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Final White Paper: Effects of Brain Balance Exercises and Interactive Metronome on Children with Attention Deficit Hyperactivity Disorder are Similar to the Effects of Stimulant Medication

SUMMARY

Effects of a 15-week at-home training program consisting of up to 75 sessions of Brain Balance exercises and Interactive Metronome sessions (BB/IM) was evaluated in children of either sex between 8-14 years of age recruited from the community and confirmed to have ADHD through structured diagnostic interview. Clinical response was assessed based on parent ratings on the revised Conner's parent rating (CPRS), clinician ratings on the Attention Deficit Hyperactivity Disorder for DSM-IV rating scale (ADHD-RS), the Quotient ADHD System (which provides objective assessment of hyperactivity, inattention and impulsivity), and on computerized neuropsychological tests. Overall, n=57 participants were enrolled, and nine participants were disqualified as they did not meet diagnostic criteria for ADHD and were not typical developing controls. Over the course of the study N = 23 participants (59%) with ADHD and one control (11%) discontinued treatment or withdrew. Hence, complete pre-treatment / post BB/IM treatment data were available from n = 16 ADHD participants and from n = 8 typical developing controls. ADHD participants consisted of 14 males and 2 females with mean age of 10.8 ± 1.7 years. Controls consisted of 4 males and 4 females with mean age of 11.0 ± 1.8 years. In addition, data were also included from n = 19 participants, who closely matched the ADHD participants in their pre-treatment Quotient ADHD System pre-treatment indices. These individuals received treatment with morning light therapy to address issues of daytime sleepiness, but this intervention was not intended to ameliorate symptoms of ADHD. These participants were included in some of the analyses to highlight the potential effects of BB/IM via comparison to a contrast group receiving a treatment believed to be less efficacious.

Parent Ratings. Treatment with BB/IM was associated with a mean reduction of 7.4 points in ADHD symptoms on CPRS-R in children with ADHD ($p < .0002$) indicative of a large therapeutic effect size (Cohen's d paired = 1.29). BB/IM did not however fully normalize scores. Prior to treatment ADHD youths had ADHD Index scores that were, on average, 21 points greater than typically developing controls. Following BB/IM treatment their scores were about 12 points greater than re-test scores in controls. There were large therapeutic effect size reductions in oppositional behavior, inattention and hyperactivity.

Clinician Ratings. Treatment with BB/IM was associated with a 7-point reduction in Total ADHDRS Scores ($p < .02$), indicative of a medium therapeutic effect size (Cohen's d = 0.74). The effect of BB/IM was associated with a large therapeutic effect size (Cohen's d = 0.83, $p < .005$) on the Hyperactivity Impulsivity subscale and a medium effect size (Cohen's d = 0.58, $p < .04$) on the Inattention subscale. While BB/IM reduced the difference in ADHDRS scores between ADHD participants and typically developing controls, significant group differences persisted.

Objective Measures – Rate Dependency. There was a great deal of variability in pre-treatment versus post-treatment Quotient scaled scores. Some of the participants with high levels of hyperactivity and inattention prior to treatment showed a marked improvement. Conversely, post-test scores in ADHD participants with essentially normal pretreatment measure were often elevated to a substantial degree. This is indicative of a '*rate-dependent effect'* which we, and others, have previously observed in terms of response to stimulants[79]. As initially

formulated, rate-dependency describes the observation that stimulants exert behavioral effects that are inversely correlated to the basal rate of the behavior[19]. Specifically, stimulants tend to decrease behaviors that normally occur at high rates and to increase behaviors that occur at low rates. For children with ADHD, this means that the more hyperactive, distractible, or impulsive the child is, the more effectively stimulants will act to enhance attention and reduce activity. Conversely, stimulants will activate a child who is sluggish or drowsy[26,57,79].

For these analyses we compared the BB/IM participants, and the previously studied participants receiving treatment with phototherapy for morning sleepiness, to an original sample of youths used to establish the test-retest reliability of the instrument as part of the FDA clearance. They key consideration was whether BB/IM was associated with a greater rate-dependent effect than could be accounted for by a regression-to-the-mean artifact. BB/IM was associated with a significant rate-dependent effect on scaled hyperactivity score versus the test-retest validation sample ($p = 0.004$) and this was also true for the Global Severity Score ($p = 0.03$). Results for the inattention scaled score fell short of significance ($p = 0.1$). Use of phototherapy, which can have a stimulating effect, also showed a rate-dependent like effect, but in none of these comparisons was phototherapy use associated with a statistically significant difference from the test-retest validation sample.

To further explore the similarity of BB/IM to the action of methylphenidate we assessed the effects of BB/IM on four measures from the Quotient test on which we had previously published the rate-dependent effects of low (0.5 mg/kg/d), intermediate (0.8 mg/kg/d) and high (1.5 mg/kg/d) doses of methylphenidate[79]. Briefly, the slope of the regression line observed for BB/IM ($b = -.60$, $p = .002$) was nearly identical to the slope for the low dose of methylphenidate ($b = -.58$) but was not as steep as the slope for the intermediate and high doses. This suggests that BB/IM was exerting a rate-dependent effect that was equivalent to the rate-dependent effect of a low dose of methylphenidate. However, the correlation coefficient was much higher with BB/IM ($r = -0.81$) than with low dose of methylphenidate ($r = -0.46$). This indicates that BB/IM produced an effect on their ability to sit still that was equivalent, on average, to the effects of a low dose of methylphenidate, but that the participants responded in a more consistent and predictable manner to BB/IM than to methylphenidate. Similarly, BB/IM was associated with rate-dependent effects on CPT performance that were remarkably similar to low doses of methylphenidate.

Neuropsychological Measures. A key question that we sought to answer with neuropsychological testing during phase II was whether effects of Brain Balance / Interactive Metronome were due to the intervention or simply to the 15-week passage of time. Hence, N=6 participants with ADHD were assessed at baseline, reassessed on neuropsychological tests after 15 weeks without any intervention and then assessed a third time after BB/IM. The three neuropsychological tests used were: Corsi Block Tapping Task, Tower of London and the Mackworth Clock.

Overall, there was no significant effect of BB/IM on performance on the Corsi Block Tapping Task, which assesses visuo-spatial short-term working memory[15]. Brain Balance / Interactive Metronome was found to diminish the discrepancy in performance between participants with ADHD and typically developing controls on the Mackworth Clock Test, as a measure of sustained attention[37]. Controls differed significantly from ADHD participants in total hits prior to training ($p = 0.03$) but not after BB/IM ($p = 0.22$). Controls also had a much lower false alarm rate than ADHD participants prior to training $p = 0.008$), but ADHD participants and controls had a comparable false alarm rates after BB/IM ($p = 0.57$).

Interestingly, there were substantial effects of BB/IM on performance on the Tower of London which was designed to assess executive functioning specifically to detect deficits in planning[63]. BB/IM was associated with alteration in performance in Total Score ($p = 0.01$), Mean Solution Time $p = 0.053$) and Mean Execution Time ($p < 0.008$). Most importantly, there was evidence on the Tower of London task that BB/IM exerted a rate-dependent effect on performance that was not seen in the participants who were evaluated before and after an equivalent waiting period without BB/IM training. As expected with a rate-dependent effect, solution times increased in participants with ADHD who initially responded most quickly and decreased in participants with ADHD who initially responded most slowly.

Brain Imaging – Functional Connectivity. To assess the neurobiological effects of Brain Balance / Interactive Metronome training we focused on resting-state functional connectivity (rs-FC). This is a functional magnetic resonance imaging (fMRI) procedure designed to assess the degree of interconnection or functional coupling between brain regions. This property is measured by comparing patterns of blood flow fluctuation between brain regions. Regions that are significantly interconnected have correlated blood flow patterns suggesting that they are coupled and working together with each other. Interestingly, some brain regions show an inverse or anticorrelated pattern so that when blood flow goes up in one region it goes down in the other. This is indicative of a reciprocal or inhibitory pattern. Theoretically, BB/IM may work by strengthening or weakening the degree of positive or negative coupling between brain regions. We focused or rs-FC as this is a highly modifiable aspect of brain function and it is likely that effective treatments produce noticeable changes in behavior and clinical outcome by modifying this aspect of neurobiology. Resting state functional connectivity is the brain measures that relates most directly to Robert Melillo's theories regarding disconnection[42] and reconnection[43].

We used multiple strategies to study the effects of Brain Balance / Interactive Metronome on resting state functional connectivity. First, we compared rs-FC profiles in children with ADHD prior to BB/IM to those in typical developing controls to delineate abnormalities associated with ADHD. Second, we assessed whether these differences persisted following treatment with BB/IM. Third we assessed whether there were now any discernible differences between ADHD following BB/IM and healthy controls that were not present prior to treatment. Fourth, we identified functional connection in ADHD that were specifically modified following BB/IM. In this analysis we identified pathways that showed a significant overall increase or decrease in connectivity. Finally, we identified pathways in participants with ADHD that correlated with BB/IM associated rate-dependent changes in activity (microevents) and attention (% accuracy).

•*Pretreatment differences between participants with ADHD and typical developing controls.* Overall, there were 5 significant differences between these groups. First, rs-FC between the left lateral prefrontal cortical and right posterior parietal nodes within the frontoparietal network was reduced in participants with ADHD. The frontoparietal network contributes to executive control by providing top-down regulation of processes in other brain regions[13,70]. The particular part of the frontoparietal network affected appears to be associated with the default mode network and preferentially involved in the regulation of introspective processes. Deficiency in this component of the frontoparietal network may lead to problems with mind wondering and a diminished ability to stay on task[11].

Another key difference between the ADHD participants and controls was increased connectivity of the right amygdala with the left anterior insula hub of the salience network in youths with ADHD. The "salience network" is a collection of brain regions with key cortical hubs in the anterior cingulate and anterior insular cortex[61]. The network selects which stimuli are deserving of attention and is critical for detecting behaviorally relevant stimuli and coordinating our response to them[61]. Alterations in the configuration and connectivity within the salience network has been reported to be associated with greater susceptibility to distraction[71].

The third difference was a greater inverse correlation between right planum polare and the left 4th and 5th lobes of the cerebellum in participants with ADHD. The planum polare is part of a cortical network involved in language and music processing. Inattention in individuals with ADHD has been associated with abnormal activity within the planum polare[58]. Cerebellar abnormalities have frequently been reported in individuals with ADHD. Cerebellar dysfunction is associated with problems in the ability to predict when events are going to occur and other problems with timing and this has been identified as a key problem in children with ADHD, which is linked to poor inhibitory control[66]. Interactive metronome training is designed specifically to enhance timing.

The fourth finding was reduced rs-FC between the 7th lobule of the cerebellar vermis and the right inferior temporal gyrus. The vermis is the central portion of the cerebellum and abnormalities in the vermis has been frequently reported in ADHD[83]. Abnormalities in this specific portion of the vermis correlated with impaired neurocognitive abilities[38]. The inferior temporal gyrus is part of the ventral visual stream and plays a critical role in our ability to identify what we see. Reduced connectivity between these regions may significantly impact aspects of visual memory and comprehension.

The final finding was enhanced rs-FC between cerebellar vermis IX and cerebellar lobe X. Vermis lobe IX is part of the posterior cerebellar vermis and is involved in emotional regulation[74]. Reduced volume in this portion of the vermis is one of the most consistent findings in ADHD[25] and correlates with symptom severity[73]. Cerebellar lobule X is the substrate of the vestibulocerebellum, which receives vestibular and visual information and is involved with balance, vestibular reflexes, and eye movements. Hyperactivity, as observed in children with ADHD, is most clearly characterized by difficulty sitting still, and problems related to postural control and balance contribute substantially to their hyperactivity[50].

•*Post-treatment differences between participants with ADHD and typical developing controls.* Most importantly, none of the aforementioned significant differences between participants with ADHD and typical developing controls were detected in the comparison between youths with ADHD receiving BB/IM and typical developing controls retested after a 15-week waiting period. Hence, it appears that BB/IM reduced these differences to the point that they were no longer statistically significant.

However, a number of significant differences emerged between ADHD participants and typical developing controls following BB/IM. The most striking changes were in the connectivity of the left hippocampus which was reduced with 12 other regions including the frontal orbital cortex, frontal pole, inferior frontal gyrus as well as multiple portions of the temporal lobe. This is consistent with Dr. Melillo's theory and his prediction that "Brain Balance by removing bottom up interference, by integrating reflexes and then specifically stimulating the underdeveloped right hemisphere would help stimulate growth and maturation in the right side helping to restore synchrony between networks. This would promote integration and it may dampen activity that may have been overactive in the left hemisphere creating a balance between these areas." The hippocampus is involved in memory function with the left more specialized for verbal episodic and right more specialized for visual-spatial memory processes[20]. Neuropsychological testing in children with ADHD typically reveals greater abnormalities in spatial than verbal memory storage and manipulation[40]. Our thought is that prior to BB/IM training that ADHD participants were relying more on verbal working memory, but training may have improved visual-spatial working memory leading to more balanced use of the two memory systems reflected in reduced rs-FC of the left hippocampus.

A number of other alterations were observed in connectivity in the participants with ADHD. Interestingly, two of these involved regions contralateral to those reported to have abnormal connections prior to treatment (i.e., salience network – anterior insula L pre / R post; planum polare R pre / L post). We suspect that this may reflects some degree of right/left balancing of these regions as the Brain Balance treatment is intended to promote. Many of these changes involve connection with the salience network, and as noted above alterations in the configuration and connectivity within the salience network has been reported to be associated with greater susceptibility or resistance to distraction[71].

•*Alterations in resting state functional connectivity in ADHD participants following Brain Balance / Interactive Metronome treatment.* There were four connections associated with a significant increase and three with a significant decrease. The most notable was an increase in the reciprocal connectivity between the default mode network and the salience network. The default mode network is active at rest when individuals are not focused on the outside world and the brain is at wakeful rest, such as during daydreaming and mind-wandering[69]. The default mode network is reciprocally interconnected with other brain networks involved in performing tasks and attending to stimuli in the outside world[2]. Individuals with ADHD typically show patterns of altered connectivity between the default mode, attention and salience networks[64]. Enhancing the reciprocal connection between the salience and default network may help to reduce daydreaming and mind wandering. BB/IM was associated with increased connectivity of the default mode to the parahippocampal gyrus. The parahippocampal gyrus, which is involved in memory coding and retrival, links the default-mode network with the medial temporal lobe memory system[85]. The parahippocampal gyrus is interconnected to the superior frontal gyrus through the cingulum bundle[9], and connectivity between these regions was reduced following BB/IM. The superior frontal gyrus is implicated in several tasks including motor movement, working memory, resting-state, and cognitive control[9]. This may be associated with an enhanced ability to perform tasks automatically without thinking through each step.

There was a significant decrease in connectivity between the right central opercular cortex (aka subcentral gyrus) and the third lobule of the cerebellar vermis. A series of recent papers have reported an increase in activity in the subcentral area (BA43) when individuals and engaged in eye-to-eye communication[29], face-to-face interaction between opponents (poker game)[52] and in human-to-human verbal communication[28]. Interestingly, the vermis III also appears to be involved in impaired human-to-human communication associated with stuttering[91]. This suggests that BB/IM may be exerting some effect on the interaction between regions involved in human communication.

•*Relationship between Resting State Functional Connectivity and Rate-Dependent Changes in Attention.* There were 5 functional pathways in which change in connectivity following BB/IM correlated with rate-dependent effects on accuracy. Two of these pathways involved connections to the precuneus, which is a key component of the default mode. One connection was with the left inferior frontal gyrus, which is a part of Broca's area and plays a critical role in the expression of language. It also appears to be primarily responsible for one's inner voice[47]. The default mode, including the precuneus, is active when individuals are not focused on the outside world and the brain is at wakeful rest, such as during daydreaming and mind-wandering[69]. Hence, the more this internal voice connects to the default mode network the more likely individuals are to be distracted by internal voices and mind-wandering and have reduced accuracy. Similarly, the precuneus has its strongest connections with the thalamus[17]. Cunningham et al[17] has proposed that the thalamus is part of a DMN subsystem that plays an important role in switching between internal and external awareness. Diminished connectivity may shift the balance toward external awareness and improved attentional performance.

