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Lonnie A. Nelson, Margaret MacDonald, Christina Stall, and Renee Pazdan
Defense and Veterans Brain Injury Center, Fort Carson, Colorado

Objective: We report preliminary findings on the efficacy of interactive metronome (IM) therapy for the remediation of cognitive difficulties in soldiers with persisting cognitive complaints following blast-related mild-to-moderate traumatic brain injury (TBI). ***Method:*** Forty-six of a planned sample of 50 active duty soldiers with persistent cognitive complaints following a documented history of blast-related TBI of mild-to-moderate severity were randomly assigned to receive either standard rehabilitation care (SRC) or SRC plus a 15-session standardized course of IM therapy. Primary outcome measures were Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Index Scores. Secondary outcome measures included selected subtests from the Delis–Kaplan Executive Functioning System (Trail Making Test and Color–Word Interference) and the Wechsler Adult Intelligence Scale–Fourth Edition (Symbol Search, Digit–Symbol Coding, Digit Span, and Letter–Number Sequencing) as well as the Integrated Visual and Auditory Continuous Performance Test. ***Results:*** Significant group differences (SRC vs. IM) were observed for RBANS Attention ($p = .044$), Immediate Memory ($p = .019$), and Delayed Memory ($p = .031$) indices in unadjusted analyses, with the IM group showing significantly greater improvement at Time 2 than the SRC group, with effect sizes in the medium-to-large range in the adjusted analyses for each outcome (Cohen's $d = 0.511$, 0.768, and 0.527, respectively). Though not all were statistically significant, effects in 21 of 26 cognitive outcome measures were consistently in favor of the IM treatment group (binomial probability = .00098). ***Conclusion:*** The addition of IM therapy to SRC appears to have a positive effect on neuropsychological outcomes for soldiers who have sustained mild-to-moderate TBI and have persistent cognitive complaints after the period for expected recovery has passed.

Keywords: blast-related brain injury, cognitive rehabilitation, attention, memory, mTBI, recovery of function

Although the majority of mild traumatic brain injuries (mTBIs) resolve spontaneously within a few months (Vanderploeg, Curtiss, Luis, & Salazar, 2007), a minority of patients may experience lasting cognitive sequelae postinjury (Hartikainen et al., 2010; Luethcke, Bryan, Morrow, & Isler, 2011; Roebuck-Spencer et al., 2012; Zakzanis, McDonald, & Troyer, 2011). These reports may be more frequent in soldiers injured in the line of duty overseas, and difficulties experienced may be exacerbated by the presence of comorbid symptoms of posttraumatic stress disorder (PTSD; Bogdanova & Verfaellie, 2012; Brenner et al., 2010; Halbauer et al., 2009). Some reports have suggested that the mechanism of injuries related to blast exposure may also play a role in these reported difficulties (Bogdanova & Verfaellie, 2012; Brenner et al., 2010). Verification of these reports by formal neuropsychological testing may be complicated by situational factors, pain from other injuries, conversion symptoms, and effort issues (Armistead-Jehle, 2010; Cooper et al., 2010; Cooper, Nelson, Armistead-Jehle, & Bowles, 2011; Lange, Pancholi, Bhagwat, Anderson-Barnes, & French, 2012). Nonetheless, it is likely that at least some degree of cognitive dysfunction is present in at least a subset of those presenting with persistent cognitive complaints following mTBI (Bogdanova & Verfaellie, 2012; Nelson, Yoash-Gantz, Pickett, & Campbell, 2009; Ozen & Fernandes, 2012; Roebuck-Spencer et al., 2012; Sponheim et al., 2011). Further, several studies have demonstrated functional connectivity and other brain changes after mTBI, lending some physiological credence to this possibility (Arciniegas, 2011; Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011; Sponheim et al., 2011). It would be reasonable to expect that disruptions of brain functional connectivity might produce information processing inefficiencies, with minimal structural change.

Literature Review

Cognitive rehabilitation is generally held to be somewhat effective following severe-to-moderate TBI (Cicerone et al., 2005; Cicerone et al., 2011; Gordon et al., 2006; Rohling, Faust, Beverly,

Lonnie A. Nelson, Margaret MacDonald, Christina Stall, and Renee Pazdan, Defense and Veterans Brain Injury Center, Fort Carson, Colorado.
Lonnie A. Nelson is now at the University of Washington School of Public Health, Department of Health Services.

