), including poorer performance on tests of EF reflected in response patterns that are slower, highly variable, and more prone to errors (Barkley, 1997; Willcutt et al., 2005). However, these group differences are usually medium-sized effects (Cohen's  $d = 0.4-0.7$ ), with not all children with ADHD showing EF deficits (Willcutt et al., 2005).

This lack of consistency in finding EF impairments among children with ADHD may be explained in several ways. First, the methods used to measure EFs are widely variable; not only are there multiple versions of the same test, but multiple dependent variables may be extracted with varying levels of sensitivity (see Seidman, 2006). Second, EFs are extremely difficult to operationalize or capture, as each EF consists of several non-shared components (A.M.C Kelly et al., 2006; Miyake, Friedman, Emerson, Witzki, & Howerter, 2000). Third, there may be multiple EF profiles subsumed under the broader ADHD diagnostic category (Nigg et al., 2005); some children show their greatest difficulties with impulsivity related to response inhibition, others struggle with cognitive flexibility in shifting attention between tasks, and still others display neuropsychological profiles comparable to their typically developing peers (Castellanos et al., 2006; Fair, Bathula, Nikolas, & Nigg, 2012; Nigg et al., 2005). In fact, these three EF subtypes

have been recently supported by emerging evidence from a study employing cluster analyses (Roberts, Martel, & Nigg, 2017). Fourth, neuropsychological tests may not be sensitive enough to detect the EF deficits of all children diagnosed with ADHD, as they tend to reflect the end product of underlying cognitive processes in the form of a behavioral response. The majority of EF measures have adequate predictive validity for ADHD (i.e., true positives); however, an average performance on a neuropsychological test cannot rule out an ADHD diagnosis (i.e., false negatives; Doyle et al., 2000; Hinshaw et al., 2002; Lovejoy et al., 1999). Thus, such tests are not recommended as the only method to establish an ADHD diagnosis, but are useful in providing cognitive profiles of strengths and weaknesses for treatment purposes and assessing changes in cognitive functioning over time (Seidman & Bruder, 2003; Seidman & Toomey, 1999).

To better elucidate the cognitive processes that increase the risk for ADHD, neuropsychological tests have been paired with methods that directly capture brain function. In this regard, electrophysiological measures, such as event-related potentials (ERPs), provide a window to detect the cascade of neural processes before, during, and after a behavioral response. ERP measures tend to be highly reliable and heritable, with results across studies consistently finding abnormal neural functioning in ADHD (Biederman et al., 2017; Kuntsi, McLoughlin, & Asherson P, 2006; McLoughlin et al., 2005). ERP components routinely examined in the ADHD studies include the P3 (i.e., positive deflection occurring at around 300ms after the stimulus at posterior parietal locations) and N2 (i.e., negative deflection occurring at around 200ms after the stimulus at fronto-central sites) elicited during neuropsychological tests (e.g., Cued Go/No-Go task), as they index performance monitoring associated with inhibitory and attentional control (Donkers & van Boxtel, 2004). Studies in children with ADHD usually show attenuated P3 amplitudes during Go and No-Go trials and attenuated N2 amplitudes during No-Go trials (Albrecht et al., 2008; Barry, Johnstone, & Clarke, 2003; Brandeis et al., 2002; Johnstone & Barry, 1999; Wiersema et al., 2006; Yong-Liang et al., 2000). In turn, these components evidence moderate heritability (~60%) and genetic associations with ADHD risk variants (see Tye et al., 2014 for review).

Several treatment outcome studies have used ERPs to evaluate the effects of medications for ADHD on brain function. Some work suggests that stimulant medications (i.e., methylphenidate) increases P3 (Groom et al., 2010; Ozdag, 2004) and N2 amplitudes in children with ADHD during Go and No-Go trials such that they are comparable to healthy control children (Broyd et

al., 2005; Groom et al., 2010; Ozdag et al., 2004). Medication effects have also been shown for ERP latencies, with P3 latencies reduced (i.e., earlier response to infrequent targets) and N2 latencies enhanced (i.e., later response to infrequent targets) following treatment (Ozdag et al., 2004; Sunohara et al., 1999). Interestingly, Broyd et al. (2005) found that for younger children with ADHD (aged 8 to 11 years), the Go N2 amplitude was significantly *larger* than the No-Go N2 amplitude pre-medication and the expected No-Go N2 effect (i.e., No-Go N2 > Go N2), as seen in healthy controls, was found post-medication. Overall, these results suggest that these ERP measures have the potential to be improved by ADHD interventions.

The purpose of the present study is to evaluate the impact of a non-pharmacological treatment for ADHD on ERP measures (i.e., N2, P3). The treatment, an Integrated Brain, Body, and Social (IBBS) intervention, was explicitly designed to broadly target EF deficits associated with ADHD. This is particularly important as non-pharmacological interventions have the potential to produce change without the unwanted side effects associated with ADHD medication and to maintain this change even after active treatment has ended. Although recent work suggests that the effects of cognitive working memory training (CWMT) may not transfer to untrained domains (e.g., ADHD symptomatology, other related cognitive processes) (Beck et al., 2010; Chacko et al., 2014; Gray et al., 2012; Green et al., 2012; Holmes et al., 2010; Johnstone et al., 2012; Klingberg et al., 2005; Mawjee et al., 2015; Shalev, Tsal, & Mevorach, 2007; Smith et al., 2016; van der Donk et al., 2015; van Dongen-Boomsma et al., 2014), including one recent ERP study with adults (i.e., Liu et al., 2017), issues concerning the dose and broadness of these training programs could have also contributed to a lack of treatment effects. To this end, we examined the efficacy of a cognitive training intervention targeting a range of executive functions relevant to ADHD, imbedded within a behavioral treatment regimen.