The pathway in which increased connectivity correlated with enhanced accuracy was between the supplemental motor area (SMA) and the medial prefrontal cortex. It has been observed in humans that the SMA and the medial prefrontal cortex plays a critical role in action monitoring[8]. This is the process of evaluating ongoing activities to adjust them in order to improve subsequent actions, and this capacity is often deficient in individuals with ADHD. Being better able to monitor performance and adjust accordingly should substantially improve accuracy on the continuous performance cognitive control task that is part of the Quotient Test.

•*Relationship between Resting State Functional Connectivity and Rate-Dependent Changes in Hyperactivity.* Overall, 5 pathways were identified that showed a statistically significant correlation with the rate-dependent effects of BB/IM on movements (microevents). Three of the pathways were connections of the angular gyrus, middle temporal gyrus and the cuneus with the subcallosal gyrus. The subcallosal gyrus, which includes the subgenual cingulate, (Brodmann Area 25 - BA25), is crucial for emotional expression and equilibrium.
A number of recent studies have revealed an important relationship between ADHD and the subgenual cingulate. Resting-state analysis ridentified a disconnected functional network between the subgenual cingulate and multiple regions in the occipital lobe (including the cuneus) and the cerebellum in children with ADHD. Similarly, diffusion tensor imaging data showed disrupted white matter integrity in the subgenual cingulum bundle. Both the resting state and diffusion tensor measures were significantly correlated with measures of hyperactivity-impulsivity and inattention[14,93]. Activity in the subgenual cingulate to emotional stimuli was reduced in drug-naive males with ADHD but was normal in males with ADHD treated with methylphenidate[60]. Hence, it makes sense that alterations in the connectivity of the subgenual cingulate may be affected by BB/IM and have rate-dependent effects on hyperactivity.

Another interesting pathway that correlated with rate-dependent changes in hyperactivity was between the right superior temporal gyrus (STG) and the left middle temporal gyrus (MTG). The MTG is a brain region unique to humans, with no homology in non-human primates[89]. The anterior and sulcal portions of the MTG connect strongly with the STG[89]. The anterior portion connects though the STG and the uncinate fasciculus with the anterior frontal cortex. The sulcal portion connects with frontal areas through the inferior fronto-occipital fasciculus and extends directly into the putamen via the external capsule[76]. Hence, it makes sense that increasing connectivity would be associated with decreasing hyperactivity.

Overall, this detailed exploratory analysis of the potential influence of Brain Balance / Interactive Metronome on resting-state functional connectivity suggests that this type of training may exert widespread effects on patterns of brain connectivity. Future research will need to establish whether these effects are replicable, whether they are enduring and if age at the time of training influences which connections are more likely to be altered.

Conclusion. It is noteworthy that training with Brain Balance / Interactive Metronome, in this open study, appeared to have clinical, behavioral and neurobiological effects on par with pharmacological treatment. This is very encouraging as we believe that the ultimate goal in psychiatry is to develop non-pharmacological treatments for psychiatric disorders that exert enduring beneficial effects.

FULL REPORT

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders of childhood, and it often persists into adulthood[4]. ADHD is characterized by a triad of symptoms: inattention, hyperactivity and impulsivity[4]. Although common, it is a serious disorder associated with a 10-fold increased incidence of antisocial personality disorder[33,86], up to 5-fold increased risk of drug abuse[24,33], 25-fold excess risk for institutionalization for delinquency[59], and up to 9-fold increased risk of incarceration[39]. ADHD is often highly responsive to medications, but the gains are transient and wear off after each dose[80]. To compound matters, compliance is usually poor[51]. There is a pressing need to identify treatments that provide enduring benefits. Children with ADHD often have severe deficits in timing and the ability to utilize temporal information[55,67,68,82,90]. Hence, we sought to evaluate whether temporal training on the Interactive Metronome, coupled with 'Brain Balance' exercises that foster right hemisphere development and right-left hemispheric integration[44,45], would have beneficial effects on children with ADHD. The focus on cerebellar function, right-hemisphere development and right-left hemispheric integration fits with what we and others have observed neurobiologically [1,5,7,10,12,36,48,54,84,88,92].

Specific Aims

I. To test in an open study whether Brain Balance Exercises[44,45] and Interactive Metronome Training[6,16,62] are associated with measurable improvements in attention, impulse control and activity on parent and clinician ratings, the Quotient ADHD System and in performance on computerized neuropsychological tests.

II. To identify, using resting-state functional connectivity, brain changes associated with beneficial effects of Brain Balance exercises and Interactive Metronome Training.

Methodology

Participants were children of either sex between 8-14 years of age recruited from the community and confirmed to have ADHD through structured diagnostic interview (K-SADS-PL[31]). Treatment consisted of 15-weeks of Brain Balance[44,45] and Interactive Metronome[6,16,62] training (up to 75 sessions). Brain Balance and Interactive Metronome Training consisted of a series of online web-based training exercises. The exercises were standardized and the same for every participant. Participants had neither the benefit of personalized tailoring of the exercises to fit their specific needs nor the benefit of supervised training by an experienced administrator.

Clinical response was assessed based on parent ratings on the revised Conner's parent rating, clinician ratings on the Attention Deficit Hyperactivity Disorder for DSM-IV rating scale (ADHD-RS) and using the Quotient ADHD System. This Quotient Test was developed by Dr. Teicher, has been cleared by the FDA, and has been licensed through McLean Hospital to BioBehavioral Diagnostic Company/Pearson for commercialization. Briefly, children sit in front of a computer and take a monotonous but demanding cognitive control task called the Star CPT[78] while an infrared motion analysis system tracks head movements throughout the test period[50,77].

This test is highly responsive to the effects of medication[79,81], correlates with blood levels of methylphenidate[80] but is not responsive to placebo[75]. Indeed, we reported in N=30 children receiving placebo that only 7% showed a greater than 25% improvement and none had a 40% or greater improvement in Quotient scaled scores. In contrast, 47% and 27% had this degree of improvement on clinical ratings, which are highly subjective. Similarly, spatial working memory, which is the executive function most noticeably impaired in ADHD[29] was objectively assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB™).

Participants

As seen in the CONSORT flow chart (Fig. 1), n = 57 participants were enrolled across the two phases of the study. Nine of these participants were disqualified as they did not meet diagnostic criteria for ADHD and were not typical developing controls. All of the subjects enrolled during phase I and most during phase II were selected to be included in the ADHD group and to receive the combined Brain Balance/Interactive Metronome (BB/IM) treatment. A select group of typically developing controls were recruited and included in phase II to ascertain the extent to which BB/IM treatment normalized clinical ratings and brain measures in the ADHD participants. Controls were also scanned twice with the same time lag between scans as the ADHD participants, but controls did not receive any treatment or intervention between scans. Also, as part of phase II, n = 6 ADHD participants received a second baseline MRI and series of neuropsychology tests to provide evidence that MRI changes were related to BB/IM treatment and not simply to the passage of time between the baseline and post-treatment scans.

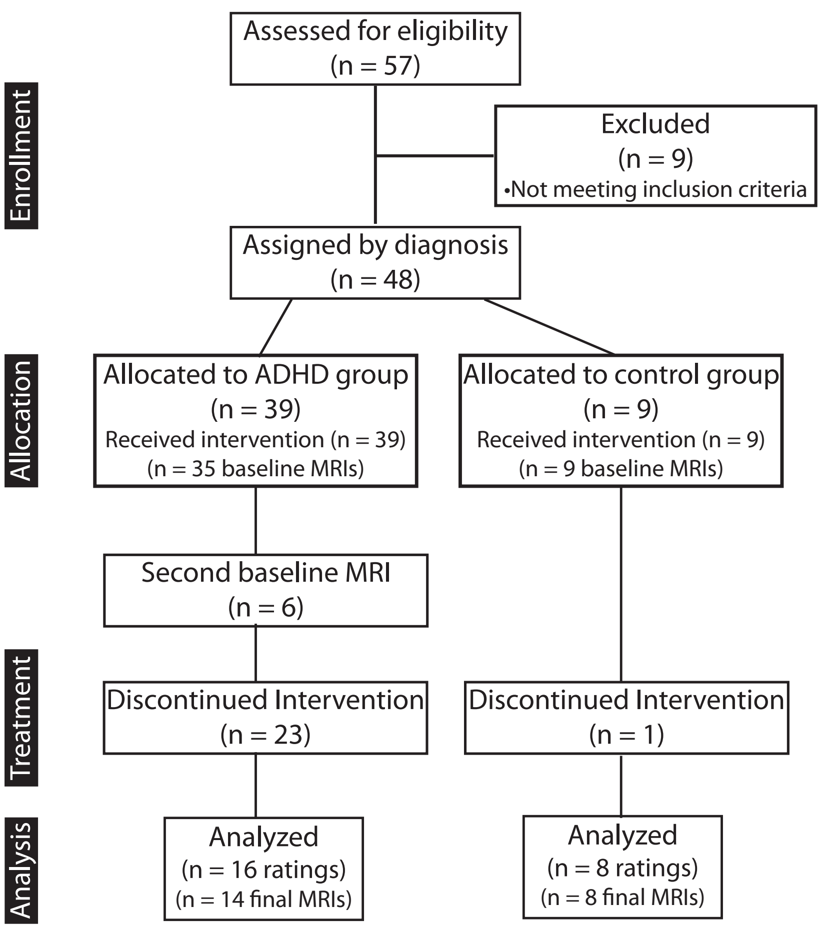


Figure 1. CONSTART flow diagram for phase I and phase II of the clinical trial.

Overall, n = 23 of the ADHD participants who enrolled discontinued treatment. N = 12 of these formally withdrew and n = 11 were lost to follow up. Only one participant discontinued in the control group.

Hence, complete pre-treatment / post BB/IM treatment data are available from n = 16 ADHD participants and from n = 8 typical developing controls. ADHD participants consisted of 14 males and 2 females with mean age of 10.8 ± 1.7 years. Controls consisted of 4 males and 4 females with mean age of 11.0 ± 1.8 years. These groups did not differ significantly in age (Welch's t = 0.27, df =. 13.4, p > .3) or gender distribution (Fisher exact test p = .13).

In addition, we also included data from n = 19 participants, who closely matched the ADHD participants in their pre-treatment Quotient ADHD System pre-treatment indices. These individuals received treatment with morning light therapy to address issues of daytime sleepiness, but this intervention was not intended to ameliorate symptoms of ADHD. These participants were included in some of the analyses to highlight the potential effects of BB/IM via comparison to a contrast group receiving a treatment believed to be less efficacious. Mean age of these 7-male and 12-female participants was 16.9 ± 1.3 years of age.

Results: Parent Ratings

As illustrated in Figure 2, and presented in Table 1, treatment with BB/IM was highly effective in reducing parent ratings of ADHD symptoms on Conner's Parent Rating Scale revised (CPRS-R). BB/IM was associated with a marked reduction in scores on the ADHD Index ($t_{15} = 5.2$, $p < .0002$). They declined, on average by about 7.4 points and this was indicative of a large therapeutic effect size (Cohen's d paired = 1.29). BB/IM did not however fully normalize scores. Prior to treatment ADHD youths had ADHD Index scores that were, on average, 21 points greater than typically developing controls. Following BB/IM treatment their scores were about 12 points greater than controls. Degree of reported improvement by parents did not vary based on pre-treatment severity (r = -.17, p > 0.5). ADHD youths with the highest ADHD Index scores showed, on average, the same degree of reduction in scores as ADHD youths with the lowest index scores. Discernible benefits were reported by parents for 13 out of 16 of the ADHD youths.

Similar effects were observed on the subscales of the CPRS. Oppositional behavior declined by nearly 3 points (p < .004). And this was also a large therapeutic effect size. Prior to treatment the ADHD youths were significantly more oppositional than typically developing controls. Following BB/IM the difference in ratings of oppositional behavior fell slightly short of statistical significance (p < 0.1). Degree of reduction in oppositional behavior appeared consistent across ADHD youths and did not vary as a function of pretreatment severity (r = -.293, p > .4). The cognitive inattention subscale of the CPRS dropped by over 4 points after BB/IM (p<0.00006), which was also indicative of a large therapeutic effect size (Cohen's d = 1.4). Differences between ADHD youths and typical developing controls fell, on average, from 11.4 to 6.7 points, though the ADHD youths were still significantly less attentive (p<0.0002). Degree of reduction in inattention appeared to be relatively consistent across ADHD youths and though there was a trend for the degree of reduction to diminish with increasing initial severity (r = -.65, p = .08).

Finally, parents also reported a highly significant reduction in ratings of hyperactivity, which declined by 3.4 points (p<0.002) and was also associated with a large therapeutic effect size (Cohen's d = 0.94). Differences between ADHD youths and typical developing controls fell from 8 points to 4 points but were still significantly greater after treatment (p<0.02). Degree of reduction did not vary based on initial parent reported severity (r = -.24, P > 0.5). Ratings of hyperactivity by parents fell by to a meaningful degree in 12 of 16 ADHD youths.

Table 1. Effects of treatment on Conner's Parent Rating Scale – Revised Scores.

	ADHD Pre Rx	ADHD Post Rx	Pre Post Differences			ADHD vs Control Differences Pre Rx			ADHD vs Control Differences Post Rx		
Measures	mean ± sd	mean ± sd	mean diff	p	Cohen's d	mean diff pre	p	Cohen's d	mean diff post	p	Cohen's d
Conner's ADHD Index	25.54 ± 5.85	18.10 ± 8.90	-7.44	p<0.0002	1.29	-21.24	$p<10^{-8}$	4.22	-12.42	p<0.0003	1.72
CPRS Oppositional	7.01 ± 4.19	4.21 ± 3.55	-2.8	p<0.004	0.86	-4.57	p<0.003	1.33	-2.32	p<0.1	0.73
CPRS Inattention	13.05 ± 3.34	8.80 ± 4.53	-4.25	p<0.00006	1.4	-11.38	$p<10^{-9}$	4.27	-6.69	p<0.0002	1.8
CPRS Hyperactivity	9.40 ± 3.77	6.05 ± 5.01	-3.35	p<0.002	0.94	-8	$p<10^{-5}$	2.45	-4.12	p<0.02	1.02