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Correspondence concerning this article should be addressed to Margaret MacDonald, 7489 Sutherland Circle, Fort Carson, CO 80913. E-mail: margaret.e.macdonald3.ctr@mail.mil

& Demakis, 2009). But, as several authors have pointed out, these findings are likely not applicable to patients with persistent cognitive complaints following mTBI (Bogdanova & Verfaellie, 2012; Institute of Medicine, 2011). The Institute of Medicine's 2011 evaluation of the evidence on the use of cognitive rehabilitation for service members and veterans following mTBI indicated a need for increased efforts in the areas of defining, standardizing, and measuring results of cognitive rehabilitation interventions. In a recent review article on this topic, Bogdanova and Verfaellie (2012) pointed out that there is very little literature on the effects of attention remediation training in mTBI, and they focused their review, instead, on executive functions and memory. In an accurate reflection of the literature, the studies reviewed in their article focused primarily on metacognitive and compensatory strategies, with little mention of interventions aimed at recovery of lost function through neuroplastic processes.

Neuroplasticity and Recovery of Function

In a review of neuroplasticity in rehabilitation, Moucha and Kilgard (2006) emphasized that neuroplastic processes are regulated by several related factors amenable to manipulation in the therapeutic context. Among these factors are: attentional modulation, patterning of sensory activation, timing of sensory inputs, duration of experience, characteristics of the neurochemical environment, and correlation of sensory inputs. Traditional therapeutic interventions in rehabilitation medicine are able to take advantage of some of these operators. For example, during inpatient TBI rehabilitation, individuals are often prescribed a stimulant medication, which alters the neurochemical environment and assists with attentional modulation (Moucha & Kilgard, 2006). However, the more fine-grained aspects that appear to be important to neuroplastic processes, such as patterning of sensory activation, timing of inputs, and correlation of sensory inputs with motor outputs, are more difficult to standardize in traditional speech, occupational, and physical therapies. These variables are often dependent on the individual skills of the therapist, because external controls on these variables may not be in place during most therapeutic interactions.

Repetitive experience with predictable timing and pattern relationships between sensory inputs and motor outputs has been shown to enhance production of neurotransmitters (Moucha & Kilgard, 2006). Human learning and memory processes rely on systems of dopamine, norepinephrine, and acetylcholine. Recurrent firing stimulates neuroplastic responses such as dendritic sprouting and receptor upregulation. We posited that massed practice and behaviorally relevant stimulus patterning with repetitive exposure and motor demands, as instantiated in interactive metronome (IM) therapy, can encourage the restoration of impaired cognitive functions through mechanisms of cortical plasticity.

IM Therapy

IM technology is a behavioral feedback operant conditioning system, in which a patient executes various repeated movements in time to a beat, while a computer provides precision feedback on performance (Koomar et al., 2001). In biofeedback, physiological information is displayed to the patient, but, in IM therapy, otherwise unobservable information about the patient's behavioral responses is provided to them (Nelson, 2007). IM technology takes advantage of each of the above discussed factors related to neuroplastic processes and integrates them into a single set of tasks that are designed to encourage integrated neuroplastic activity under cognitively demanding circumstances. The computerized feedback is reliable, consistent, timely, and directly correlated with motor output. The feedback is also presented in a rich cognitive and sensory environment that combines instantaneous delivery of simultaneous auditory and visual feedback following the motor response. This information aids the preparation of the upcoming behavioral response. All of this feedback processing and adjustment of behavioral responses must occur in just over a second (1.111 s) when the tempo for IM training is 54 beats per minute (system default). This places a considerable temporal demand for integration across the attentional, decision making, inhibitory, and sensory and motor output operators of the cortex, thereby taxing processing speed and efficiency during training.