The Integrated Brain, Body, and Social Intervention (IBBS) is a multi-faceted program developed for children with ADHD that involves computerized cognitive training (i.e., brain component), physical exercise (i.e., body component), and an evidence-based behavior management strategy (i.e., social component). IBBS builds on previous CWMTs in two important ways. First, IBBS trains eight executive functions (i.e., sustained attention, response inhibition, speed of processing, cognitive flexibility, multiple simultaneous attention, working memory, category formation, pattern recognition) known to be implicated in ADHD (Barkley, 1997; Crippa et al., 2015; Huang-Pollock, Maddox, & Tam, 2014; Pennington & Ozonoff, 1996;

Willcutt et al., 2005) whereas standard CWMT only targets working memory. Although lacking in empirical support, the possibility of transfer effects in CWMT has been predicted in the research literature because of shared cognitive processes (i.e., focused attention, effortful control, behavior inhibition) and neural substrates (i.e., basal ganglia, prefrontal-parietal executive network) across EFs (e.g., Criaud & Boulinguez, 2013; Reddick et al., 2011; van Noordt et al., 2015). Alternatively, IBBS trains several executive functions outright in an effort to increase the likelihood of transfer effects. Second, IBBS employs an additional method of training by means of physical exercise, as previous research has shown the benefits of exercise in improving performance on neuropsychological tests (Grassmann, Alves, Santos-Galduróz, & Galduróz, 2014; Kamp, Sperlich, & Holmberg, 2014) and ratings on ADHD symptom checklists (Abramovitch, Goldzweig, & Schweiger, 2013; Smith et al., 2013; Verret, Guay, Berthiaume, Gardiner, & Béliveau, 2012). Taken together, the training of both the brain and body was intended to maximize neurocognitive benefits and promote transfer effects. Moreover, IBBS includes a behavior management technique (i.e., social component of IBBS) to encourage the engagement of children as they completed the brain and body cognitive exercises; strategies that have been employed in standard CWMT interventions (e.g., Chacko et al., 2014).

The results of a randomized controlled trial comparing IBBS versus Treatment-As-Usual (TAU) and its impact on ADHD symptomatology and neurocognitive functioning are presented elsewhere (Smith et al., 2016) and this paper reports novel ERP and behavior data from an add-on pilot study of this larger clinical trial. A more comprehensive evaluation of IBBS was deemed appropriate given that only one study has examined ERP changes following CWMT in a sample of adults (i.e., Liu et al., 2017), which is important to replicate in a sample of children, and treatment effects may occur at the neural level before behavioral changes are directly observable by raters (i.e., parents, teachers, clinicians) or seen on neuropsychological tests. The goals of this study were two-fold. First, we aimed to replicate findings of group differences in a sample of young children (ages 5 to 10 years) with and without ADHD on behavior (i.e., No-Go accuracy, Go reaction time, Go reaction time variability) and ERP measures (i.e., P3 and N2 amplitude and latencies) obtained during a neuropsychological test of sustained attention and response inhibition (i.e., Go/No-Go task). Second, we evaluated the impact of IBBS on these ERP measures in children with ADHD to determine if treatment effects occurred at the neural level. Specifically, we predicted that children randomized to IBBS would show increases in the P3 and

N2 amplitudes for Go and No-Go trials following treatment as compared to TAU. We also evaluated whether the No-Go N2 effect became more prominent following treatment with IBBS since this outcome has been found in the extant literature for children with ADHD treated with stimulant medication (e.g., Broyd et al., 2005). Finally, on an exploratory basis, changes in P3 and N2 latencies were examined, as discrepant findings have been reported within and across studies, especially for the N2 (e.g., Liu et al., 2017; Ozdag et al., 2004; Sunohara et al., 1999).

## **Methods**

### *Participants*

This study included 2 groups of participants; children with ADHD who participated in the large-scale clinical trial of IBBS (Title: Integrated Brain, Body, and Social (IBBS) intervention for Attention-Deficit/Hyperactivity Disorder; <http://clinicaltrials.gov/ct2/show/NCT01542528>) and a matched sample of typically developing children without any psychological disorders. The first group of participants recruited from the IBBS efficacy study met the following inclusion criteria: 1) age between 5 and 9 years, 2) confirmed DSM-IV-TR diagnosis of ADHD or subthreshold diagnosis of ADHD (i.e., one symptom below diagnostic criteria), 3) IQ of 80 or above, and 4) stable dose of ADHD medication for one month (if applicable). Exclusion criteria included: 1) history of a neurological disorder, concussion, or head injury, 2) severe or impairing comorbid psychological diagnosis requiring immediate therapeutic attention (e.g., psychosis, acute behavior problems, bipolar disorder), 3) psychotropic medication other than that prescribed for ADHD, and 4) motor or visual impairment that would prevent participation in the IBBS intervention.

A total of thirty-seven participants agreed to take participate in the add-on EEG study. Prior to randomization, one participant dropped out of the IBBS study. Of the remaining participants, 20 were randomized to IBBS and 16 were randomized to TAU. Thirty-two subjects completed endpoint assessments, resulting in a sample of 32 subjects with post-randomization EEG data. Of these, data from 3 participants were excluded from analyses due to a high level of motion resulting in an insufficient number of artifact-free No-Go trials at one of the time points (i.e., baseline,  $n=1$  or endpoint,  $n=2$ ). A final sample of 13 IBBS participants and 16 TAU participants were analyzed to evaluate the effects of the IBBS treatment on ERP measures of inhibitory and attentional control.