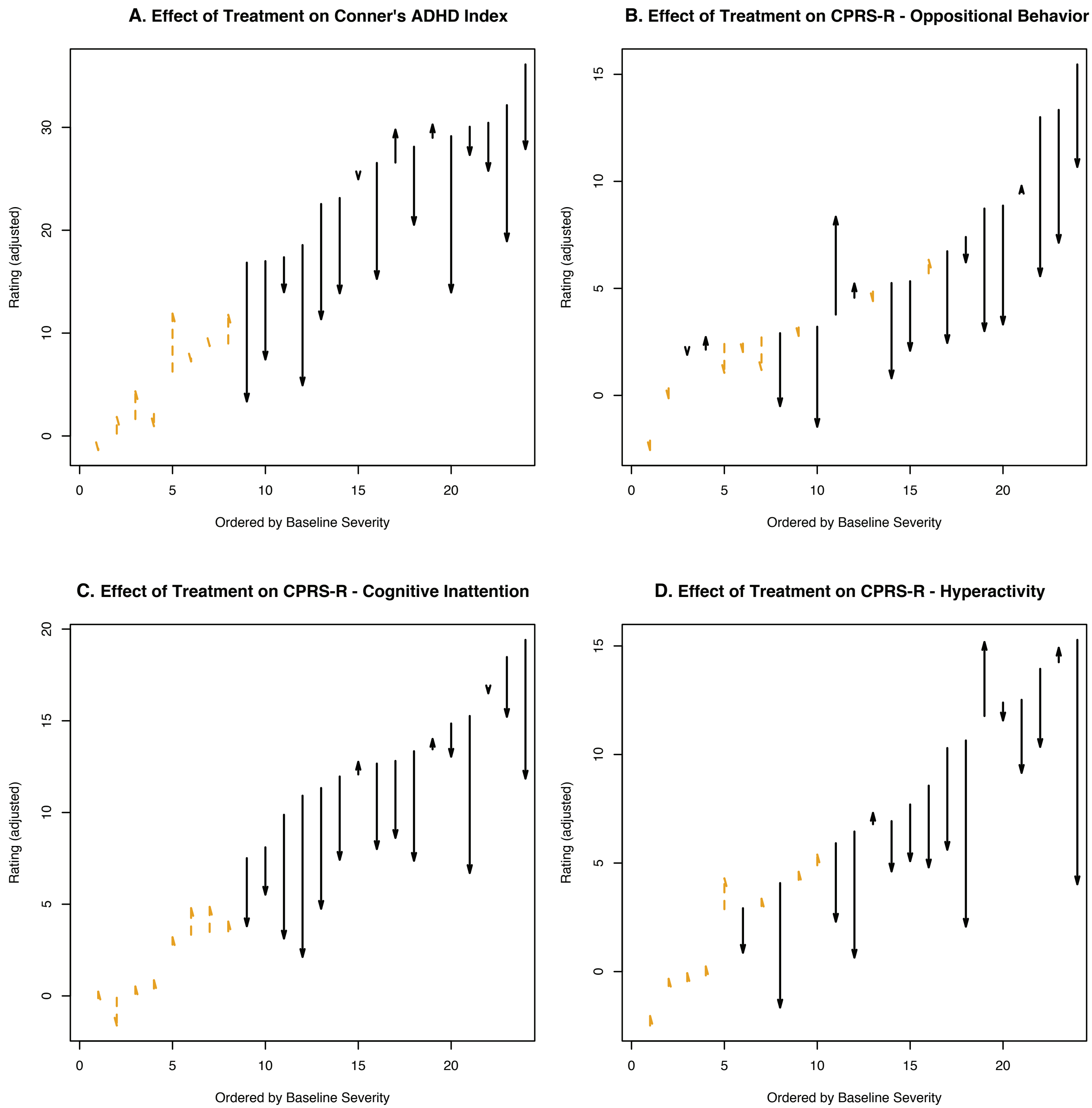
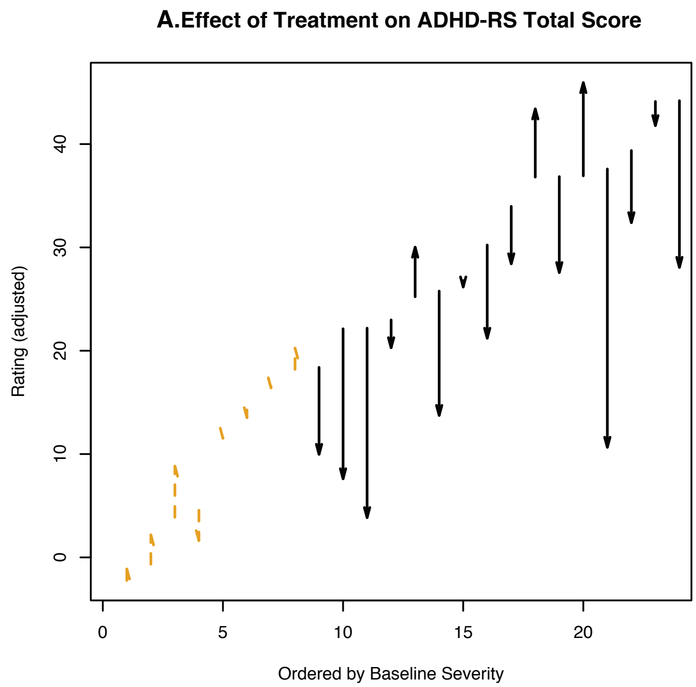
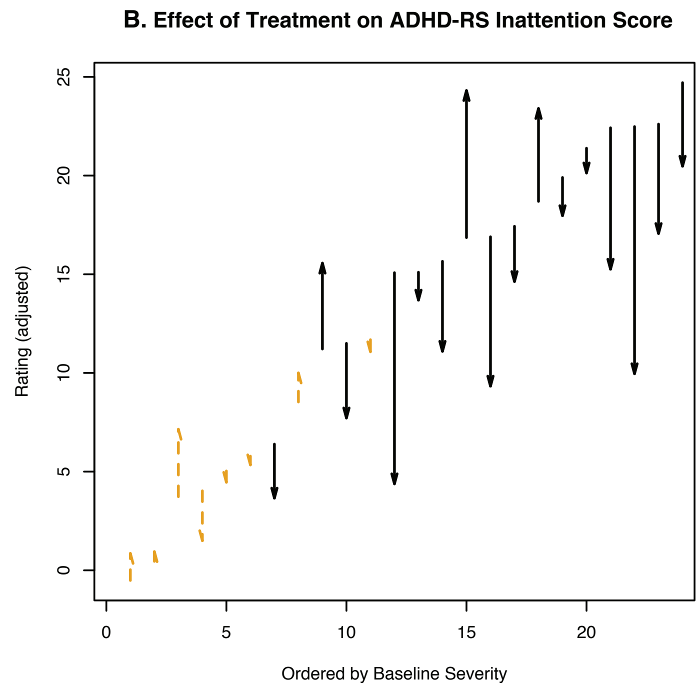


Figure 2. Conner's Parent Rating Scale Revised (CPRS-R) Arrow Plots. Figure illustrates change in individual participant scores. The end of the arrow indicates their first rating and the head of the arrow their second rating after a waiting period or treatment with Brain Balance / Interactive Metronome. Gold arrows indicate results from typical developing controls who did not receive treatment. Black arrows indicate results of youth with ADHD who received active treatment. **A.** Ratings on the ADHD Index of the CPRS-R. **B.** Ratings on the oppositional behavior subscale of the CPRS-R. **C**. Ratings on the cognitive / inattention subscale of the CPRS. **D.** Ratings on the hyperactivity subscale of the CPRS-R. Participants were ordered based on their pretreatment severity on each of the scales. Scores were adjusted to eliminate variance attributable to differences in age and sex.





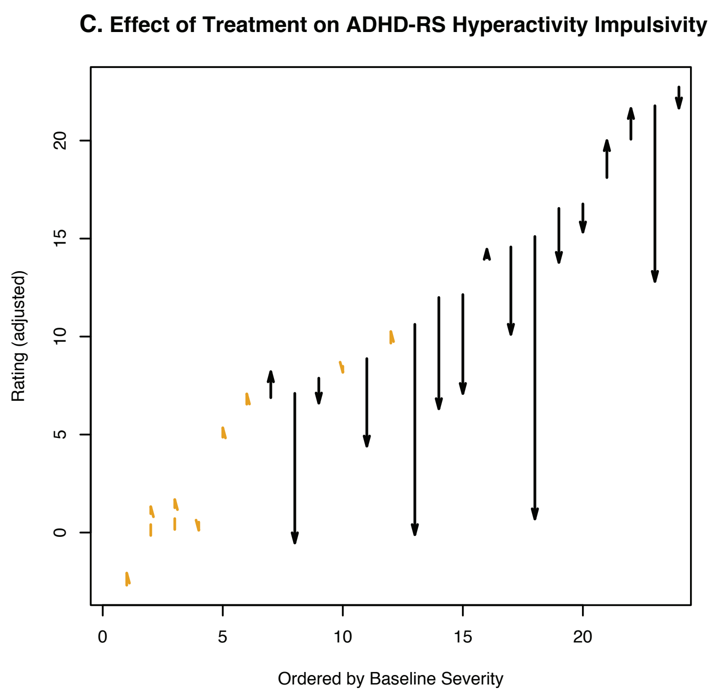


Figure 3. Attention Deficit Hyperactivity Disorder Rating Scale Revised (ADHD-RS) Arrow Plots. Figure illustrates change in individual participant scores. The end of the arrow indicates their first rating and the head of the arrow their second rating after a waiting period or treatment with Brain Balance / Interactive Metronome. Gold arrows indicate results from typical developing controls who did not receive treatment. Black arrows indicate results of youth with ADHD who received active treatment. **A.** Ratings on the ADHD-RS total scores. **B.** Ratings on the inattention subscale of the ADHD-RS. **C.** Ratings on the hyperactivity subscale of the ADHD-RS. Participants were ordered based on their pretreatment severity on each of the scales. Scores were adjusted to eliminate variance attributable to differences in age and sex.

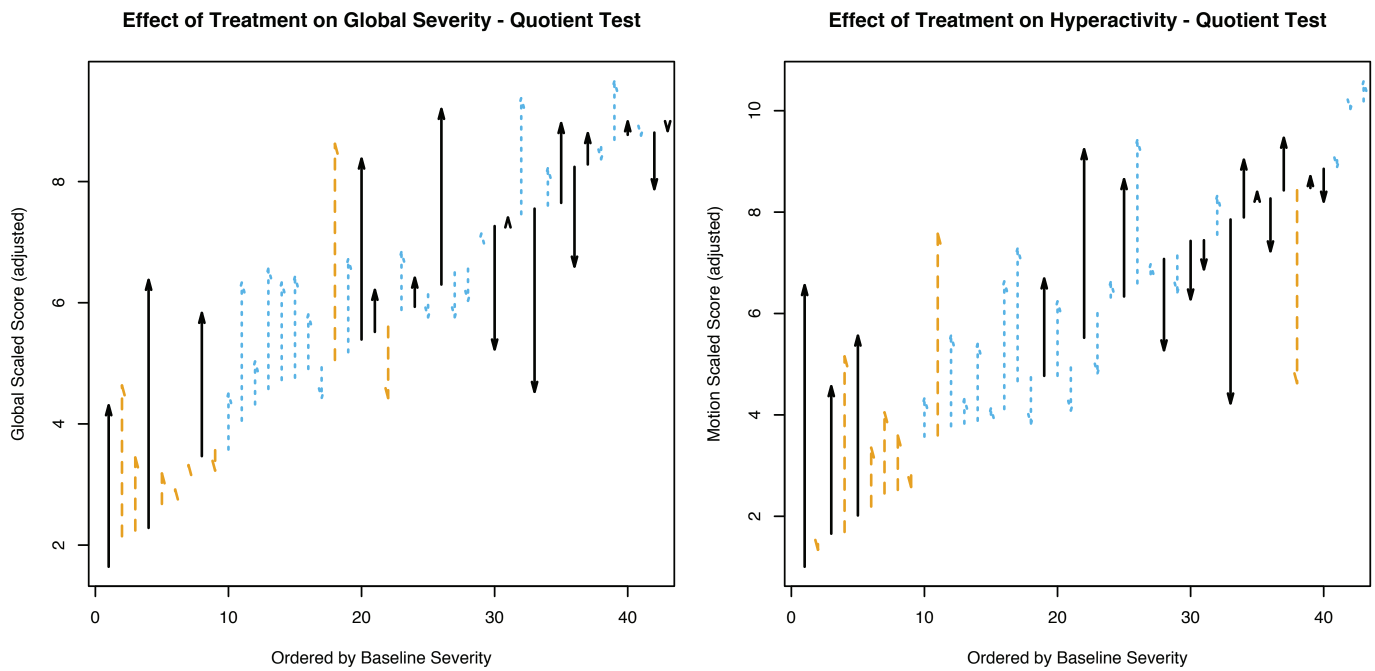
Results: Clinician Ratings

Clinical raters completed the Attention Deficit Hyperactivity Disorders for DSM-IV Rating Scale (ADHD-RS) which is based on parent and child reports as well as their own observation of the child. As illustrated in Figure 3, and summarized in Table 2, there were significant effects of Brain Balance/Interactive Metronome treatment on these ratings. Briefly, BB/IM treatment was associated with a 7 point reduction in Total ADHDRS Scores ($p < .02$), indicative of a medium therapeutic effect size (Cohen's $d = 0.74$). The effect of BB/IM on the Hyperactivity Impulsivity subscale was associated with a large therapeutic effect size (Cohen's $d = 0.83$, $p < .005$), while BB/IM was associated with a medium effect size (Cohen's $d = 0.58$, $p < .04$) on the Inattention subscale. The reduction in ADHDRS Total Scores following BB/IM, was reasonably consistent across ADHD participants, and degree of reduction did not vary as a function of baseline severity ($r = .248$, $p > .5$). On average, 10 of the 16 participants with ADHD were rated as showing a meaningful reduction in ADHDRS scores. While BB/IM reduced the difference in ADHDRS scores between ADHD participants and typically developing controls, significant group differences persisted.

Table 2. Effects of treatment on Attention Deficit Hyperactivity Disorder Rating Scale Scores.

	ADHD Pre Rx	ADHD Post Rx	Pre Post Differences			ADHD vs Control Differences Pre Rx			ADHD vs Control Differences Post Rx		
Measure	mean ± sd	mean ± sd	mean diff	p	Cohen's d	mean diff pre	p	Cohen's d	mean diff post	p	Cohen's d
ADHDRS Total Score	31.47 ± 8.28	24.44 ± 12.93	-7.03	p<0.02	0.74	-23.2	$p<10^{-5}$	2.87	-15.29	p<0.002	1.44
ADHDRS Inattention	17.40 ± 4.93	14.29 ± 6.26	-3.11	p<0.04	0.58	-12.56	$p<10^{-5}$	2.8	-9.12	p<0.0004	1.74
ADHDRS Hyperactivity	14.07 ± 5.08	10.16 ± 7.34	-3.92	p<0.005	0.83	-10.65	p<0.0001	2.21	-6.17	p<0.02	1.02

Results: Objective Measures



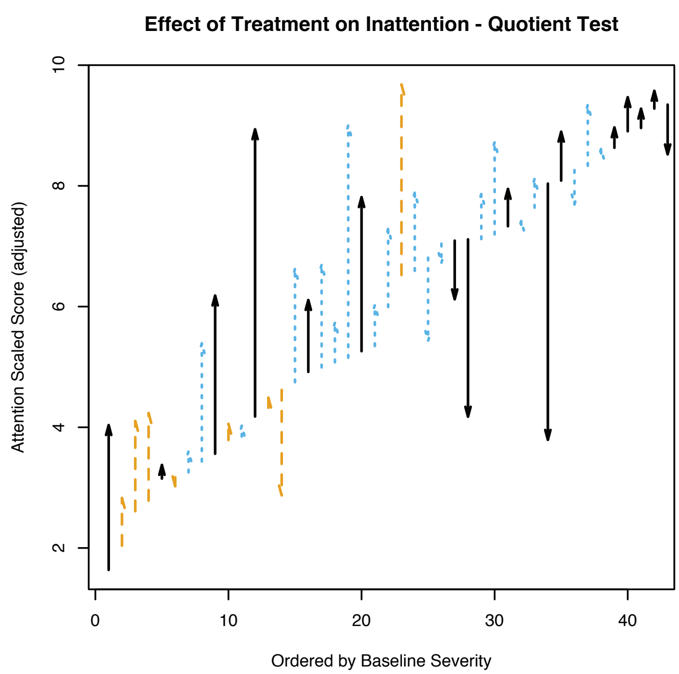


Figure 4. Quotient ADHD System Arrow Plots. Figure illustrates change in individual participant scores. The end of the arrow indicates their first rating and the head of the arrow their second rating after a waiting period or treatment. Gold arrows indicate results from typical developing controls who did not receive treatment. Blue arrows indicate results from youths with symptoms of ADHD who received treatment with light therapy for morning sleepiness. Black arrows indicate results of youth with ADHD who received active treatment with Brain Balance / Interactive Metronome. **A.** Ratings on the Quotient Global Score that includes all measures of hyperactivity, impulsivity and inattention. **B.** Ratings on the motion (hyperactivity) subscale, which summarizes a subset of activity measures and provides an index that is highly responsive to treatment. **C.** Ratings on the inattention subscale of the Quotient, which summarized a subset of attention metrics and provide a subscale score that is very responsive to treatment. Participants were ordered based on their pretreatment severity on each of the scales. Scores were adjusted to eliminate variance attributable to differences in age and sex.