When engaged in the task, the patient is performing one of 13 repetitive body movements requiring varying degrees of physical coordination. Examples of the movements are clapping the hands to trigger a sensor worn on the palm or tapping alternating toes on a floor sensor. These movements are done in time to a set beat, which is presented via headphones. The task for the patient is to attempt to depress the sensors *exactly in time* with the set beat. Every time the patient depresses a sensor, the computer provides an immediate auditory feedback sound that indicates how far away from the set beat that the response was and whether it was early or late. The feedback sound is in the left ear if the response was before the beat, and in the right ear if the response was after the target beat. Simultaneously, visual information is presented on the computer screen that indicates, in graphical and numerical form, how far off beat the response was, measured in milliseconds. The patient then uses all of this information to adjust his or her next response to be either slower or faster in order to be closer to the set beat.

A randomized clinical trial of the effects of IM training using a sample of boys with attention deficit/hyperactivity disorder (ADHD) showed positive results. Compared with a nontherapeutically designed video game active control treatment, IM training improved performance on a host of measures, including attention, motor control, language processing, reading, and parental reports of improvements in the regulation of aggressive behavior (Shaffer et al., 2001). It should be noted that these cognitive and behavioral functions are common symptom areas in individuals surviving TBI, and may also be affected in cases of blast injury (Hofman et al., 2001; Jorge, Robinson, & Arndt, 1993; Levy et al., 2005; McCauley et al., 2005; Warriner & Velikonja, 2006).

Objectives

We report the immediate posttreatment effects of IM therapy on attention and memory functioning in an initial sample of military personnel who had sustained an mTBI related to blast exposure within the previous 5 years, and who showed evidence of cognitive difficulties at the time of study enrollment. The study is still ongoing, but a regulatory delay provided an opportunity for interim data analysis for all current subjects. We hypothesized that a standardized course of 15 sessions of IM therapy, in addition to standard rehabilitation treatment, would significantly improve at-

tention and memory index scores on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) beyond gains experienced by those receiving standard treatment alone (McKay, Casey, Wertheimer, & Fichtenberg, 2007). Secondary neuropsychological measures were included to determine the effects of IM therapy on measures of processing speed and executive functioning.

Method

In the conduct of research where humans are the subjects, the investigator(s) adhered to the policies regarding the protection of human subjects as prescribed by Code of Federal Regulations (CFR) Title 45, Volume 1, Part 46; Title 32, Chapter 1, Part 219; and Title 21, Chapter 1, Part 50 (Protection of Human Subjects)." This work received human protections oversight from the Military Research and Material Command Institutional Review Board at Fort Dietrich, Maryland, and Western Region Medical Command Institutional Review Board at Madigan Army Medical Center, Joint Base Lewis-McChord, Washington. Final protocol in PDF format is available from corresponding author on request. All participants reviewed and signed an informed consent document, approved by the institutional review board, prior to any testing or study treatments.

The design of this study was a simple, two-arm, parallel, randomized controlled trial. The two treatment conditions were (a) standard rehabilitation care (SRC), to include physical therapy, occupational therapy, and traditional cognitive rehabilitation therapy delivered by a speech language pathologist, and (b) SRC plus 15 standardized, 1-hr IM treatment sessions.

Eligibility Criteria

Eligibility for participation required that participants: (a) had sustained a blast-related TBI at least 3 months but not more than 5 years prior to enrollment; (b) had an injury documented in medical record by at least one of the following: (i) loss of consciousness (LOC), posttraumatic amnesia (PTA), (ii) alteration in mental status (dazed/confused), and/or (iii) physical evidence of trauma on magnetic resonance imaging or computerized tomography showing hemorrhage or contusion; (c) met criteria for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM–IV*) diagnosis of postconcussional disorder or mild neurocognitive disorder due to a general medical condition in which the medical condition was the above-referenced injury (American Psychiatric Association, 1994); and (d) were active duty military personnel or veteran beneficiary. Men and women ages 18–55 years were eligible for enrollment.