The second group of participants included thirty-seven healthy control children matched on age and gender. Following a mass mailing, the parents of these participants indicated an interest in participating in future studies and were contacted via telephone if their children matched the demographics (e.g., age, gender, residential location) of those children with ADHD who were already enrolled in the EEG study. Three of the healthy control participants were excluded; two for insufficient artifact-free EEG data and one for not pressing down the button hard enough so responses were not consistently recorded during the Go/No-Go task. For group comparisons at baseline, the final sample comprised of 35 participants with ADHD and 34 healthy control participants. See Figure 1 for a CONSORT diagram depicting the flow of participants and Table 1 for demographic and clinical characteristics of the sample disaggregated by group (i.e., ADHD vs. HC; IBBS vs. TAU). Importantly, no group differences were found between these comparison groups for any of these measures, suggesting the ADHD and HC groups were well-matched and randomization performed as expected for the IBBS and TAU groups.

### *Procedure*

The present study was approved by the Human Investigation Committee of the University conducting this research and by the school district where the IBBS intervention was implemented. Informed written consent and assent was obtained from the parents and children participating in this study prior to the commencement of any study procedures. Participants were invited to take part in the add-on EEG study at their baseline assessment for the larger IBBS study. During this baseline assessment, eligibility status was determined primarily by means of a medical history (e.g., past & current medical conditions, treatments) and a semi-structured clinical interview (i.e., Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version [K-SADS-PL]; Kaufman, Birmaher, Brent et al., 1997) administered by a master or doctoral-level clinician. A neurocognitive assessment battery, a measure of general intellectual ability (i.e., Kaufman Brief Intelligence Test, Second Edition [KBIT-2]; Kaufman & Kaufman, 2004), and parent-rated and clinician-rated ADHD symptom checklists (i.e., Swanson, Nolan, and Pelham Rating Scale [SNAP]; Swanson, 1992) were also completed at this assessment visit. Randomization to IBBS or TAU (stratified by medication status) occurred after the baseline assessment and within the context of the larger IBBS clinical trial. For those randomized to IBBS, the intervention lasted for 15 weeks, 3 days per week for 2 hours in an after-school setting and was implemented by school personnel (i.e., teachers, school counselors)



during the first half of the school year. The TAU group were instructed to continue with the same interventions already in place for their ADHD (i.e., medication, psychotherapy, school accommodations), but refrain from modifying or adding anything new to their treatment regimen for the duration of the study. They had the option of participating in the IBBS intervention during the second half of the school year after their endpoint assessments. The same study measures were then repeated within 4 weeks after the completion of the IBBS intervention program.

Baseline and endpoint EEG visits either occurred during the IBBS assessment visits following at least a 15-minute break or at another visit that was most convenient for families within the established time frame of the IBBS baseline and endpoint assessment visits. The visit for the add-on EEG study lasted approximately 1 hour and included three computerized tasks (i.e., Go/No-Go task, resting state task, reward-feedback task) administered during electroencephalography (EEG) recordings. Participants were closely monitored by highly trained research assistants (RAs) who oversaw stimulus presentation and data acquisition to ensure the quality of EEG data. Participants were also given stickers to promote motivation in between tasks or at pre-determined breaks programmed into the tasks, which were always administered in the same order. Participants received \$40 for completing EEG study procedures at each visit.

The healthy control (HC) participants were assessed for eligibility after expressing an interest in the EEG study and giving verbal consent during an initial phone screen. The absence of a neurological condition, past head trauma, and psychiatric diagnosis was confirmed during a clinical interview and by parent-rated forms assessing ADHD and related symptomatology during a one-time study visit. All healthy control participants were medication naïve. The EEG study procedures completed by the HCs were identical to the procedures completed by the IBBS study participants. They also received \$40 compensation for their time and effort.

### *IBBS Intervention*

As mentioned previously, the IBBS intervention is comprised of three treatment components. The brain component of IBBS includes three to five child-friendly computer games that at their most basic level resemble common neuropsychological tests (e.g., Continuous Performance Task, Wisconsin Card Sorting Task). Each game consists of hundreds of levels with each level building upon itself, thereby placing greater cognitive demand on the participant. The program closely monitors the progress of each participant and knows when to refrain from or add more

cognitive challenges by means of graduation and plateau criteria. Moreover, online corrective messages help participants adopt new strategies to achieve success. The body component is a set of physical exercises designed to train the same cognitive abilities in the context of whole body activity and social activation as the brain component. The physical exercises (e.g., balance training, relay races, ball skills, aerobic dance, team sports) are presented in a manualized format with accompanying floor diagrams to facilitate implementation. They progress gradually from simple to more complicated movements, thereby training additional cognitive abilities as they increase in complexity. A bottom-up approach was taken when developing the body component, as the exercises were chosen by experts in the field of neuroscience and sports psychology based on the extant literature and whether they were theorized to make use of specific cognitive abilities. Lastly, the social component (i.e., Good Behavior Game; GBG) is the only component of treatment not specifically designed for IBBS. The GBG is easily implemented in afterschool settings, may be integrated with other evidence-based practices, and capitalizes on multiple behavior modification strategies that are evidence-based in their own right. When playing the GBG, children work as a team to follow the rules of the program (e.g., “We will try our best”, “We will follow instructions”) and are rewarded for their efforts (e.g., trip to the prize box, game of “follow the leader”). The overall aim of the GBG was to reduce disruptive behaviors that might interfere with the other components of IBBS and promote generalization to other settings (i.e., school, home, community).

The IBBS intervention program lasted 15 weeks and was implemented in an after-school setting 3 days a week for 2 hours. The social component was simultaneously carried out while the participants completed the other treatment components (i.e., 45 minutes of computer games/brain component and 45 minutes of physical exercises/body component). School personnel were always present during the brain and body training in order to implement the social component of treatment, answer any questions the children might have, or suggest alternative strategies to improve their performance. The training of school personnel involved two didactic workshops each lasting 3 hours followed by the research team modeling the treatment components until school personnel were able to independently implement the program. This training was supplemented by weekly meetings with the research team to answer any questions or address any difficulties with program implementation that came up during the study period. A more detailed description of the IBBS intervention and training of school personnel is

presented in our previous report focusing on the treatment effects of IBBS versus TAU on neuropsychological tests and ADHD symptoms (Smith et al., 2016).

