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White Paper: Profound Effects of Interactive Metronome and Brain Balance Exercises on a Subset of Children with Attention Deficit Hyperactivity Disorder

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders of childhood, and it often persists into adulthood[2]. ADHD is characterized by a triad of symptoms: inattention, hyperactivity and impulsivity[2]. Although common, it is a serious disorder associated with a 10-fold increased incidence of antisocial personality disorder[12,35], up to 5-fold increased risk of drug abuse[10,12], 25-fold excess risk for institutionalization for delinquency[22], and up to 9-fold increased risk of incarceration[14]. ADHD is often highly responsive to medications, but the gains are transient and wear off after each dose[31]. To compound matters, compliance is usually poor[19]. 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[21,25,26,33,37]. 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[15,16], 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[1,3,5-7,13,17,20,34,36,38].

Specific Aims

I. To test in an open study whether Interactive Metronome Training[4,8,23] and Brain Balance Exercises[15,16] are associated with measurable improvements in attention, impulse control and activity on the Quotient ADHD System and in spatial working memory and spatial span on CANTAB.

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

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[11]). Treatment consisted of 15-weeks of Interactive Metronome[4,8,23] and Brain Balance[15,16] training (up to 75 sessions). Interactive Metronome and Brain Balance 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 using the Quotient ADHD System. This technology 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[29] while an infrared motion analysis system tracks head movements throughout the test period[18,28].

This test is highly responsive to the effects of medication[30,32], *correlates with blood levels of methylphenidate*[31] *but is not responsive to placebo*[27]. *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™).

Neuropsychological Results

To date, 5 of 14 children (36%) with ADHD who completed Interactive Metronome and Brain Balance training had a 40% or greater improvement in Quotient measures of Hyperactivity or Inattention or CANTAB measure of Spatial Working Memory. This is a degree of improvement that we have not previously observed in children with ADHD unless they were receiving medications, and then only if they were receiving the correct medication at optimal dose.

Examples

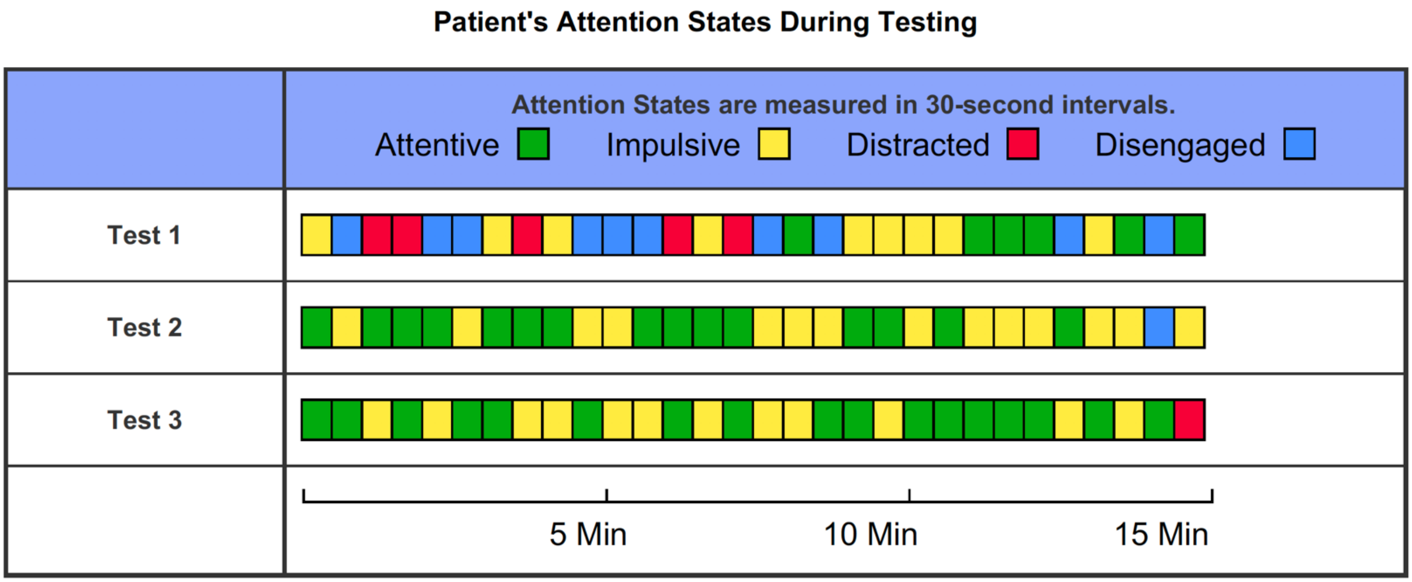
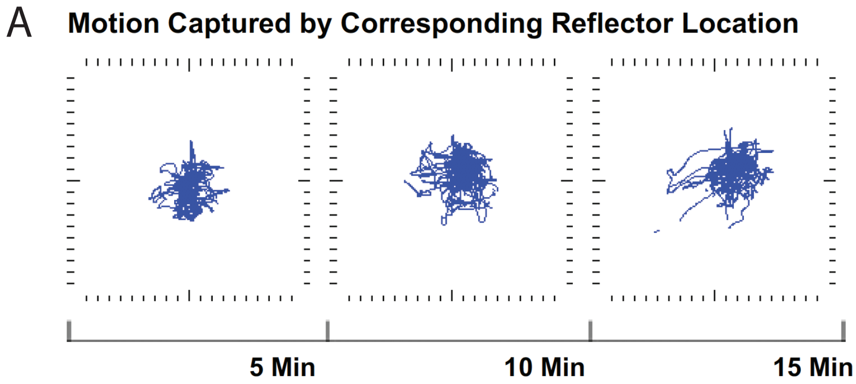