Factors excluding patients from eligibility for participation were: (a) having had a current or prior (6 months) unstable medical condition that could affect current brain function (e.g., clear anoxic episode, cardiac arrest, current uncontrolled diabetes); (b) being status post craniectomy prior to cranioplasty; (c) having a prior history of moderate-to-severe TBI, not including present injury; (d) having current (last 3 months) active suicidal or homicidal ideation or intent; (e) having current (last month) drug and/or alcohol abuse or dependence as determined by interview and/or a possible score of 5 or higher on the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C); (f) using benzodiazepine or narcotic medications; (g) participation in a concurrent drug or treatment trial; and (h) being physically unable to complete the treatment tasks (including sensory functions). For reasons of ecological validity, we determined that exclusion based on a history of ADHD or mood disorders would be overly restrictive and artificial, given the population of interest. It should be noted that due to repeated failures of potential participants to meet the AUDIT-C criterion, potential participants evaluated after January 20, 2011, who did not meet *DSM–IV* criteria for alcohol abuse or dependence, but scored above a 5 on the AUDIT-C, were enrolled with brief counseling on alcohol use during brain injury rehabilitation and a signed statement in which they agreed to reduce their alcohol consumption during their participation in the study. This included a total of 12 participants who scored 5 or higher, with four participants scoring a 6. One individual was initially excluded due to a score of 10, but was later allowed to participate after decreasing his alcohol consumption. Although alcohol consumption was not measured during participation, the groups did not differ significantly on prerandomization AUDIT-C scores, and mean scores for both groups were less than 5 (see Table 1).

Participants

Sample size was determined via power analysis, and indicated that 25 participants in each group would provide a power of at least 80% to detect changes sufficient to restore patients to average range attention and memory functioning, as measured by the RBANS, assuming initial impairment on the order of severity reported by McKay et al., (2007). The current report reflects the initial treatment effects for the first 46 participants who were randomly assigned to the two treatment conditions. Participants were recruited by referral from the Neuropsychology and Neurology Services at the Warrior Recovery Center (WRC), Evans Army Community Hospital, at Fort Carson, Colorado. The study assessments and treatment sessions were conducted within the WRC rehabilitation services clinic. The sample was entirely male (N = 46, 100%). Their ages ranged from 21–49 years, with a mean of 33.0 years (SD = 7.9). The majority of participants were combat arms or combat support personnel (78.3% by military occupational specialty classifications) (Department of the Army, 1999). The sample included a wide range with regard to rank and number of combat deployments (see Table 1). The average number of blast injuries sustained by participants was 2.9 (SD = 1.6), with a mean time since injury of 28.6 months (SD = 23.9).

Randomization and Blinding

Participants were randomized using the baseline assessments. Thus, randomization condition was unknown at the time of baseline assessment. Due in part to the behavioral nature of the intervention, and in part to other logistic factors, no other assessments were conducted with unawareness of treatment condition assignment. Randomization was generated by computer, using a web service (at http//:www.randomizer.org). One set of 50 numbers (1 or 2) were generated in unsorted format, with place markers within the set to define the order of position allocation. These numbers were then placed on sheets of paper, and sealed within separate envelopes, with the corresponding enrollment order number marked on the outside of the envelope by a colleague in the