### *Measures*

#### Go/No-Go Task

This 15-minute Go/No-Go task has been well-piloted in neuroimaging and electrophysiological studies with children in the age range and diagnostic classification of the present study. In this version of the task, participants were presented with everyday, neutral objects (e.g., furniture, clothing) enclosed in red or green frames. Participants were directed to press a button if the frame was green (Go condition) and withhold this response if the frame was red (No-Go condition). Stimuli had a minimum presentation time of 800ms and a maximum presentation time of 1150ms with an inter-trial interval ranging from 500-1500ms. Go and No-Go stimuli were presented pseudo-randomly with at least 3 Go trials proceeding a No-Go trial to build up a strong pre-potent response. Following a short practice, two blocks of 150 trials were completed consisting of 240 Go trials (75%) intermixed with 60 No-Go trials (25%). An earned points display was presented after every 25 trials and was calculated based on participant performance with respect to correctly responding to Go (worth 1 point) and No-Go (worth 2 points) stimuli. The task resumed by pressing the spacebar on a keyboard controlled by the RA overseeing administration. E-prime 2.0 software (Psychology Software Tools, Inc.) was used to control stimulus presentation and record the accuracy and reaction time of responses. The behavior measures of interest for this task were No-Go accuracy, Go reaction time, and Go reaction time variability.

#### EEG data acquisition and preprocessing

EEG channels were recorded during the Go/No-Go task using a high density array of 128 Ag/AgCl electrodes arranged into a net (Geodesic Sensor Net, EGI Inc.) with a sampling rate of 250Hz by means of high impedance amplifiers (0.01 Hz high-pass, 100 Hz low-pass). Impedances were kept at or below 40kohms and all electrodes were referenced to Cz during recording. Netstation 4.4 software package (EGI, Inc.) was used to record and preprocess all EEG data.

Data were then filtered offline with a 30-Hz low-pass filter and segmented to epochs of 100ms before and 1100ms after stimulus onset. Segments with extreme voltage fluctuations defined as exceeding a threshold of 200  $\mu$ V were marked as bad segments. Channels with greater

than 40% bad segments were marked as bad channels. Bad channels and segments were replaced by spline interpolation. Eye blinks and eye movements were detected when vertical or horizontal eye channels, respectively, exceeded a threshold of 150  $\mu$ V. Eye blinks/movements were corrected by the Ocular Artifact Removal Tool from NetStation. Trials were then re-referenced from Cz to an average reference, baseline corrected to a 100ms pre-stimulus interval, and averaged within each condition for each participant. Trials with more than 10 bad channels were rejected. A minimum of 10 usable ERP No-Go trials were required for analyses, which is a threshold that has been used in other ERP studies evaluating the impact of cognitive training treatment (e.g., Lui et al., 2017).

Automatic detection identified peak amplitude and latency for the stimulus-locked component of N2 at frontocentral sites (average signal recorded at Fz and surrounding 10 electrodes; Fig. 1) between 100 and 300ms after stimulus onset for correct Go and No-Go trials. Average amplitude was used for the P3 at posterior parietal sites (average signal recorded at Pz and surrounding 6 electrodes; Fig. 2) between 300 and 900ms after the stimulus for correct Go and No-Go trials. Decisions of where and when to look for these ERP components were based on prior research with ADHD children and their typically developing peers using similar Go/No-Go tasks during EEG recordings (e.g., Groom et al., 2010; Wiersema et al., 2006) including the larger time window for the P3, which captured this ERP component for the full sample.

### *Statistical Analyses*

Prior to conducting analyses, the assumption of normality was evaluated for the ERP and behavior measures by graphically reviewing their distributions via Boxplots and calculating skewness and kurtosis values. Two measures at time 1 and three measures at time 2 violated the assumption of normality and were also found to have outliers. Once these outliers were handled by means of winsorization (Wilcox, 2012), the values for skewness and kurtosis fell within acceptable limits.

Group comparisons between the ADHD and HC groups on demographic characteristics, ERP measures, and behavior measures at time 1 were made using one-way ANOVAs for continuous variables and chi-square tests for categorical variables. A series of ANCOVAs were used to test the difference between IBBS versus TAU at time 2 for all ERP measures of inhibitory and attentional control. For each ERP measure, the model included its measurement at time 2 as the

dependent variable, group (IBBS vs. TAU) as the independent variable, and its measurement at time 1 as a covariate. This ANCOVA method was selected, as this approach has been shown to have more power than Repeated Measures ANOVAs (Rausch, Maxwell, & Kelley, 2003; van Breukelen, 2013) and has been employed by other research teams with similar study designs investigating treatment effects of cognitive training interventions for ADHD (e.g., Solanto, Marks, Wasserstein, Mitchell, Abikoff, Alvir & Kofman, 2010; van Dongen-Boomsma, Vollebregt, Buitelaar, & Slaats-Willemse, 2014). The same ANCOVA models were then conducted to test changes in the Go/No-Go behavior measures following treatment. Partial eta squared (i.e., unique variance explained by each predictor variable) was used as estimates of effect size where a value of .01 was interpreted as a small effect, a value of .10 was interpreted as a medium effect, and a value of .25 was interpreted as a large effect (Vacha-Haase & Thompson, 2004). Given this was a pilot study with a relatively small sample, the results of this study are reported without controlling for multiple comparisons.

## Results

### *Group comparisons of ADHD versus HC groups*

#### Behavior Measures

A significant group difference was found for Go reaction time (RT),  $F(1, 66) = 13.04, p = .001, \eta^2 = .16$ , where the ADHD group ( $M = 513.17, SD = 70.11$ ) had a slower RT than the HC group ( $M = 459.25, SD = 54.51$ ). A marginally significant group difference was also found for RT variability,  $F(1, 66) = 3.03, p = .06, \eta^2 = .05$ . The ADHD group ( $M = 134.25, SD = 28.91$ ) had greater RT variability than the HC group ( $M = 122.87, SD = 20.61$ ). There were no significant group differences for the remaining Go/No-Go behavior measures (i.e., Go and No-Go accuracy).