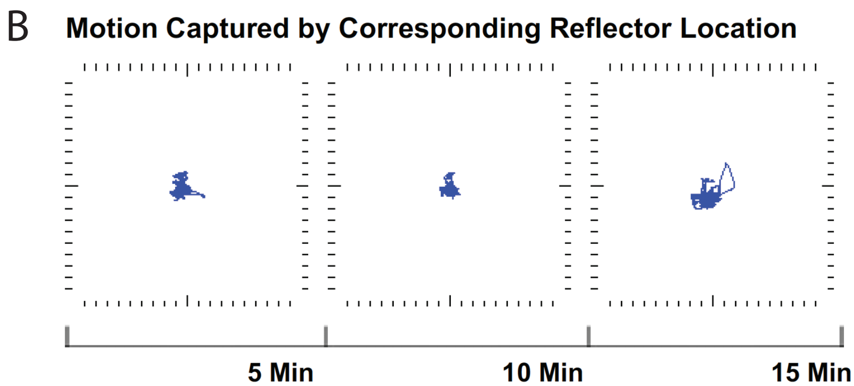
Figure 1. Attention performance on Quotient in participant BB001. A determination was made every 30 seconds as to whether the participant was fully attentive, was partially attentive but making some impulsive errors, was partially attentive but making a few distracted errors or was disengaged and not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

Figure 2. Spatial Working Memory test performance on CANTAB in participants BB005 and BB008 prior to and following Interactive Metronome and Brain Balance treatments. Note marked reduction in between errors. The Spatial Working Memory test requires retention and manipulation of visuospatial information. This self-ordered test has notable executive function demands and provides a measure of strategy as well as working memory errors.



Motion Results

Measure	Age Percentile t ≤ 16 Age Percentile
Immobility Duration:	6^{t}
Movements:	5^{t}
Displacement:	6^{t}
Area:	15^{t}
Spatial Complexity:	15^{t}
Temporal Scaling:	3^{t}