Table 1
Descriptive and Clinical Information for Study Sample

Characteristics	SRC group *M* (*SD*) or *n* (%)	IM group *M* (*SD*) or *n* (%)	*t* or χ^2, *df* (*p*)
Descriptive information			
Age in years	31.1 (7.9)	34.8 (7.5)	−1.625, 44 (.111)*
Male	24 (100.0)	22 (100.0)	*ns*
Education years	12.7 (1.6)	13.1 (2.1)	−0.656, 39 (.516)
Number of deployments	2.33 (1.8)	2.45 (1.1)	−0.280, 44 (.781)
Rank			
E1–E4	11 (46)	5 (23)	2.862, 3 (.413)
E5–E9	11 (46)	14 (64)	
O1–O3	1 (4)	2 (9)	
O4–O6	1 (4)	1 (5)	
MOS			
Combat arms	19 (79)	13 (59)	2.443, 2 (.295)
Combat support	1 (4)	3 (14)	
Combat service support	4 (17)	6 (27)	
Clinical information			
Number of blast injuries	2.9 (1.7)	2.9 (1.5)	0.025, 43 (.98)
Months since last injury	22 (21.4)	35 (25.6)	−1.734, 43 (.09)*
LOC worst			
AOC only	17 (71)	12 (57)	1.09, 3 (.78)
LOC < 5 min	5 (21)	6 (29)	
LOC 5–20 min	1 (4)	1 (5)	
PTA worst			
None	10 (42)	13 (62)	3.54, 2, (.17)
<30 min	14 (58)	7 (33)	
>30 min	0 (0)	1 (5)	
Comorbid PTSD diagnosis	7 (30)	7 (30)	0.038, 1 (.85)
Self-report measures			
Rivermead PCSQ	30.3 (9.9)	30.4 (10.4)	−0.024, 44 (.981)
AUDIT-C	3.17 (1.93)	2.64 (1.97)	0.924, 44 (.361)
SWLS	19.9 (6.8)	22.2 (6.1)	−1.206, 44 (.234)
MPAI-4			
Ability	16.6 (5.6)	18.6 (7.9)	−0.846, 44 (.402)
Adjustment	17.3 (7.7)	16.6 (5.6)	0.306, 44 (.761)
Participation	6.7 (4.8)	6.4 (4.5)	0.216, 44 (.830)
Total score	34.2 (18.5)	37.8 (12.1)	−0.798, 40 (.430)**

Note. SRC = standard rehabilitation care; IM = interactive metronome; M = Mean; E = enlisted; O = officer; MOS = military occupational specialty; AOC = alteration of consciousness/mental state; LOC = loss of consciousness; PTA = posttraumatic amnesia; PTSD = posttraumatic stress disorder; PCSQ = Post Concussion Symptoms Questionnaire; AUDIT-C = Alcohol Use Disorders Identification Test–Consumption; SWLS = Satisfaction With Life Scale; MPAI-4 = Mayo–Portland Adaptability Inventory–4.
* Trend toward significance. ** Equal variances not assumed.

Neuropsychology Service of the WRC with no control over order of consenting or assessment and consequent assignment of treatment condition. Participants opened the envelopes containing their randomization assignment themselves at the end of the feedback session in which the results of their baseline assessments were shared with and explained to them by the study neuropsychologist or physician (first and second authors, respectively), who were blind to the contents of the envelope.

Measures and Assessments

Assessments were conducted by study staff specifically trained in the standardized administration of all measures. Outcome measures were administered for all participants at three time points: (a) prerandomization, (b) within 2 weeks after completion of treatment phase, and (c) follow-up assessment at 6 months posttreatment. We will report the results from follow-up assessments in a future publication. All outcome assessment sessions were conducted in the morning, beginning at 8:00 a.m., and completed between 12:00 m. and 1:30 p.m. The assessment sessions consisted of a brief battery of neuropsychological tests, followed by completion of a brief set of self-report questionnaires, and, finally, electrocortical recordings (exploratory measures to be reported in a subsequent paper).

Neuropsychological Tests

Neuropsychological assessments included the following: Wechsler Test of Adult Reading (WTAR; Mathias, Bowden, Bigler, & Rosenfeld, 2007), RBANS (Forms A or B; McKay et al., 2007), Integrated Visual and Auditory Continuous Performance Test (IVA- CPT; Tinius, 2003), Delis–Kaplan Executive Functioning System (D-KEFS) Trail Making and Color–Word Interference subtests (Bagiella et al., 2010), Test of Memory Malingering (TOMM; Tombaugh, 1997), Grip Strength and Grooved Pegboard (Millis et al., 2001), as well as selected subtests from the Wechsler Adult Intelligence Scale–Fourth

Edition (WAIS-IV), including Digit Span, Letter–Number Sequencing, Digit–Symbol Coding, and Symbol Search subtests. If any of these measures were present in the potential participant's medical record, from administration in the previous 6 months from the baseline testing date, those test scores were used as measures of baseline performance in lieu of repeat administration, to reduce participant burden and to maintain test validity. The form used for RBANS administration in the medical record was noted, and the alternate form was administered for the 2-month follow-up assessment. RBANS Form A was otherwise used for all baseline assessments, Form B for the 2-month follow-up assessment, and Form A repeated at the 6-month follow-up assessment.