#### ERP Measures

As presented in Table 2, no significant group differences (ADHD vs. HC) were found for the N2 and P3 amplitudes or latencies for Go and No-Go trials. However, the N2 difference wave (i.e., No-Go N2 amplitude minus Go N2 amplitude) was significantly larger (i.e., more positive) for the ADHD group as compared to the HC group,  $F(1, 68) = 6.82, p = .01, \eta^2 = .09$ . To follow-up on this finding, the Go and No-Go N2 amplitudes were compared for the ADHD and HC groups separately. For the ADHD group, the Go N2 amplitude was significantly larger than the No-Go N2 amplitude,  $t(34) = -2.63, p = .01$ , whereas there was no significant difference between

Go and No-Go N2 amplitudes for the HC group,  $t(33) = .98, p = .34$ . Thus, neither the ADHD group nor the HC group evidenced a No-Go N2 effect, but this effect was in the opposite direction for the ADHD group (i.e., Go N2 > No-Go N2). Although the P3 difference wave was not significantly different across groups (ADHD vs. HC),  $F(1, 68) = 2.45, p = .12$ , the No-Go P3 amplitude was significantly larger than the Go P3 amplitude for the HC group,  $t(33) = -3.22, p = .003$ ; however, no significant difference was found for the ADHD group,  $t(34) = -1.38, p = .18$ . Thus, the HC group evidenced a No-Go P3 effect, but the ADHD group did not. Figure \_\_\_\_ provides a graphical depiction of ERP waveforms for the ADHD and HC groups at baseline.

### *IBBS treatment effects on ERP and behavior measures*

#### Treatment Compliance

On average, participants played the IBBS computer games for a total of 18.65 hours ( $SD = 4.45$ ) across the 15-week IBBS treatment period with a target playing time of 20 hours. Since previous studies have defined treatment compliance as completing 80% of the total number of training sessions (e.g., Chacko et al., 2014; Klinberg et al., 2005; van Dongen-Boomsma et al., 2014), we adopted this criterion and established a treatment compliance threshold of at or above 16 hours (i.e., 80% of 20 hours). Thus, 10 out of 13 participants met this threshold for treatment compliance in the IBBS group. As the results did not differ between those participants who completed baseline and endpoint evaluations (i.e., study completers) as compared to those participants who were treatment compliant (i.e., study compliers), the results presented below are from the full sample of study completers.

#### Behavior and ERP Measures for Study Completers

There were no significant treatment effects for any of the behavior measures (i.e., Go accuracy, No-Go accuracy, Go RT, and Go RT variability),  $F(1,27) = 0.32-1.10, p = .31-.58$ . There were also no significant treatment effects found for the N2 and P3 amplitudes for Go or No-Go trials. However, a significant treatment group difference in favor of IBBS was found for Go P3 latency,  $F(1,29) = 4.88, p = .04, \eta^2 = .16$ , such that it was significantly reduced for the IBBS group ( $M = 325.93, SD = 41.42$ ) as compared to the TAU group ( $M = 437.47, SD = 165.78$ ) following treatment. The N2 and P3 difference waves also did not reveal any significant group differences post-treatment (N2 difference wave:  $F(1,29) = 0.73, p = .40$ ; P3 difference wave:  $F(1,29) = 1.90, p = .18$ ). However, when comparing the Go and No-Go P3 amplitudes at time 2 for the IBBS and TAU groups separately, a No-Go P3 effect (No-Go P3 > Go P3) was

found for the IBBS group following treatment,  $t(12) = -2.24, p = .05$ , but this No-Go P3 effect was not found for the TAU group,  $t(15) = -0.48, p = .64$ . Detailed descriptive and ANCOVA test statistics are presented in Table 3 and ERP waveforms for the IBBS and TAU groups after treatment are presented in Figure \_\_\_\_.

## Discussion

A primary goal of this study was to examine whether improvements at the neural level were achieved following treatment with a novel, multi-faceted cognitive training intervention (i.e. IBBS) that was designed to augment underlying EF deficits associated with ADHD. A significant improvement on ERP measures (i.e. P3 and N2) was expected given that the intervention was carried out via two training modalities (i.e., brain and body) and the IBBS exercises made use of several higher-order cognitive processes that are theorized to comprise EFs and have been found to be less developed in individuals with ADHD (e.g., Crippa et al., 2015; Pennington & Ozonoff, 1996; Willcutt et al., 2005). It was also of interest to evaluate whether our pattern of results from a sample of young children (aged 5 to 9 years) approximated the ADHD and healthy control (HC) significant group differences found on ERP and EF measures in prior studies (e.g., Albrecht et al., 2008, Brandeis et al., 2002, Wiersema et al., 2006, Willcutt et al., 2005). Such an objective is worthwhile: improvements in neural functioning following treatment with IBBS would offer compelling evidence that this intervention is able to affect underlying neural correlates of EF deficits in children with ADHD and provide more confidence that changes post-treatment are specific to IBBS.

Although the results of this study did not find attenuated P3 and N2 amplitudes for children with ADHD as compared to HC children, it did replicate the finding of Broyd and colleagues (2005). Specifically, the Go N2 amplitude was found to be significantly *larger* than the No-Go N2 amplitude for the ADHD group, which is suggestive of a potential abnormality in inhibitory control. Our study also found no significant differences between the Go N2 amplitude and No-Go N2 amplitude for the HC group implying less developed inhibitory control at this stage of development since a No-Go N2 effect (No-Go N2 > Go N2) is typically found in older samples of typically developing children (i.e., 8 to 11 years; Broyd et al., 2005). Following from these results, a significant group difference for the N2 difference wave (No-Go minus Go) was found and indicates the magnitude of the difference between the Go N2 amplitude and No-Go N2 amplitude for the ADHD group was significantly larger (more positive) than the HC group.