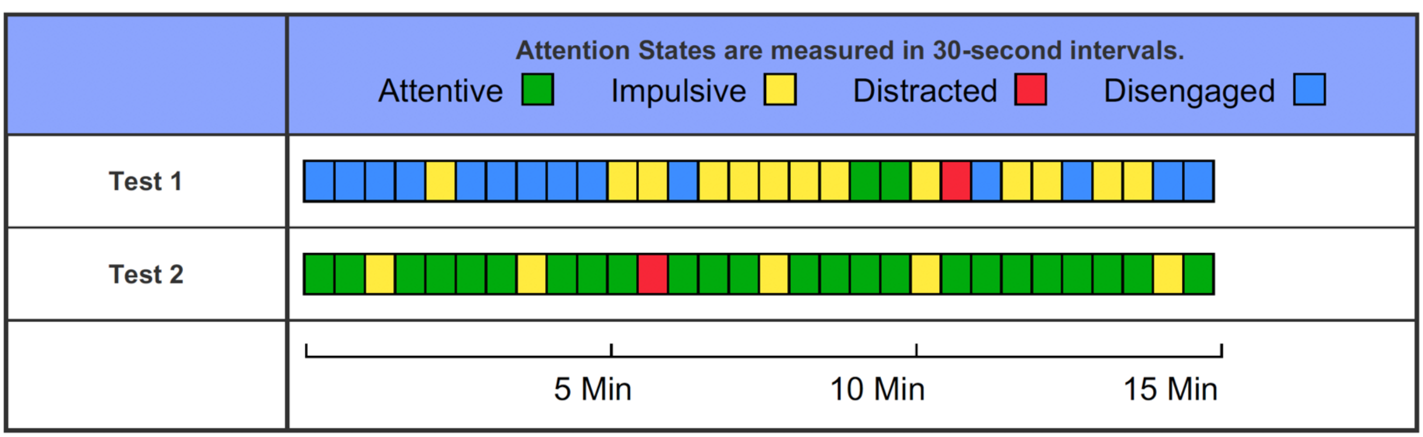


Motion Results

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

Figure 3. Measures of hyperactivity on Quotient test in BB010 (A) prior to and (B) following Interactive Metronome and Brain Balance 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.

Patient's Attention States During Testing



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 4. Measures of inattention on Quotient test in BB026 prior to and following treatment with Interactive Metronome and Brain Balance 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 Interactive Metronome and Brain Balance treatment.

Preliminary Neuroimaging Results

Data were analyzed in youths to assess the impact of number of Interactive Metronome and Brain Balance training session completed on resting state functional connectivity. Initially, we focused on effects on prefrontal cortex and striatum (caudate and putamen). These are brain regions strongly implicated in the neurobiology of ADHD. Briefly, we found that Brain Balance training was associated with increased connectivity between prefrontal cortex and the frontal pole, temporal pole, cerebellum, precentral gyrus and supramarginal gyrus. Brain balance training had relatively little influence on striatal connectivity, primarily increasing connectivity between the caudate nucleus and the precuneus and middle temporal gyrus.

What we observed instead was that Brain Balance exercises appeared to have widespread effects on connectivity of the amygdala and hippocampus, which are key limbic regions involved in implicit and explicit memory as well as stress response. Interactive Metronome and Brain balance training was associated with increased connectivity of the amygdala with supramarginal gyrus, cingulate gyrus, anterior cingulate, angular gyrus, frontal pole and precuneus. Pathways between the amygdala and cingulate typically strengthen during adolescence and provide more control over emotions and impulses. Similarly, Interactive Metronome training was associated with increased connectivity between the hippocampus and the angular gyrus, precuneus, middle temporal gyrus, lateral occipital cortex, supramarginal gyrus, cingulate gyrus and frontal pole.

The angular gyrus, supramarginal gyrus and middle temporal gyrus are all involved in language processing. The angular gyrus, in particular, is involved in language processing, memory retrieval, handwriting, ability to calculate mathematically and left/right discrimination. These language structures in the left hemisphere, which surround Wernicke's area are, according to Diedrichsen[9], most directly involved with intrinsic timing (rather than timing based on coordinated motor movements – which is cerebellar). These appear to be potent changes. Our findings of symptomatic improvement and enhanced connectivity of the supramarginal gyri with the amygdala, hippocampus, and prefrontal cortex is consistent with a recent report showing that reduced connectivity of the left and right supramarginal gyri was associated with increased symptom severity in ADHD[24]. Given the role these regions appear to play in timing makes these observations particularly compelling.