Self-Report Questionnaires

Participants completed the following self-report measures at baseline and 6-month assessment sessions: Rivermead Post Concussion Symptoms Questionnaire (King, Crawford, Wenden, Moss, & Wade, 1995), Mayo–Portland Adaptability Inventory–4 (Malec et al., 2003; Malec & Lezak, 2003), Satisfaction With Life Scale (Corrigan, Bogner, Mysiw, Clinchot, & Fugate, 2001), and the AUDIT-C (Bradley et al., 2007). The 6-month follow-up data were not available for a sufficient number of participants to analyze at the time of writing this report and, therefore, will be reported in a forthcoming publication.

Interventions

The standardized course of IM treatment consisted of 15 one-hour sessions. The goal for treatment intensity was three sessions per week (Mondays, Wednesdays, and Fridays), but many participants' duty obligations prevented this schedule from being strictly kept. The actual time range to complete the 15-session course of IM treatment ranged from a minimum of 5 weeks to a maximum of 17 weeks, with a mean completion time of 7.5 weeks. See the Appendix for the session contents and schedule.

SRC was delivered as recommended by the clinic's multidisciplinary rehabilitation team. The average numbers of physical therapy sessions ($M = 1.8$, $SD = 3.7$), occupational therapy sessions ($M = 0.6$, $SD = 1.1$), and cognitive rehabilitation therapy ($M = 3.1$, $SD = 2.4$) delivered by a speech language pathologist did not differ significantly across groups for the prerandomization to posttesting interval ($p = .23$, .41, and .329, respectively).

Statistical Analyses

All statistical analyses of neuropsychological test scores were completed using SPSS/PASW, Version 18, for Windows. The sample was described by calculation of mean and standard deviations for demographics (see Table 1) and for initial neuropsychological test standard and index scores (see Table 2). Baseline differences between groups were assessed using independent-samples *t* tests for continuous measures and chi-square tests for categorical variables.

Evaluation of Treatment Effects

Unadjusted analyses were conducted using a repeated-measures generalized estimating equations (GEEs) for each outcome measure. Unadjusted analyses included no covariates, and were not adjusted for multiple comparisons. Specifics for all unadjusted analyses are reported in Table 3.

Adjusted analyses were carried out using repeated-measures GEE. Separate GEE models, including the baseline assessment score, were calculated for each posttreatment test score. The following subject-level variables were entered as covariates: age in years, education in years, severity of worst injury (composite of duration of LOC and PTA), number of blast injuries sustained, PTSD diagnosis (binary indicator), number of speech therapy sessions received between baseline and posttreatment testing, and time between evaluations (measured in days). We used sequential Sidak adjustments to correct all pairwise comparisons for multiple comparisons (see Table 4).

Results

Participant Flow

Figure 1 shows the sample flow, beginning with participants who were referred to the study and consented to participate ($N = 56$), then showing the number of those who consented to participate and completed the baseline assessment session ($n = 46$), followed by the number who were randomized to treatment groups ($n = 45$), the numbers from each treatment group who completed at least a portion of measures administered in the posttreatment assessment sessions (SRC, $n = 18$; IM, $n = 18$), and, finally, the number of participants who completed the follow-up assessments (to be reported in future publication of 6-month findings).

Descriptives

Table 1 shows the demographic and baseline clinical information and questionnaire scores for the study sample, separated by group. Means and standard deviations are listed for continuous measures, while number and percentage are listed for categorical variables. Briefly, the table indicates that the overall level of TBI severity in the sample was mild based on documentation of durations of LOC and PTA, and included primarily enlisted personnel from combat or combat support military occupational specialties. Multiple deployments and multiple mild-intensity blast injuries were the norm for this sample. Separate *t* tests and chi-square analyses indicated that no significant prerandomization differences were present for demographic indicators or clinical and symptom measures between the groups.

Prerandomization Neuropsychological Functioning

Table 2 shows prerandomization (Time 1) neuropsychological test score means and standard deviations for the study sample, separated by eventual group assignment. Separate independent-samples *t* tests indicated that significant prerandomization differences existed only for WAIS-IV Digit Span Forward ($p = .017$) and Digit Sequencing ($p = .010$) subtests, with those eventually randomized to the IM group performing significantly more poorly than those in the SRC group. However, a trend toward generally lower scores in the IM group was noted for nearly all tests.