Interestingly, the results of the present study also revealed a P3 No-Go effect for the HC group, but not for the ADHD group, suggesting an abnormality in attentional processing on behalf of ADHD children. However, it should be noted that the P3 difference wave was not significantly different between the two groups. As expected, our findings on behavioral measures were consistent with previous research (e.g., Wilcutt et al., 2005), as the ADHD group showed significantly slower response times and there was a trend towards more variability in their response times as compared to the HC group. Overall, these results suggest the presence of an atypical pattern of neural and behavioral functioning in this sample of ADHD children.

As argued by Liu and colleagues (2017), it is important to examine the potential impact of cognitive training on ERP measures as a way to more comprehensively evaluate its promise considering behavioral and symptom measures may not be as sensitive to treatment effects. Although their findings were not as expected and did not provide strong evidence that cognitive training improves neural correlates of EF deficits in adults with ADHD, we predicted improvements in ERP measures following treatment with IBBS given its integrative nature and how it builds upon existing cognitive training programs (e.g., multiple EFs exercised via two modalities of training). Contrary to our predictions and the results of medication studies finding changes in ERP measures post-treatment (e.g., Groom et al., 2010, Ozdag et al., 2004), the P3 and N2 amplitudes did not increase for the IBBS group relative to the TAU group, which is consistent with the results of the Liu et al. study (2017). However, we did find a treatment effect in favor of IBBS on Go P3 latency such that the P3 response for Go trials was earlier for the IBBS group as compared to the TAU group. This finding is somewhat consistent with prior medication studies, yet this treatment effect has been typically found for No-Go trials and not Go trials (e.g., Ozdag, 2004). Although a significant group difference was not found for the N2 and P3 difference wave, a No-Go P3 effect was revealed for the IBBS group and not the TAU group following treatment. Given the ADHD group did not show a No-Go P3 effect prior to treatment, this improvement post-treatment lends support to the notion that this effect may be specific to IBBS and this intervention may show promise in altering neural indices of attentional control. It is important to note that Liu and colleagues (2017) did not evaluate changes in No-Go effects for P3 and N2 following cognitive training. Considering these ERP measures differentiated ADHD from HC groups and showed some improvement following treatment with IBBS, it is



recommended that future studies consider using these ERP measures when evaluating the treatment efficacy of ADHD interventions.

Our results for behavioral measures of the Go/No-Go task comparing IBBS and TAU post-treatment aligned well with findings from the larger IBBS clinical trial (Smith et al., 2016), considering the majority of the EF measures used in the larger study did not show significant treatment effects in favor of IBBS except for one measure assessing verbal working memory. Past research typically finds improvements in EF domains that were specifically trained by cognitive training interventions (e.g., working memory), but results are less consistent for untrained EF domains and on measures assessing ADHD symptomatology (e.g., Chacko et al., 2014; Mawjee et al., 2015; van der Donk et al., 2015; van Dongen-Boomsma et al., 2014). Since IBBS treatment effects were only found for ERP measures and not behavioral measures, it is important that treatment outcome studies, particularly those studies testing cognitive training interventions, are as exhaustive as possible in their evaluative approach and incorporate methods that directly capture brain function.

Our study results warrant replication in a larger sample. Although promising, our results were not sufficiently robust to suggest IBBS in its current form produces adequate improvement to warrant wide-spread dissemination, especially when considering the amount of time and resources required to implement this intervention. Nonetheless, our findings, coupled with previous work on cognitive training, offer important insights as to the direction new interventions should take in offsetting EF deficits associated with ADHD. For example, future studies could establish individual neurocognitive profiles of children and then tailor cognitive training to meet their needs in real-world situations.

Considering that IBBS is comprised of intervention components known to improve ADHD symptomatology and associated EF deficits (i.e., physical exercise, Good Behavior Game), it is important to discuss why additional changes at the neural level were not found if ERP measures are indeed more sensitive to treatment effects. First, it is possible that the neurocognitive component of IBBS did not make use of the same neural pathway engaged by the Go/No-Go paradigm or that engagement without real-world application is not enough to evidence significant change. Second, the body component focused on skill acquisition rather than periods of aerobic physical exercise and perhaps there is a certain threshold of energy that must be exerted in order to produce treatment effects (Ng et al., 2017). The social component of IBBS

(i.e., Good Behavior Game; GBG) was used to limit off-task and disruptive behaviors during the neurocognitive and body components of treatment. However, the GBG is typically implemented for the entire school year with participants' classmates. These two implementation procedures for the GBG were not adopted when IBBS was put into practice as an after-school program. Finally, the timing and dosage of the intervention may have been sub-optimal to result in improvements across multiple outcome measures in favor of IBBS. Indeed, cognitive training that occurs consistently in the classroom and immediately prior to reading and math curriculum activities have been shown to improve students' performance on standardized achievement tests (Wexler et al., 2016), thus highlighting the need to consider when interventions should take place to maximize benefits.

### *Conclusion*

Our study provides initial evidence that attentional control systems in the brain might show changes following treatment with IBBS. Considering that these changes were specific to ERP measures and did not translate into improvements on behavioral measures, it is unlikely that that IBBS in its present form provides a substantial benefit to children with ADHD. As such, there is still much work to be done to identify what form cognitive training interventions might take to capitalize on environmentally-induced neural plasticity to remediate ADHD symptoms and associated EF deficits. A potential avenue for future studies is to find the optimal timing and dosage of the three components of IBBS so that changes are evidenced across multiple levels of functioning.