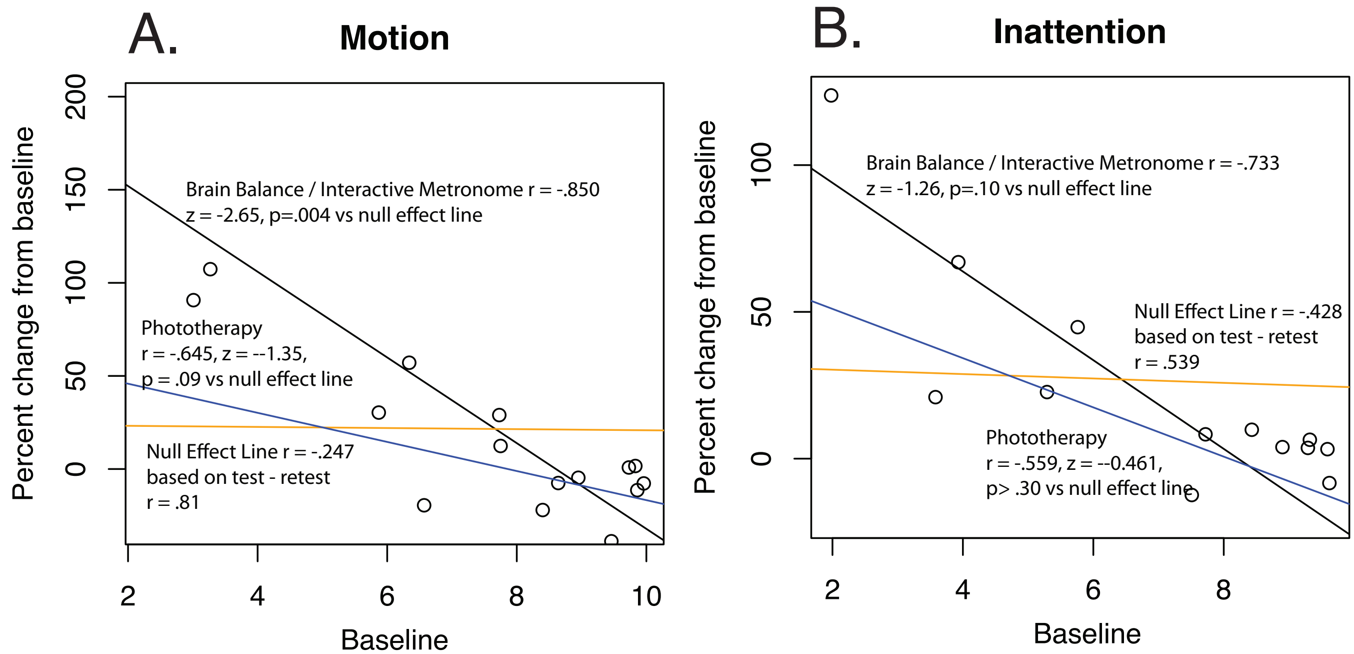
Potential effects of BB/IM on objective measures of hyperactivity, impulsivity, inattention and measures of spatial memory were less clear cut than parent and clinician ratings. This was not unexpected as these objective measures are not enhanced by the added benefits of placebo response. Previous research has shown that only about 40% of youths with ADHD have a highly beneficial response to a specific class of medications (i.e., amphetamine-based versus methylphenidate-based stimulants). Hence, we anticipated that an effective non-pharmacological treatment, administered in one set way (i.e., not tailored to the specific needs of each participants) would, at most, produce meaningful benefits in 40% of participants.

As illustrated in Figure 4 there was a great deal of variability in pre-treatment versus post-treatment Quotient scaled scores. Focusing on the group treated with BB/IM (black arrows) shows increasing objective findings of inattention, hyperactivity and their global composite, particularly in participants with low pretreatment measures. Conversely, some of the participants with high levels of impairment prior to treatment showed a marked improvement, as indicated by a reduction in scores following treatment.

This is indicative of a '*rate-dependent effect'* which we, and others, have previously observed in terms of response to stimulants[79]. As initially formulated, rate-dependency describes the observation that stimulants exert behavioral effects that are inversely correlated to the basal rate of the behavior[19]. Specifically, stimulants tend to decrease behaviors that normally occur at high rates and to increase behaviors that occur at low rates. For children with ADHD, this means that the more hyperactive, distractible, or impulsive the child is, the more effectively stimulants will act to enhance attention and reduce activity. Conversely, stimulants will activate a child who is sluggish or drowsy[26,57,79].

A rate-dependent effect shows up as a downward slope on a graph of percent change versus baseline rating. The statistical challenge is distinguishing a rate-dependent effect from a regression to the mean artifact, which can frequently be observed in test-retest data as a single measure of an individual's performance or ability is an estimate. Individuals who performed somewhat better than their actual ability will usually not perform as well on retest whereas those that performed somewhat below their actual ability will typically do better on retest, producing a regression to the mean. The degree to which this regression occurs, as we have previously shown[79], depends on the test-retest reliability of the measure. Highly reliable tests show little regression to the mean. Tests with low reliability will demonstrate a large regression to the mean artifact. The magnitude of the regression to the mean artifact varies from $r = -.707$ to $r = 0$, following the formula $-\sqrt{(1-\rho)/2}$, where ρ is the test-retest reliability of the instrument. A treatment is considered to be 'rate-dependent' if the correlation between percent change is significantly more negative than the null effect line derived from the test-retest reliability of the instrument.

Figure 5 illustrates the results of analyses assessing whether use of BB/IM was associated with a statistically significant rate-dependent effect. For these analyses we compared the BB/IM participants, and the previously studied participants receiving treatment with phototherapy for morning sleepiness, to an original sample of youths used to establish the test-retest reliability of the instrument as part of the FDA clearance application. As seen in first image, which assessed the rate-dependent effects on a scaled severity measure of hyperactivity, use of BB/IM was associated with a more negative slope and correlation than use of phototherapy, and the correlation between percent change and baseline was significantly different in the BB/IM group than the null effect line derived from the test-retest validation sample ($p = 0.004$). This was also true for the Global severity score, which differed significantly from the test-retest null effect line in the BB/IM group ($p = 0.03$). Results for the inattention scaled score fell short of significance for the BB/IM group ($p = 0.1$). Use of phototherapy, which can have a stimulating effect, also showed a rate-dependent like effect, but in none of these comparisons was phototherapy use associated with a statistically significant difference from the null effect test-retest line. This analysis provides evidence that several weeks of treatment with BB/IM altered performance of youths with ADHD and this change was similar in nature and magnitude to the reported effects of methylphenidate (Ritalin™)[79].



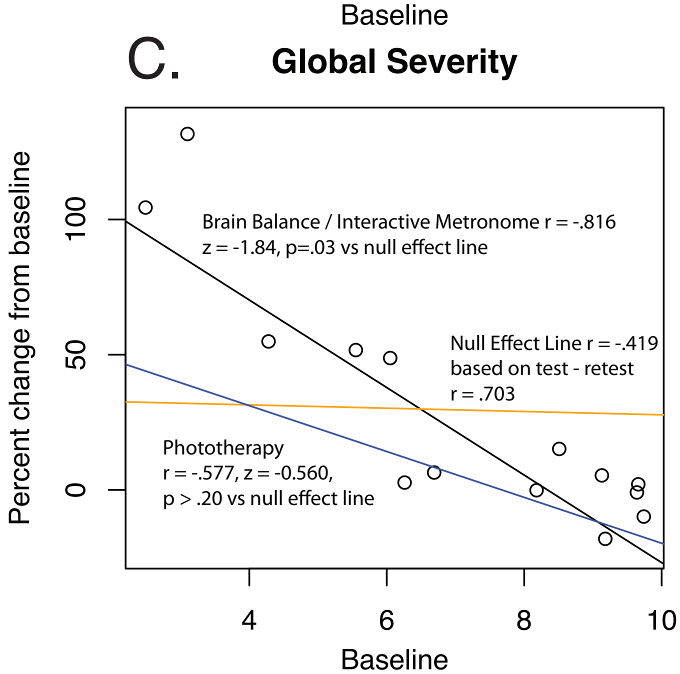
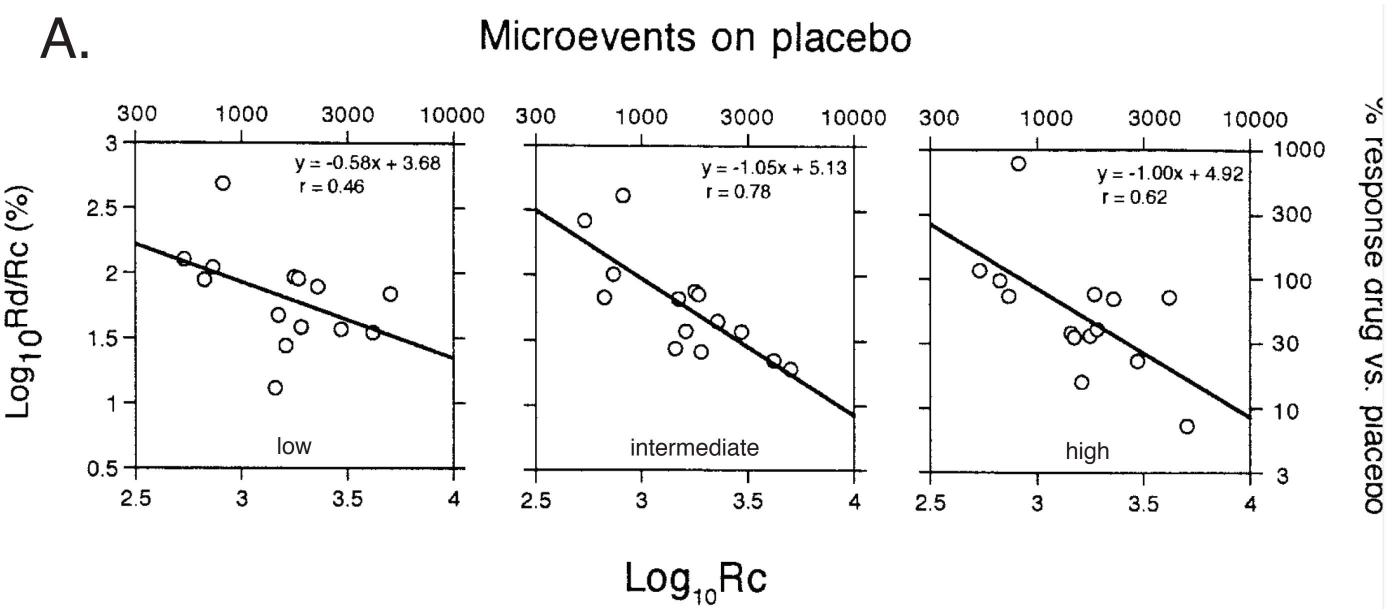


Figure 5. Rate-Dependent Analysis of Quotient Scaled Scores. A. Motion (hyperactivity) scaled score. B. Inattention scaled score. C. Global severity scaled score. Open circles represent response of individual subjects receiving treatment with Brain Balance / Interactive Metronome. Black line indicates linear regression relationship between percent change in score and baseline ratings. Orange lines indicate null effect line based on test-retest reliability of the measures. Blue line indicates result from comparator group receiving phototherapy to attenuate morning drowsiness. Note that the linear regression coefficient for the Brain Balance / Interactive Metronome Treatment for measures of Motion and Global Severity differed significantly from the regression coefficient of the null effect line indicating a significant rate-dependent relationship. The regression coefficient for the phototherapy group did not differ significantly from the null effect line.

To further explore the similarity of BB/IM to the action of methylphenidate we contrast in Figure 6 and Tables 3-4, the effects of BB/IM on four measures from the Quotient test (previously called the McLean Motion and Attention Test) on which we had previously published the rate-dependent effects of low (0.25 mg/kg, bid), intermediate (0.4 mg/kg, bid) and high (0.75 mg/kg, bid) doses of methylphenidate[79]. This publication preceded the development of the scaled scores and examined specific measures of performance rather than the composite scaled scores presented in Figure 5. Figure 6A shows our previously reported rate-dependent results in a sample of youths who blindly received treatment with placebo, low, intermediate and high doses of methylphenidate in random order. These analyses depicted the log-log relationship between baseline measures of movements (microevents) and the ratio of response to drug versus their baseline response to placebo. (A linear relationship was used in Figure 5 as the scaled scores transformed response across multiple measures into a linear composite). Figure 6B shows the effects of Brain Balance / Interactive Metronome showing the log-log relationship between movements prior to treatment versus the ratio of movements after BB/IM to movements prior to BB/IM. Two things are noticeable. First, the slope of the regression line observed for BB/IM (b = -.60) was nearly identical to the slope for the low dose of methylphenidate (b = -.58) but was not as steep as the slope for the intermediate and high doses. This suggests that BB/IM was exerting a rate-dependent effect that was equivalent to the rate-dependent effect of a low dose of methylphenidate. However, the correlation coefficient was much higher with BB/IM (r = -0.81) than with low dose of methylphenidate (r = -0.46). This indicates that the effect was more consistent between participants than the effects of low doses of methylphenidate which were more variable. Indeed, the correlation coefficient for BB/IM treatment was most similar to the correlation coefficient for the intermediate dose of methylphenidate. What these two measures (slope and correlation coefficient) indicate are the expected magnitude of the effect (how much their activity will change) and the likelihood that they will have this degree of change (how close their scores fall along the regression line). In short, it appears that BB/IM produced an effect on their ability to sit still that was equivalent, on average, to the effects of a low dose of methylphenidate, but that the participants responded in a more consistent and predictable manner to BB/IM than to methylphenidate. Because response to BB/IM was more consistent than response to low dose methylphenidate the rate-dependent relationship for BB/IM was highly significant (p = .002) while the rate-dependent relationship for the low dose of methylphenidate was not.



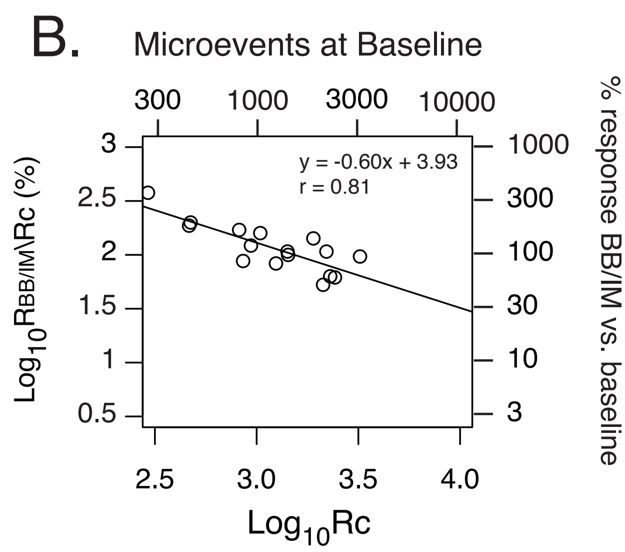


Figure 6. Rate-dependent Analysis of Movements During the Quotient Test. A. Previously published data showing the rate-dependent effects of low, intermediate and high daily doses of methylphenidate. B. Rate-dependent effects of Brain Balance / Interactive Metronome Treatment. Open circles represent response of individual subjects receiving treatment. Black line indicates log-log regression relationship between ratio of treated score to baseline score (i.e., placebo or pretreatment).

Tables 3 and 4 provide a comparable analysis of the rate-dependent effects of methylphenidate and Brain Balance / Interactive Metronome on different measures of performance on the continuous performance attention task

(CPT) that is part of the Quotient ADHD System. Table 3 reprints our previously published results for low, intermediate and high doses of methylphenidate. Note that one specific aspect of performance on the CPT was on accuracy, which changed in a rate-dependent manner on all three doses. Rate-dependency indicates that performance substantially improved with methylphenidate in participants with very low accuracy on placebo, but either did not improve or worsened in participants with higher levels of accuracy on placebo. There was a trend for commission errors to show a rate-dependent effect that fell short of significance, but no evidence of a rate-dependent effect on latency to respond.