The cerebellum is also critically involved in timing and time perception, so we assessed the effects of Interactive Metronome training on resting state functional connectivity of the cerebellum. Briefly, training on the Interactive Metronome was associated with increased resting state functional connectivity between: cerebellum I and middle frontal gyrus; cerebellum II and inferior temporal gyrus/fusiform gyrus; cerebellum IV-V and parahippocampal gyrus and inferior temporal gyrus/fusiform gyrus; cerebellum VII and lateral occipital cortex; cerebellum VIII and superior frontal gyrus and cerebellum IX and lingual gyrus and postcentral gyrus. Interactive metronome training was also associated with decreased resting state functional connectivity between cerebellum III and anterior cingulate gyrus and cerebellum VI and lateral occipital gyrus.

Further work is in progress to better define the constellation of changes associated with Interactive Metronome and Brain Balance training and their relationship to clinical outcome.

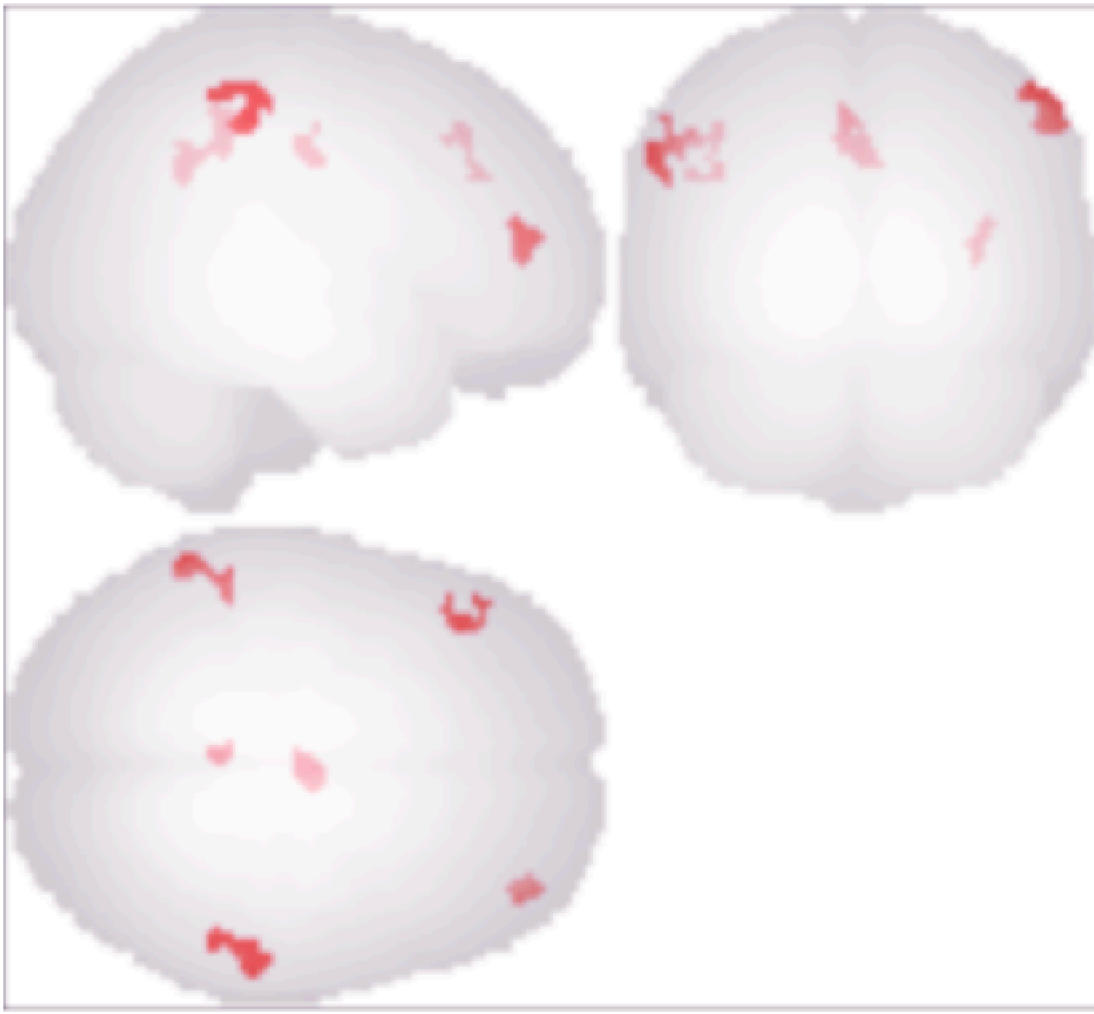


Figure 5. Regions in which number of Interactive Metronome and Brain Balance sessions completed were associated with change in functional connectivity with the amygdala (bilateral seeds). These regions included: supramarginal gyrus, cingulate gyrus, anterior cingulate, angular gyrus, frontal pole and precuneus.