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Figure 1. CONSORT Flow Diagram

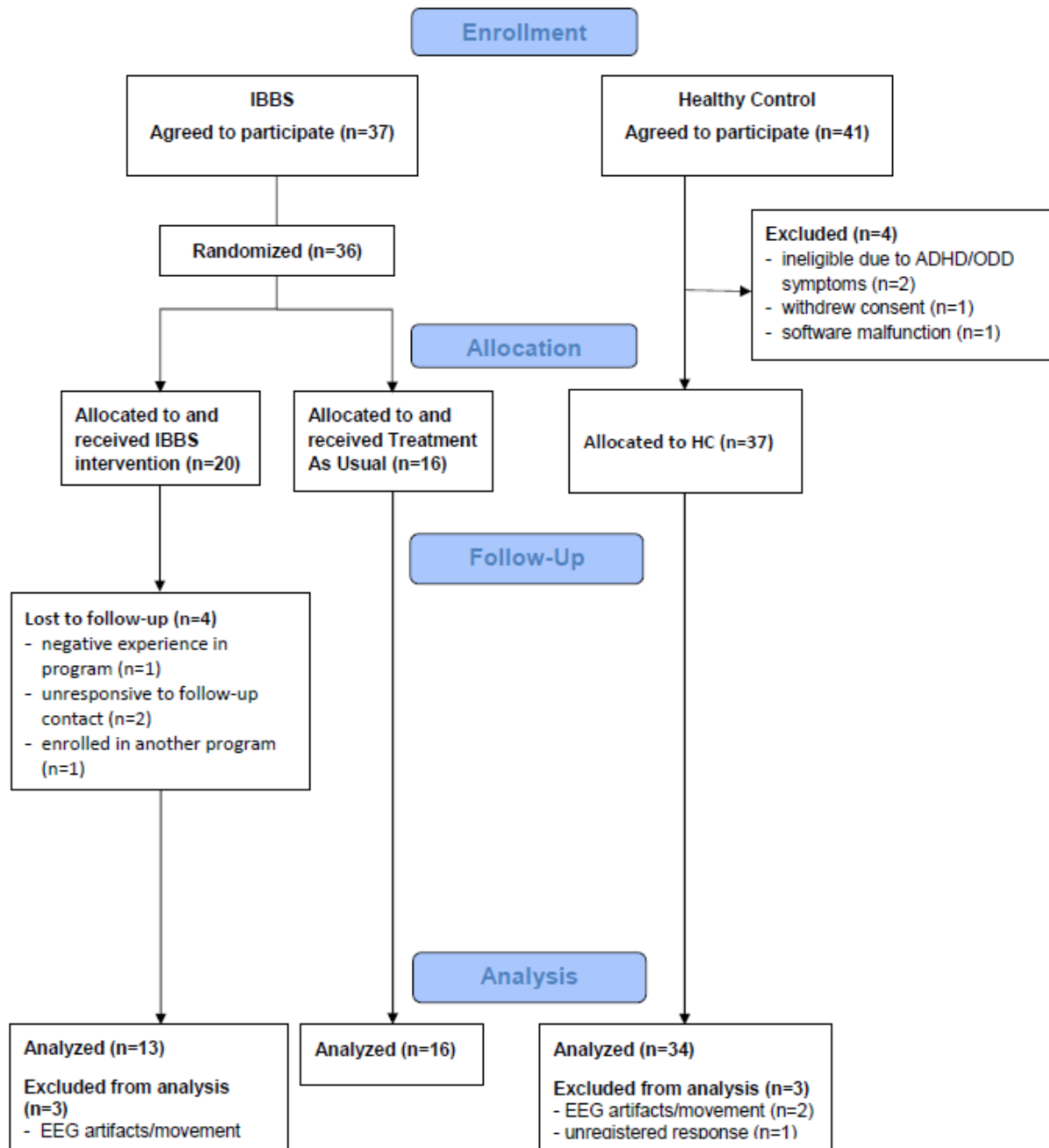


Table 1. Demographic and clinical characteristics of ADHD vs. HC groups and IBBS vs. TAU groups.

	ADHD M (SD) N=35	HC M (SD) N=34	Group Differences Test statistic	IBBS M (SD) N=13	TAU M (SD) N=16	Group Differences Test statistic
Age (years)	7.03 (1.32)	7.18 (1.22)	$F(1,68) = .23, p=.63$	13 (7.23)	16 (7.06)	$F(1,27) = .13, p=.72$
Sex, N (%)						
Male	20 (57.1)	21 (61.8)	$X^2(1) = .15, p=.70$	7 (53.8)	8 (50.0)	$X^2(1) = .04, p=.84$
Female	15 (42.9)	13 (38.2)		6 (46.2)	8 (50.0)	
Race, N (%)						
White	15 (42.9)	17 (50.0)	$X^2(3) = 1.91, p=.59$	5 (38.5)	7 (43.8)	$X^2(3) = .36, p=.95$
African American	15 (42.9)	9 (26.5)		6 (46.2)	6 (37.5)	
Hispanic	2 (5.7)	3 (8.8)		1 (7.7)	1 (6.3)	
Other	3 (8.6)	4 (11.8)		1 (7.7)	2 (12.5)	
KBIT	103.69 (12.67)	107.82 (13.67)	$F(1,68) = 1.70, p=.20$	107.46 (14.66)	99.63 (11.52)	$F(1,27) = 2.60, p=.12$
Parental Education (years)	15.24 (2.55)	15.31 (2.53)	$F(1,65) = .02, p=.90$	15.46 (2.29)	14.80 (2.78)	$F(1,26) = .46, p=.50$
ADHD Subtype, N (%)						
Inattentive	---	---	---	5 (38.5)	5 (31.3)	$X^2(3) = .51, p=.92$
Hyperactive-Impulsive	---	---	---	2 (15.4)	2 (12.5)	
Combined	---	---	---	4 (30.8)	7 (43.8)	
Subthreshold for ADHD	---	---	---	2 (15.4)	2 (12.5)	
Medications, N (%)						
ADHD Medication	---	---	---	4 (30.8)	2 (12.5)	$p=.23^{\#}$
Stimulants	---	---	---	4 (30.8)	2 (12.5)	$p=.23^{\#}$
Non-stimulants	---	---	---	2 (15.4)	---	$p=.19^{\#}$
Comorbidity, N (%)						
Anxiety Disorder	---	---	---	1 (7.7)	5 (31.3)	$p=.14^{\#}$
Oppositional Defiant Disorder	---	---	---	2 (15.4)	4 (25.0)	$p=.44^{\#}$
Autism Spectrum Disorder	---	---	---	1 (7.7)	1 (6.3)	$p=.70^{\#}$