Assessment of Treatment Effects

Results of unadjusted analyses are shown in Table 3, which shows the difference in estimated marginal means between the

Table 2
Prerandomization Neuropsychological Test Scores by Group

Neuropsychological test	SRC group *n*, *M* (*SD*)	IM group *n*, *M* (*SD*)	*t*, *df* (*p*)
WTAR standard score	24, 108 (13.4)	22, 103 (14.6)	1.183, 44 (.243)
RBANS Index scores			
Attention Index	24, 87 (16.2)	22, 78 (15.8)	1.849, 44 (.071)
Immediate Memory Index	24, 89 (13.0)	22, 84 (16.3)	1.213, 44 (.232)
Delayed Memory Index	24, 95 (14.2)	22, 89 (19.6)	1.277, 44 (.208)
Language Index	24, 89 (12.4)	22, 84 (15.2)	1.066, 44 (.292)
Visuospatial/Constructional Index	24, 105 (10.9)	22, 104 (16.4)	0.360, 44 (.720)
WAIS-IV subtests			
Digit Span Forward	24, 8.9 (2.3)	22, 7.0 (2.7)	2.486, 44 (.017)*
Digit Span Backward	24, 10.5 (3.0)	22, 9.1 (2.1)	1.702, 44 (.096)
Digit Sequencing	24, 11.3 (2.8)	21, 9.3 (2.1)	2.693, 43 (.010)*
Letter–Number Sequencing	24, 9.7 (2.1)	21, 9.6 (2.9)	0.186, 43 (.854)
Symbol Search	24, 9.5 (2.9)	22, 9.2 (3.1)	0.355, 44 (.724)
Digit–Symbol Coding	24, 8.3 (2.5)	22, 8.0 (2.2)	0.480, 44 (.633)
D-KEFS subtests			
Trail Making 1	24, 9.2 (3.2)	22, 9.6 (4.1)	−0.439, 44 (.663)
Trail Making 2	24, 10.0 (2.7)	22, 9.1 (3.4)	0.908, 44 (.369)
Trail Making 3	24, 9.5 (3.2)	22, 9.0 (3.5)	0.501, 44 (.619)
Trail Making 4	24, 9.4 (2.9)	22, 9.0 (2.6)	0.571, 44 (.571)
Trail Making 5	24, 11.2 (1.3)	22, 10.6 (1.8)	1.219, 44 (.229)
Color–Word Interference 1	24, 8.4 (3.2)	22, 7.8 (2.8)	0.630, 44 (.532)
Color–Word Interference 2	24, 9.6 (2.6)	22, 8.3 (3.6)	1.436, 44 (.158)
Color–Word Interference 3	24, 8.8 (3.3)	22, 7.2 (3.7)	1.499, 44 (.141)
Color–Word Interference 4	24, 7.3 (3.7)	22, 6.6 (3.7)	0.561, 44 (.577)
IVA-CPT			
FSAQ	24, 55 (38)	22, 62 (38)	−0.556, 44 (.581)
AAQ	24, 59 (37)	22, 65 (34)	−0.577, 44 (.567)
VAQ	24, 63 (37)	22, 68 (38)	−0.471, 44 (.640)
FSRCQ	24, 66 (27)	22, 70 (24)	−0.430, 44 (.669)
ARCQ	24, 68 (29)	22, 71 (27)	−0.231, 44 (.818)
VRCQ	24, 72 (24)	22, 77 (18)	−0.840, 44 (.405)

Note. SRC = standard rehabilitation care; IM = interactive metronome; WTAR = Wechsler Test of Adult Reading; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; WAIS-IV = Wechsler Adult Intelligence Scale–Fourth Edition; D-KEFS = Delis–Kaplan Executive Functioning System; IVA-CPT = Integrated Visual and Auditory Continuous Performance Test; FSAQ = Full Scale Attention Quotient; AAQ = Auditory Attention Quotient; VAQ = Visual Attention Quotient; FSRCQ = Full Scale Response Control Quotient; ARCQ = Auditory Response Control Quotient; VRCQ = Visual Response Control Quotient.
* Trend toward significance.

pooled baseline measures and the posttreatment IM group, and the differences in estimated marginal means between the IM group and the SRC group at posttreatment for all neuropsychological tests.