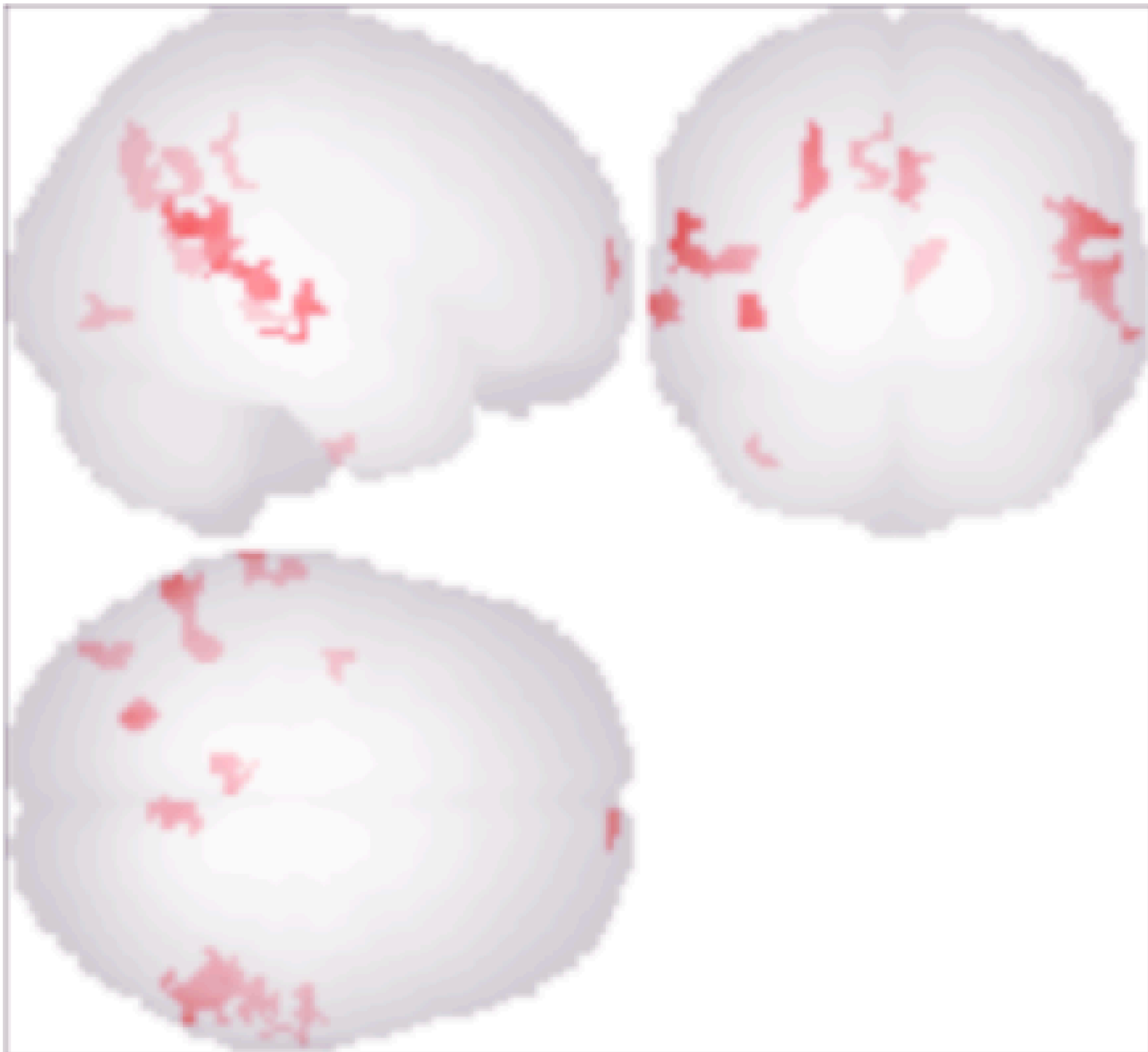


Figure 6. Regions in which number of Interactive Metronome and Brain Balance sessions completed were associated with change in functional connectivity with the hippocampus (bilateral seeds). These regions included: angular gyrus, precuneus, middle temporal gyrus, supramarginal gyrus, lateral occipital cortex, cingulate gyrus and frontal pole.

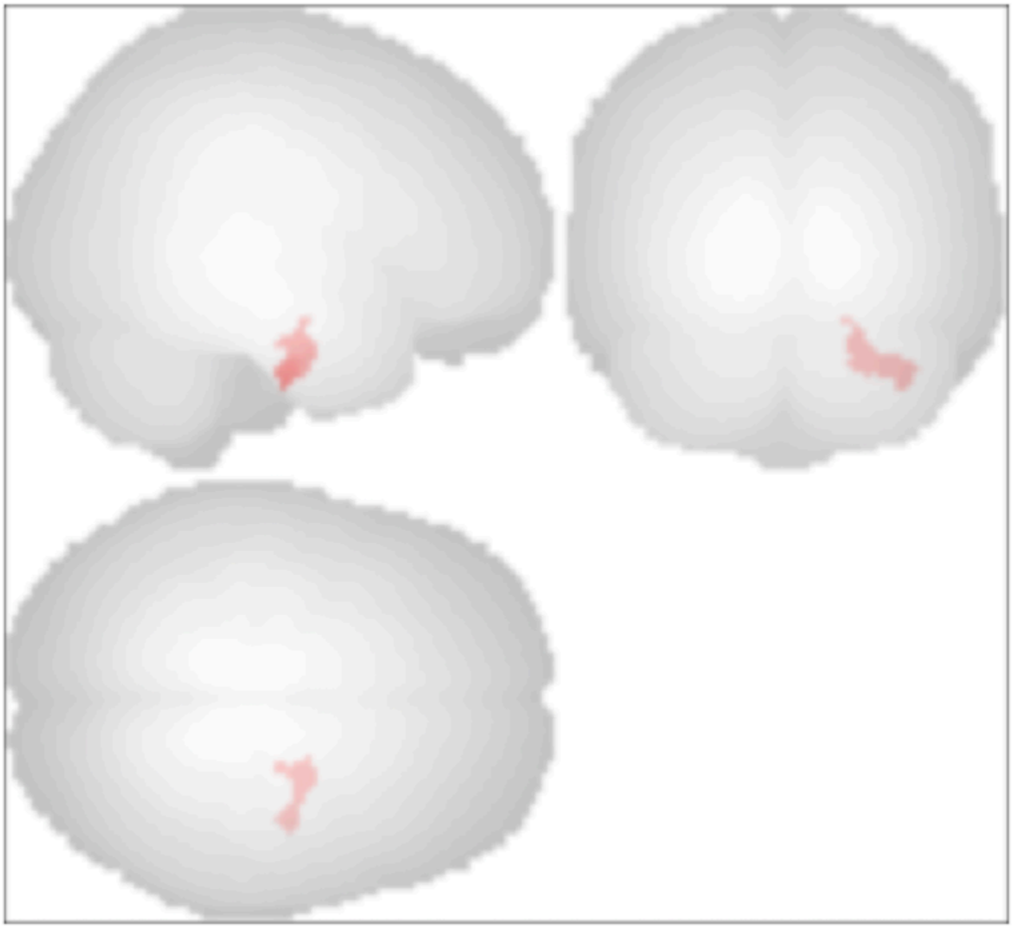


Figure 7. Regions in which number of Interactive Metronome and Brain Balance sessions completed were associated with change in functional connectivity with the lobule V of the cerebellum, which is most directly involved in state-dependent motor timing[9]. Functional connectivity was enhanced in the parahippocampal gyrus / temporal fusiform area.

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