Table 3. Reprint of Table from Teicher et al[79] showing rate-dependency analysis of low, intermediate, and high doses of methylphenidate on continuous performance attention task results.

Attention parameters	*Test-retest reliability*	*Null hypothesis regression coefficient*	*Dose (mg/kg)*	j *(slope)*	*Actual regression coefficient*	p
Commission errors (%)	0.859	−0.266	0.5	−0.75	−0.63	0.07
			0.8	−0.94	−0.59	0.1
			1.5	−0.85	−0.57	0.12
Correct responses (%)	0.941	−0.172	0.5	−0.86	−0.68	0.02
			0.8	−0.93	−0.98	0.0001
			1.5	−0.96	−0.99	0.0001
Latency	0.773	−0.337	0.5	−0.18	−0.29	0.6
			0.8	−0.25	−0.48	0.3
			1.5	−0.15	−0.19	0.73

Note. The table shows the null hypothesis regression coefficient, log-log slope, obtained regression coefficient, and *p* values indicating the probability that the effect shown was not due to random chance but rather a bona fide rate-dependent effect.

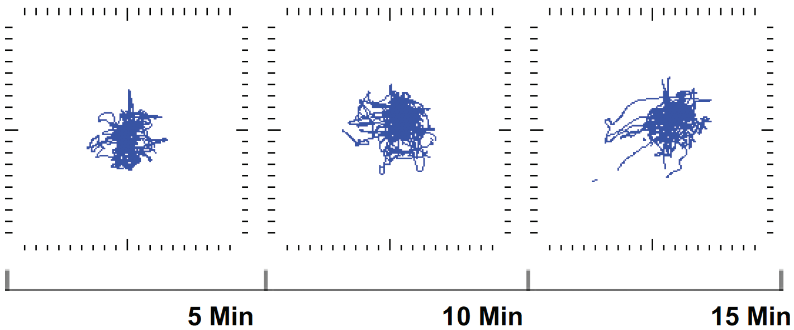
As seen in Table 4 BB/IM appeared to produce effects on CPT performance that were remarkably similar to low doses of methylphenidate. Note that the regression slope for BB/IM on commission errors was nearly identical to the regression slope for methylphenidate, but the regression coefficient was greater, producing a statistically significant log-log relationship. The effects of BB/IM on correct response (%) was similar to low doses of methylphenidate (with a slightly less but not significantly different slope) and a very similar regression coefficient. Brain Balance / Interactive Metronome did not exert a rate-dependent effect on response latency which shows that had the same pattern of effects on CPT performance as methylphenidate.

Table 4. Rate-dependency analysis comparing effects of Brain Balance / Interactive Metronome to previously reported effects of low doses of methylphenidate on continuous performance attention task results.

Attention parameters	*Test-retest reliability*	*Null hypothesis regression coefficient*	*Rx*	*j (slope)*	*Actual regression coefficient*	p
Commission errors (%)	0.859	-0.266	BB/IM	-0.76	-0.69	0.04
			MPH 0.5 mg/kg	-0.75	-0.63	0.07
Correct response (%)	0.941	-0.172	BB/IM	-0.75	-0.65	0.03
			MPH 0.5 mg/kg	-0.86	-0.68	0.02
Latency	0.773	-0.337	BB/IM	-0.35	-0.49	0.5
			MPH 0.5 mg/kg	-0.18	-0.29	0.6

Examples. A few examples are presented to illustrate the results of Brain Balance / Interactive Metronome training on objective indices of hyperactivity and inattention. Specifically, these are some examples of youths showing a greater than 40% improvement in scores, which is a degree of improvement that we have not observed in youths treated with placebo[75].

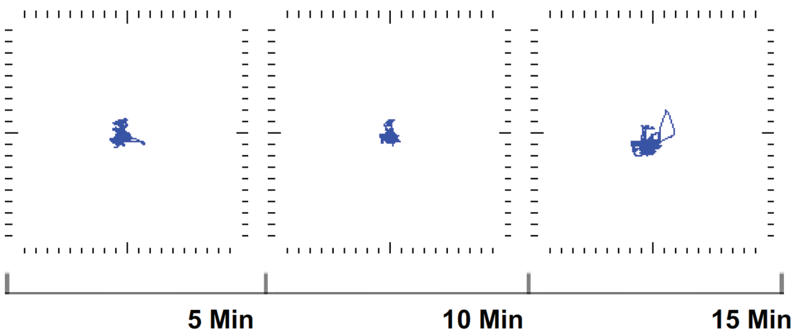
A **Motion Captured by Corresponding Reflector Location**



Motion Results

Measure	Age Percentile $t \leq 16$ Age Percentile
Immobility Duration:	6^t
Movements:	5^t
Displacement:	6^t
Area:	15^t
Spatial Complexity:	15^t
Temporal Scaling:	3^t

B **Motion Captured by Corresponding Reflector Location**



Motion Results

Measure	Age Percentile $t \leq 16$ Age Percentile
Immobility Duration:	42
Movements:	37
Displacement:	42
Area:	65
Spatial Complexity:	63
Temporal Scaling:	29

Figure 7. Measures of hyperactivity on Quotient test in BB010 (A) prior to and (B) following Brain Balance and Interactive Metronome treatment. Hyperactivity is based on infrared motion tracking of head marker during each 5 -minute test period. Note that prior to treatment the subject was in the top 3-15% of most hyperactive individuals within their age range. Following treatment their activity measures were in the 29th to 65% percentile indicating that they were no longer clinically hyperactive and well within normal range.

Measure	Age Percentile ($t \leq 16$ Age Percentile)	
Accuracy:	6^t	61
Omission Errors:	20	76
Commission Errors:	2^t	57
Latency:	33	84
Variability:	3^t	38
C.O.V.:	2^t	59

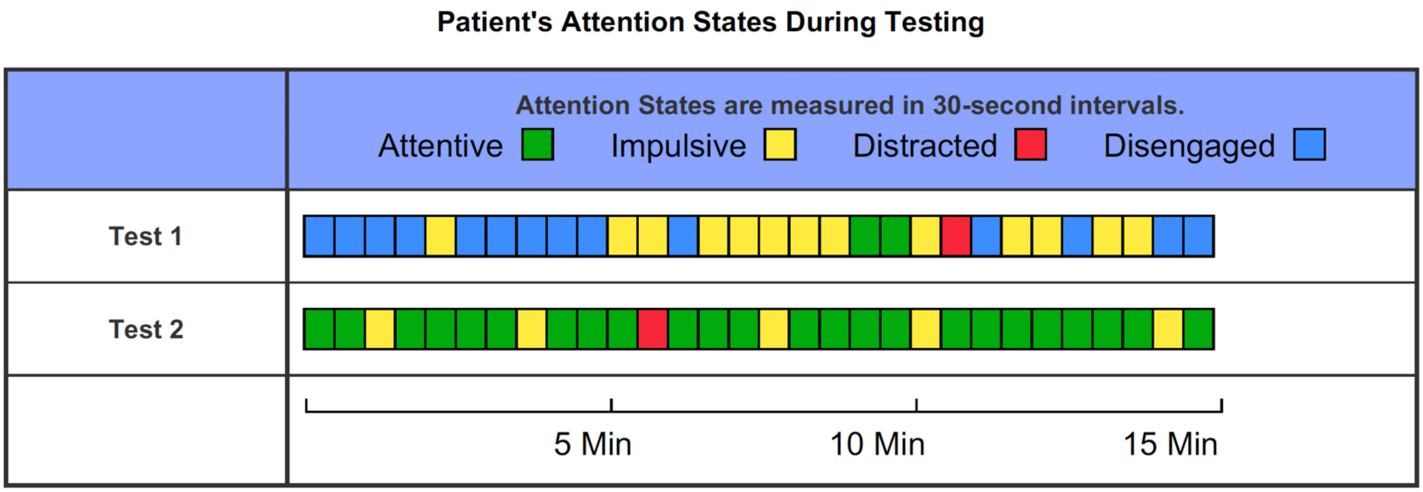


Figure 8. Measures of inattention on Quotient test in BB026 prior to and following treatment with Brain Balance and Interactive Metronome exercises. Note that prior to treatment that the participant was in the lowest 2 - 6 percentile for accuracy, errors of commission (impulsive errors) and performance variability (including C.O.V. – coefficient of variation), which are indicative of fluctuating attention, effort and timing. BB026 tested in the normal range on these measures (38 – 61st percentile) following Brain Balance and Interactive Metronome treatment. Similarly, assessment of attention state, made every 30 seconds, indicated that BB026 was highly disengaged during her pretreatment test and only spent 6.7% of her time fully attentive. In contrast, after BB/IM she was fully attentive during 80% of the test.

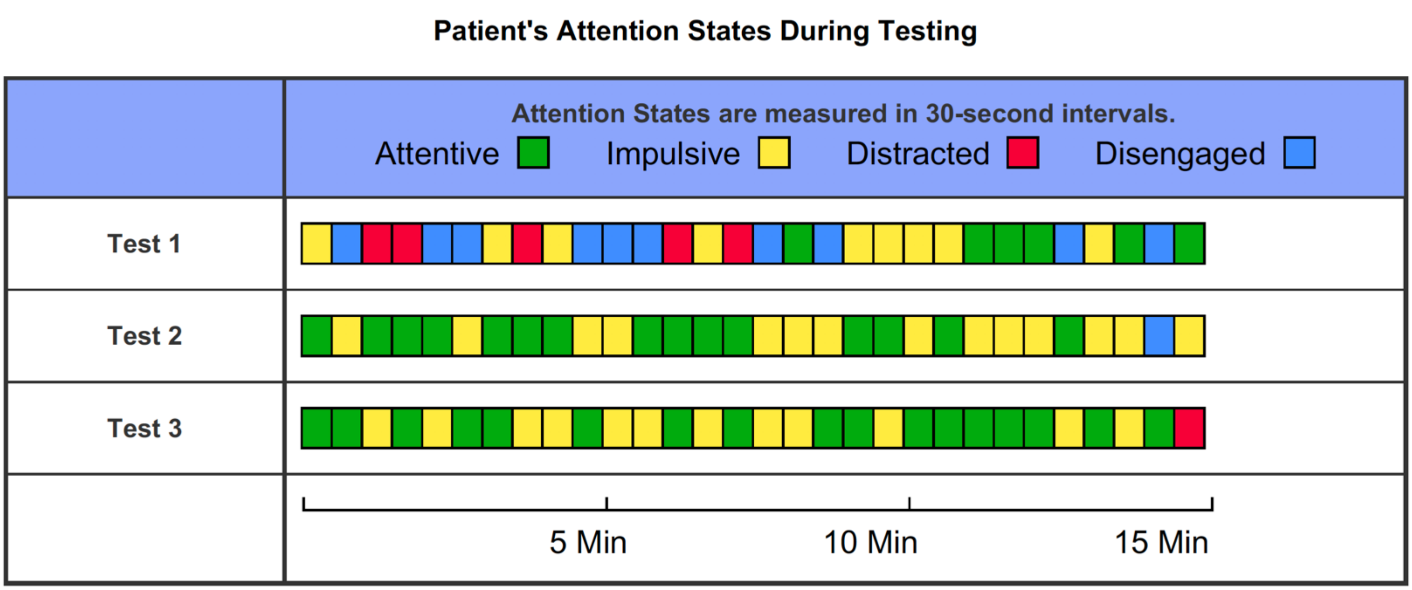


Figure 9. Attention performance on Quotient in participant BB001. A determination was made every 30 seconds as to whether the participant was fully attentive, was partially attentive but making some impulsive errors, was partially attentive but making a few distracted errors or was disengaged and not paying attention. Test 1 took place prior to Interactive Metronome and Brain Balance training. Test 2 shortly after Brain Balance and Interactive Metronome training and Test 3 took place 7 months after Test 2, indicating persistence of benefits on attention.

Results: Neuropsychological Testing

A key question that we sought to answer with neuropsychological testing during phase II was whether effects of Brain Balance / Interactive Metronome were due to the intervention or simply to the 15-week passage of time. Hence, N=6 participants with ADHD were assessed at baseline, reassessed on neuropsychological tests after 15 weeks without any intervention and then assessed a third time after BB/IM. The three neuropsychological tests used were: Corsi Block Tapping Task, Tower of London and the Mackworth Clock.

The *Corsi Block Tapping Task* assesses visuo-spatial short-term working memory[15]. Participants are presented with a screen of 9 boxes. The boxes light up in a pre-fixed sequence (constant across participants) and participants are asked to click on the boxes in the same order they were lit. The sequence length starts at level = 2 boxes and can increase to up to level 9. Participants get 2 chances at each sequence length. If one of the sequences was entered correctly, the next sequence starts. This largest correct sequence length is known as the Corsi Span, and average is about 5-6 for normal participants[21,32].

The *Tower of London Test* is designed to assess executive functioning specifically to detect deficits in planning[63]. Participants are asked to arrange, using a computer touch screen, three colorful discs on 3 provided pegs in a specific solution pattern in as few moves as possible[3]. The task is timed and provides measures of first move time, solution time and execution time. First move time is defined as the time (in milliseconds) between the presentation of the task and the first move. Solution time is defined as the time between the presentation of the task and the completion of the task. Execution time is equal to solution time minus first move time. The test is also scored according to the number of successfully completed trials based on a formula developed by Krikorian[34].

The *Mackworth Clock Test* is another type of continuous performance go/no-go test to measure an individual's ability to sustain attention in the face of monotonous stimulation[37]. Participants watch a red dot jump from one circle position to next position (m = 24 positions) in a clockwise fashion at constant speed. Occasionally, the red dot skips a position. Participants are asked to press the Spacebar whenever they notice such a skipped event (go event)[35]. Typically, this test would be run for an hour or longer to assess the decrease in vigilance that occurs over time. For this study we used a very brief version (1.5 minutes) to assess baseline differences in performance related to ADHD.

Overall, there was no significant effect of BB/IM on performance on the Corsi Block Tapping Task. Typical developing controls had, on average, 2.8 more correct responses than participants with ADHD ($F_{1,17} = 8.73$, $p < 0.009$). Controls still performed significantly better ($F_{1,14} = 7.61$, $p < 0.02$) following BB/IM. Similarly, Corsi span was significantly longer in controls than in participants with ADHD both before ($F_{1,17} = 4.46$, $p < 0.05$) and after BB/IM ($F_{1,14} = 7.26$, $p < 0.02$). In addition, there were no measures on the Corsi Block Tapping Task where BB/IM produced a rate-dependent effects in participants with ADHD.

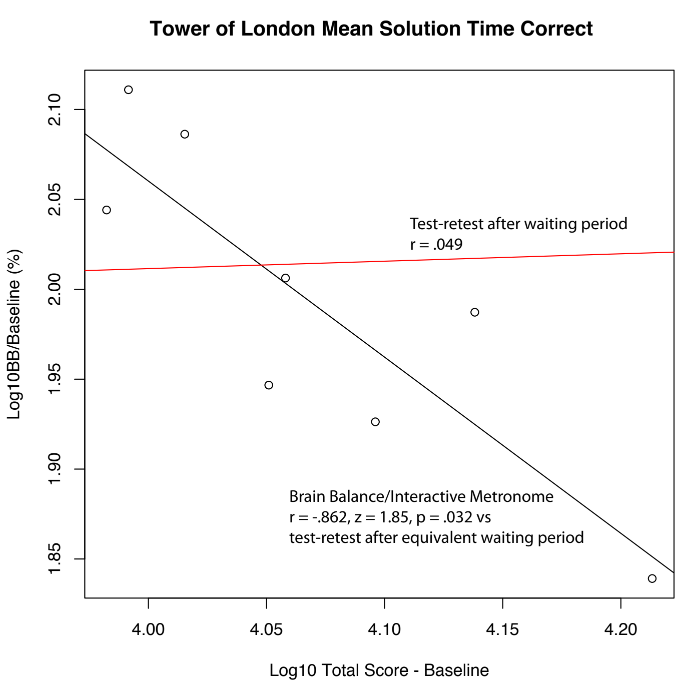


Figure 10. Rate-dependency analysis of effects of Brain Balance / Interactive Metronome (BB/IM) on mean correct solution time for Tower of London in participants who were assessed at baseline, then reassessed after a 15-week waiting period and then assessed a third time after BB/IM. Note that mean solution time was highly consistent before and after the waiting period (r = .846), which resulted in a flat rate-dependency line (in red). In contrast, following BB/IM there was a substantial rate-dependent change characterized by a steep negative slope.