HC = healthy control; IBBS = Integrated Brain, Body & Social Intervention; TAU = Treatment-As-Usual; M (SD) = mean (standard deviation); N = number of participants

<sup>#</sup>Fisher's Exact Test

Table 2. Group differences between ADHD and HC groups for ERP and behavior measures.

Measures	ADHD M(SD) N = 35	HC M(SD) N = 34	Test statistic	Effect size*	p-value
<b>ERP Measures</b>					
Go N2 amplitude	-9.18(3.35)	-8.24(3.36)	F(1,68)=.107	.002	.744
No-Go N2 amplitude	-8.24(3.36)	-9.21(3.43)	F(1,68)=1.44	.021	.235
N2 Difference Wave	.94(2.11)	-.31(1.83)	<b>F(1,68)=6.82</b>	<b>.092</b>	<b>.011</b>
Go N2 Latency	231.02(68.74)	208.75(74.73)	F(1,68)=1.66	.024	.202
No-Go N2 Latency	205.88(58.03)	193.07(68.68)	F(1,68)=.702	.010	.405
Go P3 amplitude	5.11(4.44)	3.53(2.40)	F(1,68)=3.35	.048	.072
No-Go P3 amplitude	5.95(5.68)	5.79(4.50)	F(1,68)=.017	.001	.897
P3 Difference Wave	.80(3.67)	2.26(4.08)	F(1,68)=2.45	.035	.123
Go P3 Latency	366.97(84.16)	343.51(59.46)	F(1,68)=1.78	.026	.187
No-Go P3 Latency	436.08(157.75)	397.58(122.79)	F(1,68)=1.28	.019	.263
<b>Behavior Measures</b>					
Go Accuracy	.91(.07)	.92(.07)	F(1,66)=0.75	.010	.389
No-Go Accuracy	.79(.11)	.76(.11)	F(1,66)=1.22	.018	.247
Go RT	513.17(70.11)	459.23(54.51)	<b>F(1,66)=13.04</b>	<b>.160</b>	<b>.001</b>
Go RT variability	134.25(28.91)	122.87(20.61)	F(1,66)=3.028	.050	.061

M = mean; SD = standard deviation; N = number of participants; RT = reaction time

\*Eta squared

Table 3. Test of group wise (IBBS vs. TAU) treatment differences for ERP and behavior measures.

Measures	IBBS N	IBBS-baseline M(SD)	IBBS-endpoint M(SD)	TAU N	TAU-baseline M(SD)	TAU-endpoint M(SD)	Test statistic	Effect size*	p- value
<b>ERP Measures</b>									
Go N2 amplitude	13	-8.61(3.24)	-7.44(2.29)	16	-9.30(3.83)	-8.52(3.79)	F(1,29)=0.54	.020	.468
No-Go N2 amplitude	13	-7.40(2.86)	-8.10(3.32)	16	-8.42(3.89)	-8.70(5.92)	F(1,29)=0.06	.002	.814
N2 Difference Wave	13	1.21(2.80)	-0.66(2.05)	16	0.87(1.72)	0.24(3.44)	F(1,29)=0.73	.027	.402
Go N2 Latency	13	223.38(75.40)	194.69(72.70)	16	240.32(63.88)	236.55(67.02)	F(1,29)=2.23	.079	.147
No-Go N2 Latency	13	201.31(51.84)	185.20(64.44)	16	212.50(59.07)	187.98(75.80)	F(1,29)=0.02	.001	.883
Go P3 amplitude	13	5.91(4.81)	2.90(2.69)	16	5.00(4.21)	3.76(3.39)	F(1,29)=2.10	.075	.159
No-Go P3 amplitude	13	7.17(6.23)	5.13(5.02)	16	5.55(6.10)	4.23(4.65)	F(1,29)=0.09	.004	.761
P3 Difference Wave	13	1.15(4.20)	2.23(3.59)	16	0.56(3.59)	0.48(4.03)	F(1,29)=1.90	.068	.180
Go P3 Latency	13	348.30(65.74)	325.93(41.42)	16	366.53(81.73)	437.47(165.78)	<b>F(1,29)=4.88</b>	<b>.158</b>	<b>.036</b>
No-Go P3 Latency	13	435.87(151.75)	426.15(108.77)	16	452.07(182.15)	435.82(116.26)	F(1,29)=0.05	.002	.819
<b>Behavior Measures</b>									
Go Accuracy	12	.92(.05)	.93(.05)	15	.91(.06)	.90(.09)	F(1,27)=1.10	.044	.306
No-Go Accuracy	12	.78(.14)	.78(.18)	15	.82(.07)	.76(.11)	F(1,27)=0.46	.019	.502
Go RT	12	512.45(61.44)	452.86(65.85)	15	524.94(79.41)	470.49(60.06)	F(1,27)=0.32	.013	.578
Go RT variability	12	133.10(19.47)	119.99(13.96)	15	130.17(29.50)	128.11(25.37)	F(1,27)=0.97	.039	.336

IBBS = Integrated Brain, Body, and Social Intervention; TAU = Treatment-As-Usual; N = number of participants; M = mean; SD = standard deviation; RT = reaction time

\*Eta squared