In contrast, there were substantial effects of BB/IM on performance on the Tower of London. BB/IM was associated with alteration in performance in Total Score ($F_{1,8} = 10.81$, $p = 0.01$), Mean Solution Time ($F_{1,8} = 5.15$, $p = 0.053$) and Mean Execution Time ($F_{1,8} = 12.35$, $p < 0.008$). Most importantly, there was evidence on the Tower of London task that BB/IM exerted a rate-dependent effect on performance that was not seen in the participants who were evaluated before and after an equivalent waiting period without BB/IM training. This is illustrated in Figure 10 which shows the rate-dependent effects of BB/IM on mean execution time for correct solutions (log scale). As expected with a rate-dependent effect, solution times increased in participants with ADHD who initially responded most quickly and decreased in participants with ADHD who initially responded most slowly.

Brain Balance / Interactive Metronome was found to diminish the discrepancy in performance between participants with ADHD and typically developing controls on the Mackworth Clock Test. Controls differed significantly from ADHD participants in total hits prior to training ($F_{1,16} = 5.56$, $p = 0.03$) but not after BB/IM ($F_{1,15} = 1.62$, $p = 0.22$). Controls also had a much lower false alarm rate than ADHD participants prior to training ($F_{1,16} = 9.08$, $p = 0.008$), but ADHD participants and controls had a comparable false alarm rate after BB/IM ($F_{1,15} = 0.34$, $p = 0.57$). Differential response of participants with ADHD to BB/IM versus controls was also associated with a significant interactive effect on linear mixed effects model ($F_{1,15} = 4.64$, $p < 0.05$).

Brain Imaging – Functional Connectivity

To assess the neurobiological effects of Brain Balance / Interactive Metronome training we focused on resting-state functional connectivity (rs-FC). This is a functional magnetic resonance imaging (fMRI) procedure designed to assess the degree of interconnection between brain regions. This property is measured by assessing the pattern of blood flow fluctuations in a brain region, which is driven to a large degree by fluctuations in the neuronal activity within the region and comparing it to the pattern of fluctuations in other parts of the brain. Regions that are strongly interconnected have correlated patterns of blood flow fluctuations suggesting that they are coupled and working together with each other to a significant degree. Interestingly, some brain regions show an inverse or anticorrelated pattern so that when blood flow goes up in one region it goes down in the other. This is indicative of a reciprocal or inhibitory pattern in which activity in one region leads to a decrease in the neuronal activity in the other brain region. Theoretically, BB/IM may work by strengthening or weakening the degree of positive or negative coupling between brain regions We focused or rs-FC as this is a highly modifiable aspect of brain function and it is likely that effective treatments produce noticeable changes in behavior and clinical outcome by modifying this aspect of neurobiology.

We used three approaches to study the effects of Brain Balance / Interactive Metronome on resting state functional connectivity.

1. ***Compare rs_FC ADHD participants to typically developing controls.*** The key question is how do our participants differ from controls in their pattern of rs_FC and are these differences reversed by BB/IM? A secondary question is does BB/IM result in some differences between ADHD and typically developing controls in rs_FC that were not observed prior to BB/IM?

2. ***Compare rs_FC in ADHD participants prior to and following BB/IM.*** The key question here is whether BB/IM produces a significant unidirectional effect on rs_FC in specific pathways. This is a within subject design which identifies pathways (if any) in which BB/IM was associated with either a significant increase or decrease in rs_FC between two brain regions.

3. ***Assess the relationship between rs_FC and rate-dependent changes in activity and inattention.*** This approach is similar to #2 as we are specifically looking within the ADHD group for changes induced by BB/IM. However, it differs as we are not looking for a unidirectional change. Participants with very low activity showed increased levels of activity after BB/IM while individuals with high basal rates of activity experienced a substantial decrease. Hence, this approach will enable us to identify interconnections between regions in which increasing activity, for example, may be associated with increased rs_FC between two regions while decreasing activity may be associated with decreased connectivity between the same regions.

1A. Resting State Functional Connectivity Differences between ADHD participants and Typical Developing Controls Prior to Treatment.

As seen in Figure 11 there was a handful of significant differences in functional connectivity between typical developing controls and youths with ADHD. The following findings emerged. First, functional connectivity between the left lateral prefrontal cortical and right posterior parietal nodes within the frontoparietal network was reduced in participants with ADHD. The frontoparietal network contributes to executive control and adaptive behavior by flexibly encoding task demands and desired outcomes and by providing top-down regulation of processes in other brain regions[13,70]. More recently, research suggests that there are two components to the frontoparietal control network. One part, with which the lateral PFC and the posterior parietal cortex are constituents, appears to be associated with the default mode network and preferentially involved in the regulation of introspective processes. Specifically, this component, and the rostrolateral PFC in particular, may contribute to the higher-level management of thought, exerting a general constraint that keeps one's focus on task-relevant material, but also allows for some spontaneous variability in thought[11]. Deficiency in this component of the frontoparietal network may lead to problems with mind wondering and a diminished ability to stay on task[11].

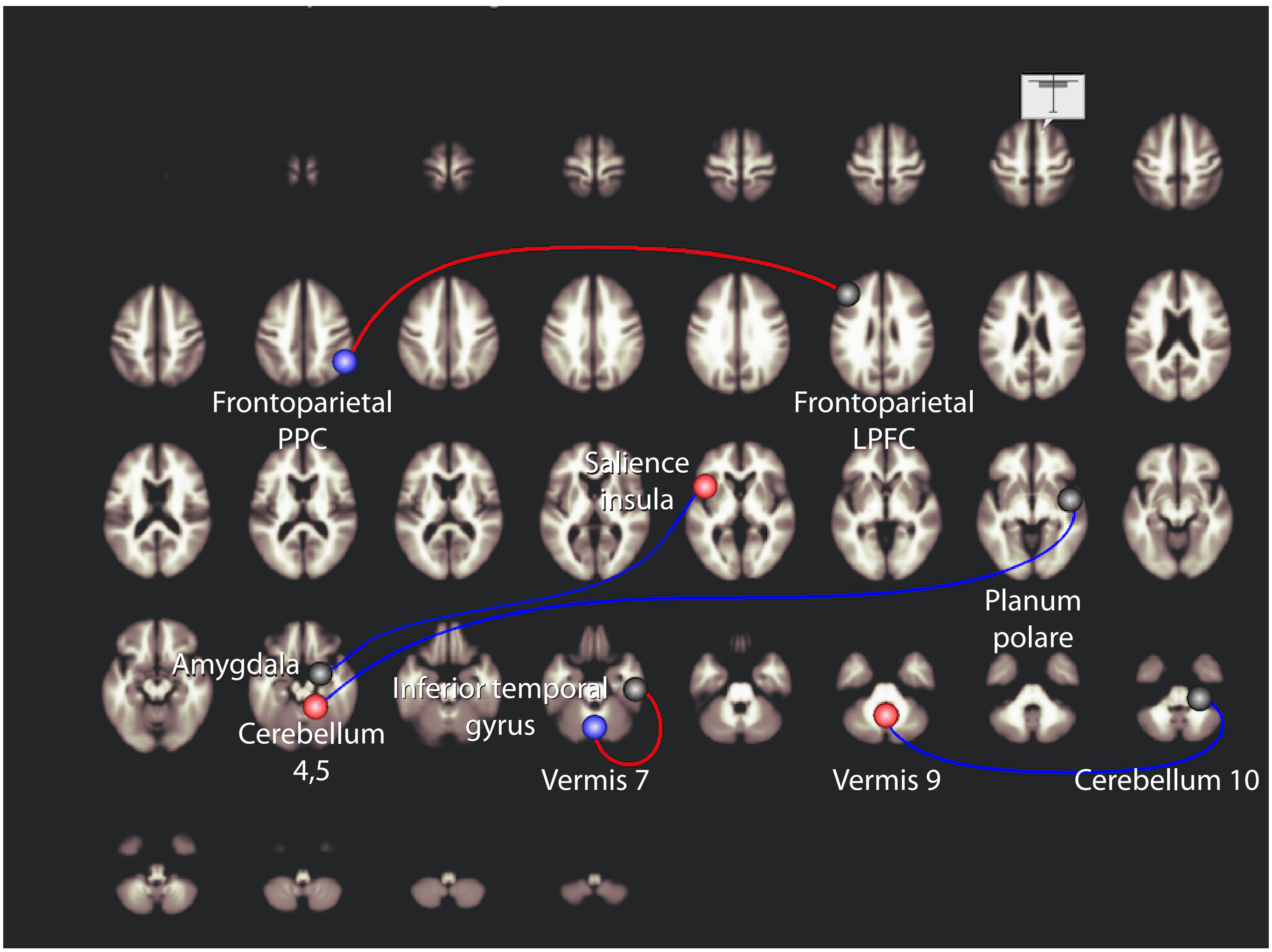


Figure 11. Functional connectivity differences between youths with ADHD vs typical developing control (ADHD > Control) prior to treatment. Red lines indicate positive connections between regions. Blue lines indicate reciprocal connections. The circles at the end of the lines are also color coded. Gray circles indicate the seed region for the connection. Red circles indicate that the connection is stronger in ADHD than controls. Blue circles indicate that the connection is stronger in controls than in ADHD.

Another key difference between the ADHD participants and controls was increased connectivity of the right amygdala with the left anterior insula hub of the salience network in youths with ADHD. The "salience network" is a collection of brain regions with key cortical hubs in the anterior cingulate and anterior insular cortex[61]. The network also includes the amygdala, hypothalamus, ventral striatum, thalamus, and specific brainstem nuclei. The network selects which stimuli are deserving of attention and is critical for detecting behaviorally relevant stimuli and coordinating our response to them[61]. Alterations in the configuration and connectivity within the salience network has been reported to be associated with greater susceptibility to distraction[71].

The third functional connection that differed between healthy controls and participants with ADHD consisted of right planum polare and the left 4th and 5th lobes of the cerebellum. Blood flow in these regions displayed a greater inverse correlation in participants with ADHD. The planum polare is located in the superior temporal lobe and is part of the cortical network involved in language and music processing. Salmi et al found that in participants with ADHD, that inattention was associated with intersubject correlations in the bilateral planum polare[58]. Cerebellar abnormalities have frequently been reported in individuals with ADHD. Cerebellar dysfunction is associated with problems in the ability to predict when events are going to occur and other problems with timing. Cerebellum 4-5 is known as the anterior quadrangular lobule and consists of the hemispheric portion of the culmen (lobules IV and V). This portion of the cerebellum is critically involved in sensorimotor processes and motor control. A key problem identified in children with ADHD are deficits in timing. These are characterized by increased motor timing variability linked to poor inhibitory control and difficulties with beat perception and duration estimation[66]. Interactive metronome training is designed specifically to enhance beat perception, duration estimation and timing.

The fourth finding was reduced functional connection between the 7th lobule of the cerebellar vermis and the right inferior temporal gyrus. The vermis is the central portion of the cerebellum, located between the right and left hemispheres, and abnormalities in the vermis has been frequently reported in ADHD[83]. Macllulich et al[38] reported that size of the third vermian area (which consists of lobules VI and VII) correlated with neurocognitive abilities on the Digit-Symbol Substitution Test (DSST), Logical memory test (LM), Visual Reproduction Text (VR) and Raven's Progressive Matrices (RPM). Good performance on the DSST requires intact motor speed, attention, and visuoperceptual functions, including scanning and the ability to write or draw[30]. LM measures verbal episodic memory, VR measures visual memory and ability to draw and RPM provides a non-verbal measures of fluid intelligence. Other studies indicate that lobule VII plays a role in regulation of cognition and emotion as well as in balance control. The inferior temporal gyrus is part of the ventral visual stream and plays a critical role in our ability to identify what we see. Reduced connectivity between these regions may significantly impact aspects of visual memory and comprehension.

The final finding was an enhancement in the inverse correlation in blood flow between cerebellar vermis IX and cerebellar lobe 10. Vermis lobe IX is part of the posterior cerebellar vermis and is involved in emotional regulation[74]. Reduced volume in the posterior inferior vermis (lobules VII -X) is one of the most consistent findings in ADHD[25]. ADHD symptom severity has been shown to correlate with the degree of reduction in the posterior inferior vermis[73]. Cerebellar lobule X has long been thought to be the substrate of the vestibulocerebellum, which receives vestibular and visual information and is involved with balance, vestibular reflexes, and eye movements. Hyperactivity, as observed in children with ADHD, is most clearly characterized by difficulty sitting still, and problems related to postural control and balance contribute substantially to their hyperactivity[50].

1B. Resting State Functional Connectivity Differences between ADHD participants and Typical Developing Controls Following Treatment with Brain Balance / Interactive Metronome.

First, and most importantly, none of the aforementioned significant differences between participants with ADHD and typical developing controls were detected in the comparison between youths with ADHD receiving BB/IM *and typical developing controls retested after a 15-week waiting period. Hence, it appears that BB/IM reduced these differences to the point that they were no longer statistically significant.*

However, significant differences in connectivity emerged between regions in treated participants with ADHD and typical developing controls that were not present prior to treatment. The most striking changes were in the connectivity of the left hippocampus. As seen in Figure 12 there was a reduction in the connection of the left hippocampus with 12 other regions including the frontal orbital cortex, frontal pole, inferior frontal gyrus as well as multiple portions of the temporal lobe. This is consistent with Dr. Melillo's theory and his prediction that "Brain Balance by removing bottom up interference, by integrating reflexes and then specifically stimulating the underdeveloped right hemisphere with multiple modalities (motor and sensory in particular) would help stimulate growth and maturation in the right side helping to restore synchrony developmentally and between networks. This would promote integration and it may dampen activity that may have been overactive in the left hemisphere creating a balance between these areas."

Why this postulated reduction in left hemisphere connectivity manifest most clearly in the hippocampus is another question. The hippocampus is involved in memory function with the left more specialized for verbal episodic and right more specialized for visual-spatial memory processes[20]. Neuropsychological testing in children with ADHD typically reveals greater abnormalities in spatial than verbal memory storage and manipulation[40]. Our thought is that prior to BB/IM training that ADHD participants were relying more on verbal working memory, but training improved visual-spatial working memory leading to more balanced use of the two memory systems reflected in reduced connectivity of the left hippocampus.

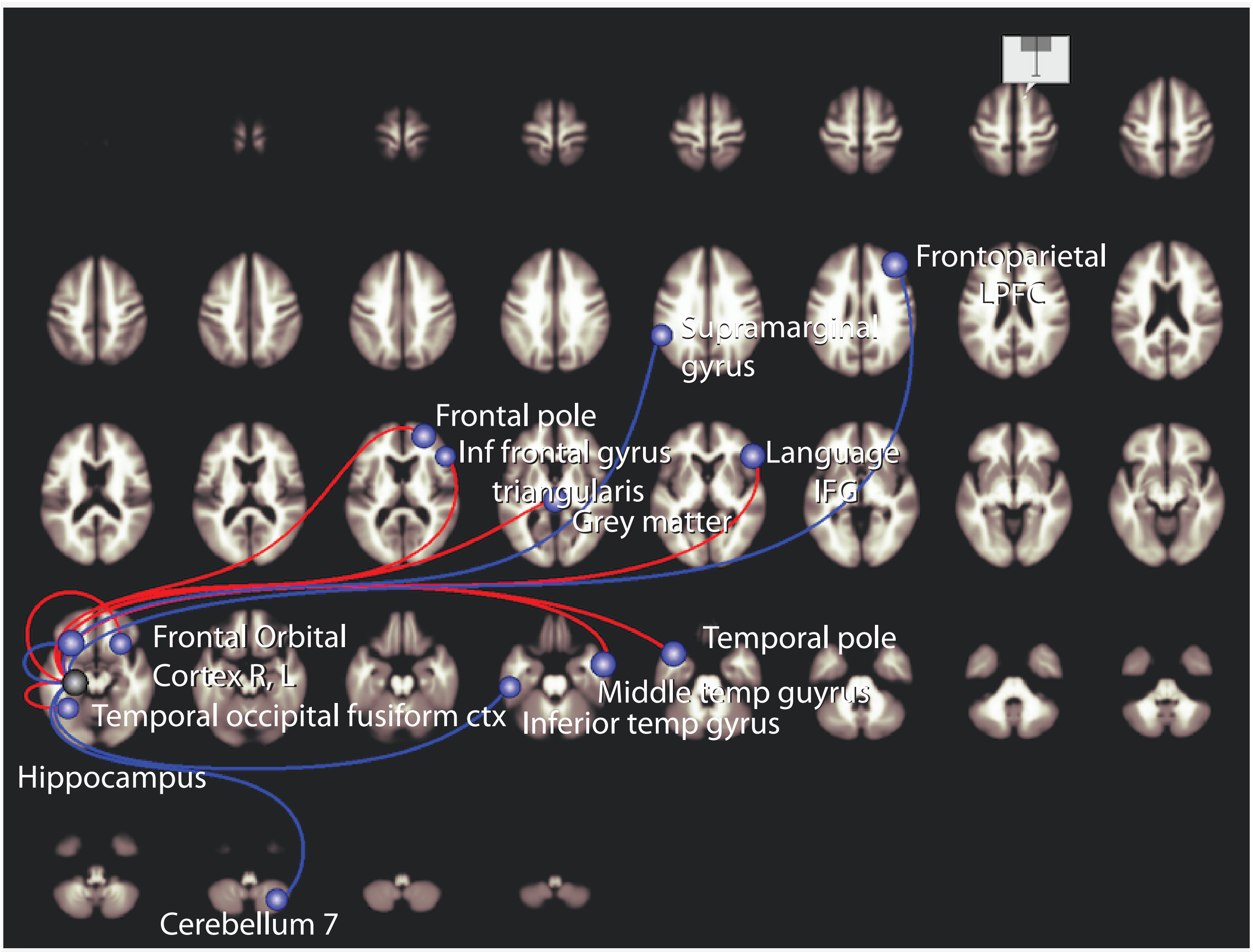


Figure 12. Functional connectivity differences between youths with ADHD vs typical developing control (ADHD

> Control) after treatment with Brain Balance / Interactive metronome. Red lines indicate positive connections between regions. Blue lines indicate reciprocal connections. The circles at the end of the lines are also color coded. Gray circles indicate the seed region for the connection. Blue circles indicate that the connection is stronger in controls than in ADHD.

A number of other alterations were observed in connectivity in the participants with ADHD (Fig. 13). Interestingly, two of these involved regions contralateral to those reported to have abnormal connections prior to treatment (i.e., salience network – anterior insula L pre / R post; planum polare R pre / L post). We suspect that this may reflects some degree of right/left balancing of these regions as the Brain Balance treatment is intended to promote. Many of these changes involve connection with the salience network, and as noted above alterations in the configuration and connectivity within the salience network has been reported to be associated with greater susceptibility to distraction[71]. These changes may help to shift performance but may do so in a rate-dependent manner enhancing attention in those in which it was most imbalanced but imbalancing it to some degree in others that were better balanced to begin with. One connection that was enhanced was between the lateral occipital cortex and vermis X, which is a portion of the posterior inferior vermis and is involved in emotional regulation. A possible consequence of increased connectivity between these regions may be enhanced processing of emotional body language[22].

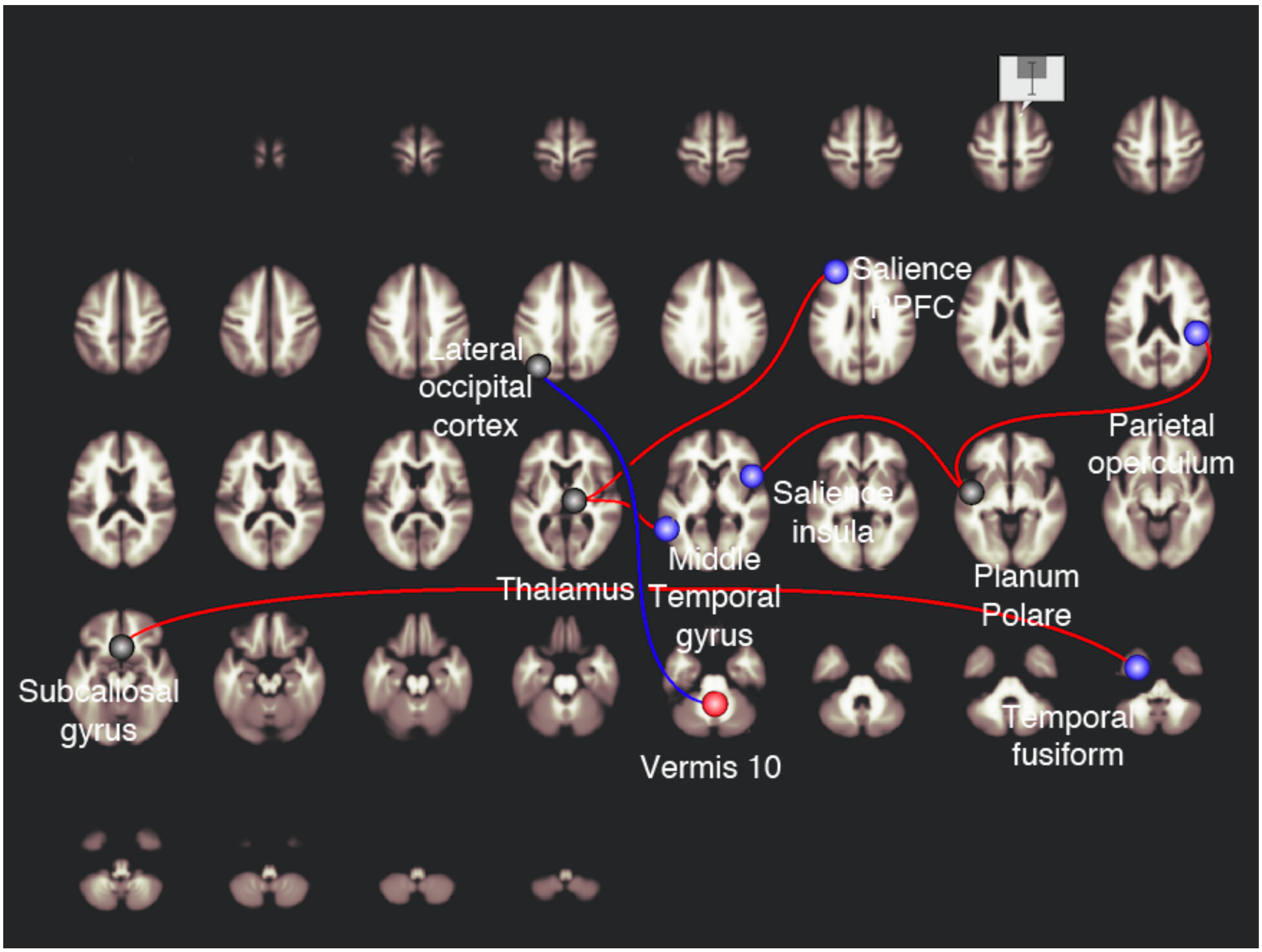


Figure 13. Functional connectivity differences between youths with ADHD vs typical developing control (ADHD > Control) after treatment with Brain Balance / Interactive metronome. Red lines indicate positive connections between regions. Blue lines indicate reciprocal connections. The circles at the end of the lines are also color coded. Gray circles indicate the seed region for the connection. Red circles indicate that the connection is strong in ADHD than controls. Blue circles indicate that the connection is stronger in controls than in ADHD.

2. Alterations in resting state functional connectivity in ADHD participants following Brain Balance / Interactive Metronome treatment.

In this analysis we identified alteration in functional connectivity between regions that produced a statistically significant difference in mean connectivity. As seen in Figure 14, there were four connections associated with a significant increase and three with a significant decrease. The most notable was an increase in the reciprocal connectivity between the default mode network and the salience network. The default mode network is active at rest when individuals are not focused on the outside world and the brain is at wakeful rest, such as during daydreaming and mind-wandering as well as in some tasks involving autobiographical memory and mentalization[69]. The default mode network appears to be reciprocally interconnected with other brain networks involved in performing tasks and attending to stimuli in the outside world[2]. Individuals with ADHD typically show patterns of altered connectivity between the default mode, attention and salience networks[64]. Enhancing the reciprocal connection between the salience and default network may help to reduce daydreaming and mind wandering. Brain Balance / Interactive Metronome training was associated with increased connectivity of the default mode to the parahippocampal gyrus. The parahippocampal gyrus, which is involved in memory coding and retrival, links the default-mode network with the medial temporal lobe memory system[85]. The parahippocampal gyrus is interconnected to the superior frontal gyrus through the cingulum bundle[9], and connectivity between these regions was reduced following BB/IM. The superior frontal gyrus is implicated in several tasks including motor movement, working memory, resting-state, and cognitive control[9]. This may be associated with an enhanced ability to perform tasks automatically without thinking through each step.

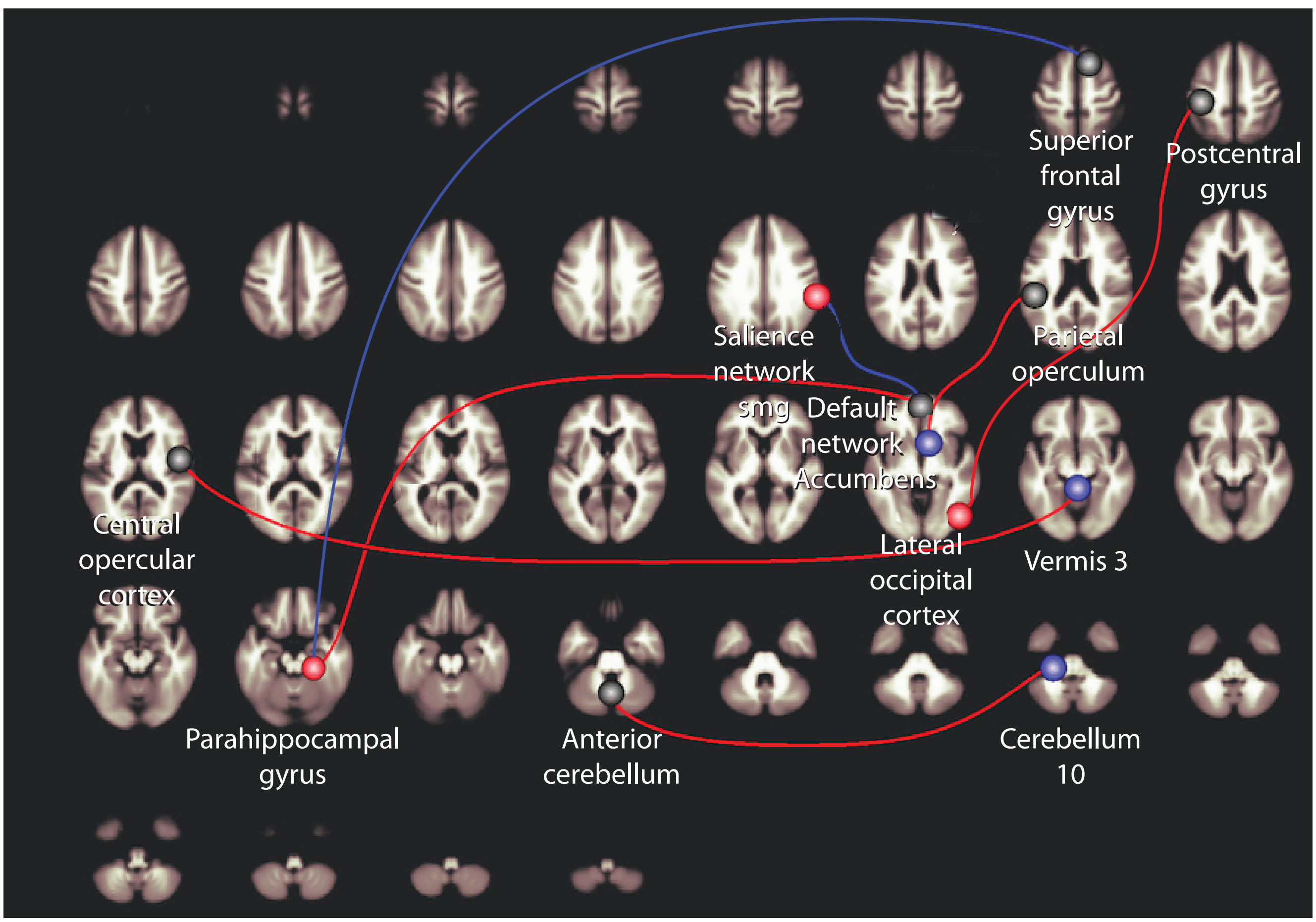


Figure 14. Functional connectivity differences between youths with ADHD prior to and following treatment with Brain Balance / Interactive metronome. Red lines indicate positive connections between regions. Blue lines indicate reciprocal connections. The circles at the end of the lines are also color coded. Gray circles indicate the

seed region for the connection. Red circles indicate that the connection was strong after treatment. Blue circles indicate that the connection was weaker after treatment.

The connection between the left postcentral gyrus and right lateral occipital cortex was enhanced by BB/IM. These regions appear to work together in processing shape and texture of objects[72]. There was a significant decrease in connectivity between the right central opercular cortex (aka subcentral gyrus) and the third lobule of the cerebellar vermis. The subcentral area (BA43) has been a region without a clearly known function. It is formed by the union of the pre- and post-central gyri at the inferior end of the central sulcus. This corresponds to the portion of the pre- and post-central gyri responsible for motor control and tactile sensations from the face. A series of recent papers have reported enhanced activity in this area when individuals and engaged in eye-to-eye communication[29], face-to-face interaction between opponents (poker game)[52] and in human-to-human verbal communication[28]. Interestingly, the vermis III also appears to be involved in at least one aspect of human-to-human communication as connectivity of vermis III to superior frontal gyurs was positively correlated with severity of stuttering while connectivity to the left cingulate gyrus and right pre-central and post-central gyri was negatively correlated [91]. This suggests that BB/IM may be exerting some effect on the interaction between regions involved in human communication.

Finally, BB/IM was associated with the anterior cerebellum and cerebellum X. The anterior lobes of the cerebellum (I-V) are primarily sensory motor. Lobule X is the vestibulocerebellum, which receives vestibular and visual information and is involved with balance, vestibular reflexes, and eye movements. It would make sense that BB/IM would affect this coupling as many of the exercises involve vestibular and visual processing, motor control and timing. Reduced connectivity may be a reflection of improved postural balance requiring less sensory motor compensation.

3A. Relationship between Resting State Functional Connectivity and Rate-Dependent Changes in Attention.

In these analyses we sought to identify functional pathways in which the magnitude and direction of functional connectivity change following BB/IM correlated with the rate-dependent effects of BB/IM on accuracy (correct response % - Table 4).

As seen in Figure 15 there were 5 functional pathways in which change in connectivity following BB/IM correlated with rate-dependent effects on accuracy. In 4 of these functional pathways there was a reciprocal relationship. What this means is that as accuracy went up connectivity went down. Conversely, connectivity went up in individuals who showed decreased accuracy. Two of these pathways involved connections to the precuneus, which is a key component of the default mode. One connection was with the left inferior frontal gyrus, which is a part of Broca's area and plays a critical role in the expression of language. It also appears to be primarily responsible for one's inner voice[47]. The default mode, including the precuneus, is active when individuals are not focused on the outside world and the brain is at wakeful rest, such as during daydreaming and mind-wandering[69]. Hence, the more this internal voice connects to the default mode network the more likely individuals are to be distracted by internal voices and mind-wandering and have reduced accuracy. Similarly, the precuneus has its strongest structural and second strongest resting state functional connectivity with the thalamus[17], specifically to thalamic association nuclei with primary corticolimbic connections rather than to relay nuclei that receive primary sensory information. Cunningham et al[17] has proposed that the thalamus is part of a DMN subsystem that plays an important role in switching between internal and external awareness. Diminished connectivity may shift the balance toward external awareness and improved attentional performance.

The pathway in which increased connectivity correlated with enhanced accuracy was between the supplemental motor area (SMA) and the medial prefrontal cortex. It has been observed in humans that the SMA plays a critical role in action monitoring[8]. This is the process of evaluating ongoing activities to adjust them in order to improve subsequent actions, and this capacity is often deficient in individuals with ADHD. The SMA rapidly evaluates successful and erroneous actions. The rostral part of medial prefrontal cortex, driven by the SMA, is then activated later and exclusively in the case of errors[8]. Being better able to monitor performance and adjust accordingly should substantially improve accuracy on the continuous performance cognitive control task that is part of the Quotient Test.

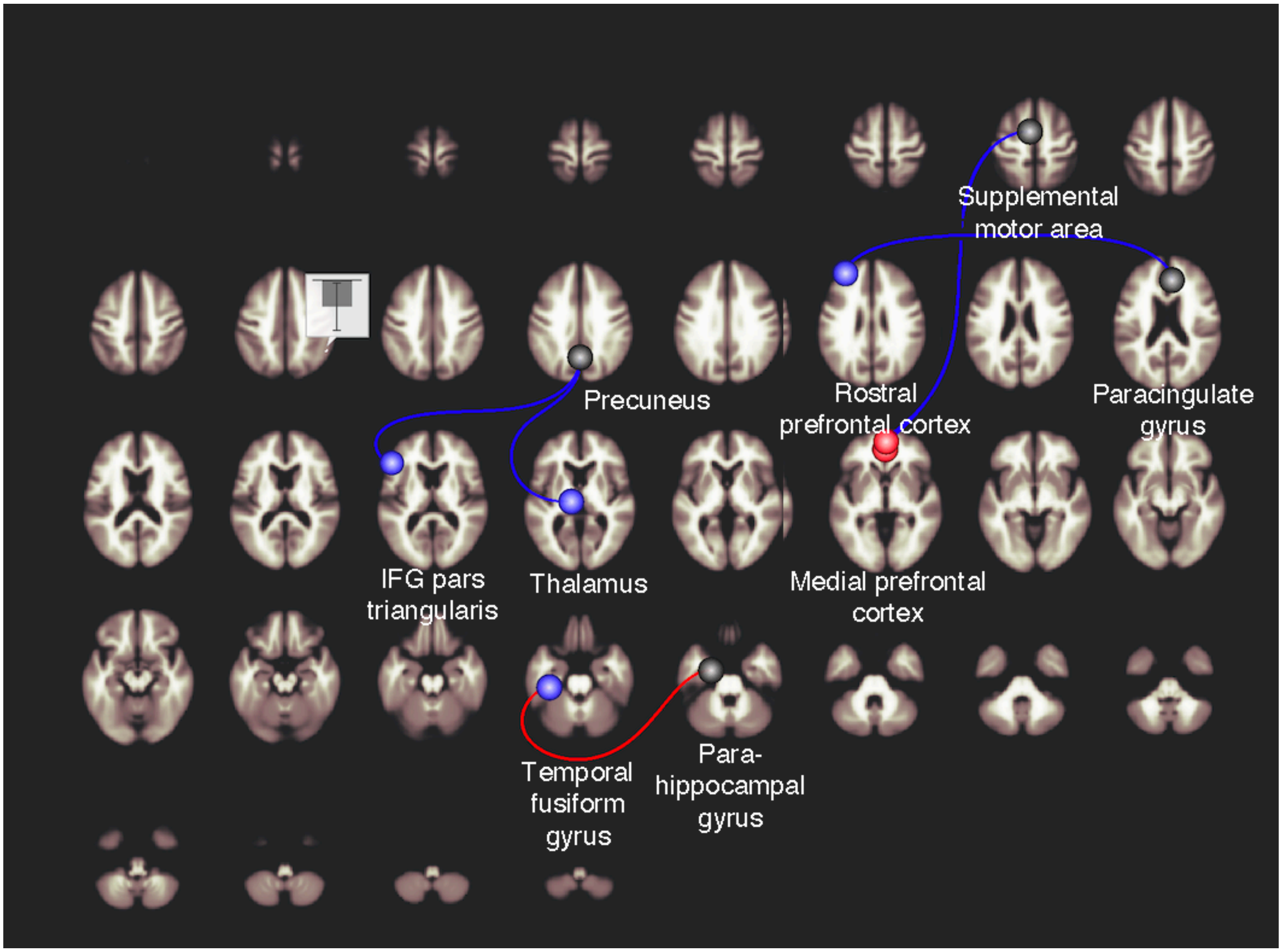


Figure 15. Functional connectivity differences in youths with ADHD prior to and following treatment with Brain Balance / Interactive metronome that correlate with rate-dependent differences in accuracy on the Quotient ADHD System Test. Red lines indicate positive connections between regions. Blue lines indicate reciprocal connections. The circles at the end of the lines are also color coded. Gray circles indicate the seed region for the connection. Red circles indicate that there was a positive correlation between post-treatment increase in connectivity and post-treatment increase in accuracy. Blue circles indicate that the there was an inverse connection between post-treatment connectivity and accuracy.

A frontal connection that was inversely correlated with performance following treatment was between the right paracingulate gyrus and the left rostral prefrontal cortex. The paracingulate cortex is cytoarchitectonically distinct from the limbic anterior cingulate cortex and it occupies a large portion of what has been termed the 'cognitive' division of the anterior cingulate[23]. This region should be activated by the cognitive control task, in which participants respond as rapidly as possible to targets, but withhold responses to non-targets, as the anterior paracingulate cortex was found to link target detection and response selection by monitoring for the presence of behaviorally significant conditions[56]. The rostral prefrontal cortex is also involved in executive function and cognition. More specifically, it supports episodic cognitive control, possibly by sending a weighting signal toward the inferior parietal and middle/inferior temporal cortices that modulate saliency and sensory processing[46]. Differences in rostral prefrontal cortex activity underlie individual differences in working memory capacity[46]. It fits with Melillo's theory that with enhanced right paracingulate performance following BB/IM that there should be less need for the left rostral prefrontal cortex to enhance and support right paracingulate performance.

The final identified pathway was between the left parahippocampal gyrus and left temporal fusiform gyrus. The parahippocampal gyrus has extensive connections to the fusiform gyrus and through this gyrus to anterior and posterior temporal lobes[53]. The parahippocamapal gyrus plays and important role in associative learning and recall of objects and faces[87]. Performance on a recognition task correlated positively with bilateral activation of the parahippocampal gyrus - fusiform gyrus[27]. Again, following Melillo's theory, the right hemisphere component of this pathway should be underdeveloped prior to BB/IM and enhanced by treatment. Following treatment the left hemisphere component would be expected to show reduced connectivity as the right hemisphere component takes on more of its share.

3B. Relationship between Resting State Functional Connectivity and Rate-Dependent Changes in Hyperactivity.

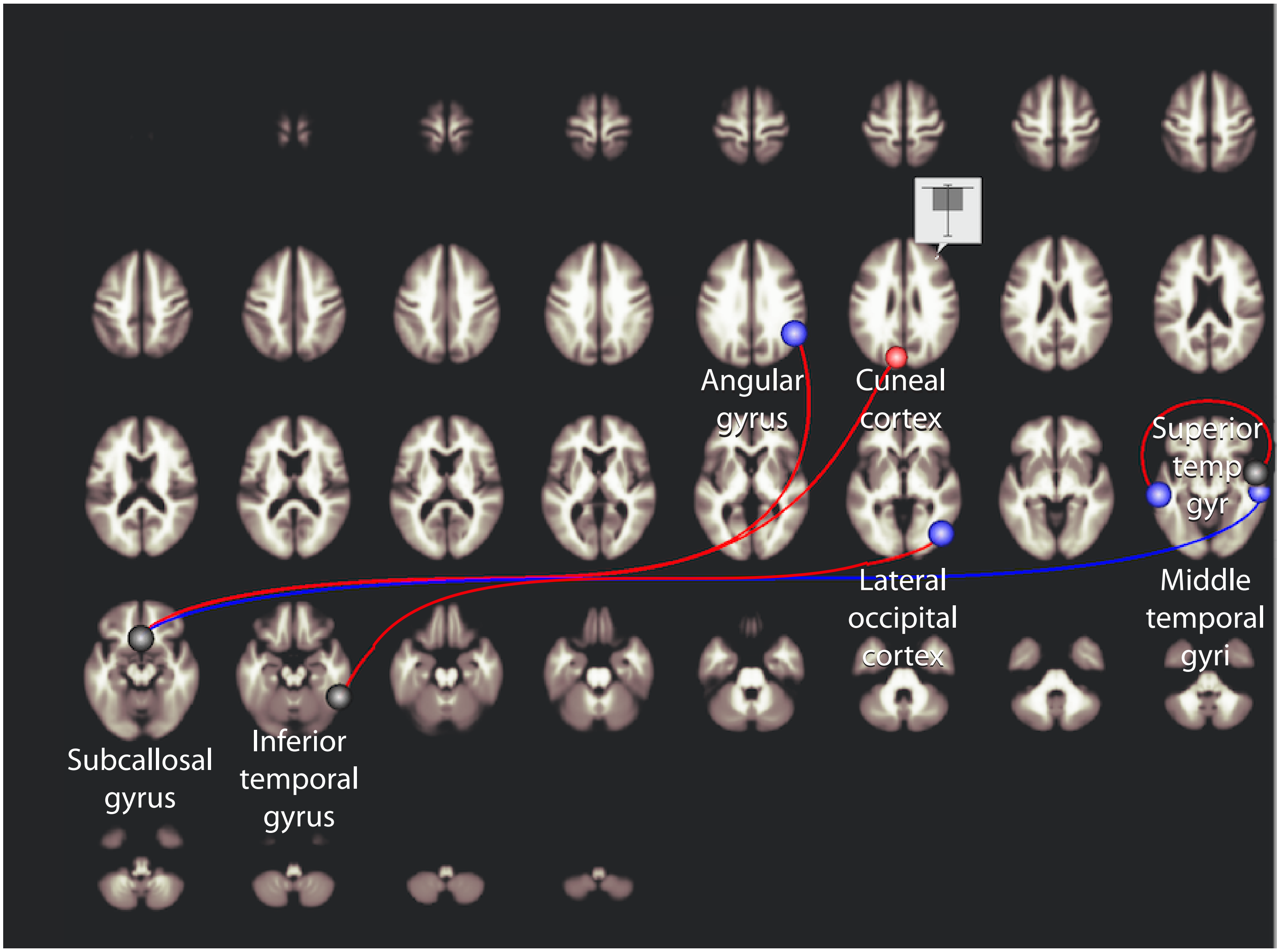


Figure 16. Functional connectivity differences in youths with ADHD prior to and following treatment with Brain Balance / Interactive metronome that correlate with rate-dependent differences in movements (microevents) on the Quotient ADHD System Test. Red lines indicate positive connections between regions. Blue lines indicate reciprocal connections. The circles at the end of the lines are also color coded. Gray circles indicate the seed region for the connection. Red circles indicate that there was a positive correlation between post-treatment increase in connectivity and post-treatment increase in activity (hyperactivity). Blue circles indicate that the there was an inverse connection between post-treatment connectivity and hyperactivity.

In these analyses we sought to identify functional pathways in which the magnitude and direction of functional connectivity change following BB/IM correlated with the rate-dependent effects of BB/IM on movements (microevents – Figure 6). Overall, 5 pathways were identified that showed a statistically significant correlation.

Three of the pathways were connections of the angular gyrus, middle temporal gyrus and the cuneus with the subcallosal gyrus. The subcallosal gyrus, which includes the subgenual cingulate, (Brodmann Area 25 - BA25), is crucial for emotional expression and equilibrium. Metabolic overactivation of BA25 has been linked to treatment-resistant depression[41] and deep brain stimulation designed to reduce overactivity in this region has been associated with a striking and sustained remission of treatment-resistant depression in a substantial subset of individuals[18,41]. BA25 has an extensive array of connections which include auditory association and memory-related areas in the middle temporal gyrus[94].

An increasing number of studies are beginning to show an important relationship between ADHD and the subgenual cingulate. Resting-state analysis revealed a disconnected functional network between the subgenual cingulate and multiple regions in the occipital lobe (including the cuneus) and the cerebellum in children with ADHD. Similarly, diffusion tensor imaging data showed disrupted white matter integrity in the subgenual cingulum bundle. Both the resting state and diffusion tensor measures were significantly correlated with clinical measures of hyperactivity-impulsivity and inattention[93]. Likewise, fractional anisotropy and radial diffusivity in the left subgenual cingulum was positively and negatively correlated, respectively with ADHD symptom scores[14]. Schlochtermeier et al[60] reported that activation in the subgenual cingulate when viewing positive and negative affective pictures was reduced in drug-naive males with ADHD but was normal in males with ADHD treated with methylphenidate. Hence, it makes sense that alterations in the connectivity of the subgenual cingulate may have rate-dependent effects on hyperactivity.

The other identified connections involved positive correlations between the right inferior temporal gyrus and right lateral occipital cortex and between the right superior temporal gyrus and left medial temporal gyrus.

The inferior temporal gyrus (ITG) is one of the higher levels of the ventral stream of visual processing. This is known as the "what" stream (in contrast to the dorsal "where" stream) and is associated with the representation of complex object features. It is also involved in face perception, and in the recognition of numbers and words[49]. The lateral occipital cortex and other early visual areas provide the building blocks for the ventral visual stream that projects to the ITG. The task the participants were performing was a visual processing task, in which they were endeavoring to rapidly identify and respond to stars of different shapes that may appear in right or left visual fields. Methylphenidate has been found to normalize target detection between the right and left hemi-fields by enhancing the right-lateralized ventral attention network[65]. In this case the weaker the connection between these areas the greater the decrease in hyperactivity. One interpretation is that the more difficulty they have in identifying the target the more they need to sit still during the task.

The final pathway was between the right superior temporal gyrus (STG) and the left middle temporal gyrus (MTG). The middle temporal gyrus (MTG) is a brain region unique to humans, with no homology in non-human primates[89]. While the STG is known to play an important part in auditory perception, and the ITG is recognized as a higher site of the ventral visual stream, less is known regarding the functions of the MTG. Recently, Wu et al[89] using tract tracing divided the MTG into four separate regions – anterior, middle and posterior with a more dorsal sulcal region overlapping part of the anterior and middle regions. It is specifically the anterior and sulcal regions of the MTG that connect strongly with the STG, and these are the components most likely to be responsible for the reciprocal interrelationship with the effects of BB/IM on hyperactivity and connectivity with the STG. Resting state functional connectivity reveals that the anterior MTG is connected with and part of the default mode network. The anterior MTG is also connected to the anterior frontal cortex via the uncinate fasciculus through the rostral STG. Hence, it makes sense that increasing connectivity would be associated with decreasing hyperactivity. The sulcal MTG is connected with frontal areas through the inferior fronto-occipital fasciculus extending directly to the putamen and insula via the external capsule. Connections of the sulcal MTG with putamen and frontal regions may directly influence motor activity[76] and help explain this reciprocal relationship.

Overall, this in depth exploratory analysis of the potential influence of Brain Balance / Interactive Metronome on resting-state functional connectivity suggests that this type of training may exert widespread effects on patterns of brain connectivity. Future research will need to establish whether these effects are replicable, whether they are enduring and if age at the time of training influences which connections are more likely to be altered.

Conclusion. It is noteworthy that training with Brain Balance / Interactive Metronome, in this open study, appeared to have clinical, behavioral and neurobiological effects on par with pharmacological treatment. This is very encouraging as we believe that the ultimate goal in psychiatry is to develop non-pharmacological treatments for psychiatric disorders that exert enduring beneficial effects.

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