Results of unadjusted analyses showed significant posttreatment group differences for RBANS Attention ($p = .044$), Immediate Memory ($p = .019$), and Delayed Memory ($p = .031$) index scores. A trend toward significance was also found for D-KEFS Trail Making Condition 1, visual scanning ($p = .063$).

Adjusted analyses are presented in Table 4. These models adjusted for individual differences in age, education, severity of worst injury, number of blast exposures, PTSD diagnosis, military occupational specialty, number of days between assessments, number of social work counseling visits, and number of speech therapy sessions received between assessments. Effect sizes (Cohen's *d*) were calculated using the difference in estimated marginal means between the IM and SRC groups at posttreatment, with the unadjusted posttreatment standard deviations for each group.

The adjusted analyses showed significant differences for RBANS Immediate Memory ($p = .020$, $d = 0.768$), with the IM group showing significantly greater improvement at Time 2 than the SRC group. We also found a significant difference between groups at posttreatment on D-KEFS Color–Word Interference Condition 1, color naming ($p < .001$, $d = -0.804$), also in favor of greater improvement in the IM group. Both of these effects are in the "large" range of effect size (Ferguson, 2009).

The adjusted analyses also showed trends toward significance for WAIS-IV Digit–Symbol Coding ($p = .055$, $d = 0.630$) and Symbol Search ($p = .061$, $d = 0.478$) subtests, as well as D-KEFS Trail Making Condition 5, motor speed ($p = .060$, $d = -0.790$). All of these trends toward significance favored the IM group, and fall within the medium and large ranges of effect size (Ferguson, 2009).

We also note that, even though no other tests remained statistically significantly different between the groups at posttreatment after adjustment for multiple comparisons, 21 of the 26 tests evaluated showed mean differences favoring the IM group at the posttreatment time point (binomial probability = .00098, see Figure 2). Several of these measures showed medium-range effect sizes (e.g., RBANS Attention and Delayed Memory indices,

Table 3
Unadjusted Neuropsychological Test Performance Pairwise Mean Differences for Raw Scores and GEE Significance Levels at Posttreatment for IM Versus Pooled Baseline and IM Versus SRC

Neuropsychological test	Mean difference (*SE*)[a]		IM–SRC *df* (*p*)
	IM pooled baseline	IM–SRC	
RBANS indices			
Attention	10.13 (3.16)***	9.38 (4.67)*	1 (.044)
Immediate Memory	18.17 (3.06)***	9.14 (3.90)**	1 (.019)
Delayed Memory	7.85 (3.06)**	8.34 (3.85)*	1 (.031)
Language	12.37 (2.26)***	5.65 (4.33)	1 (.192)
Visuospatial/Constructional	−3.57 (3.03)	0.93 (4.33)	1 (.829)
WAIS-IV subtests			
Digit Span Forward	0.45 (0.56)	0.01 (0.76)	1 (.994)
Digit Span Backward	1.21 (0.49)*	0.81 (0.65)	1 (.210)
Digit Sequencing	0.83 (0.66)	0.54 (0.75)	1 (.472)
Letter–Number Sequencing	0.45 (0.87)	−0.91 (0.99)	1 (.357)
Symbol Search	3.98 (1.29)*	1.53 (1.52)	1 (.314)
Digit–Symbol Coding	10.62 (2.78)***	5.46 (3.55)	1 (.125)
D-KEFS subtests			
Trail Making 1	−4.34 (1.17)***	−3.30 (1.77)†	1 (.063)
Trail Making 2	−7.54 (2.54)**	−2.74 (3.28)	1 (.404)
Trail Making 3	−7.70 (2.25)**	−3.99 (2.94)	1 (.174)
Trail Making 4	−4.45 (7.20)	3.06 (8.70)	1 (.726)
Trail Making 5	−7.57 (1.37)***	−2.81 (1.95)	1 (.150)
Color–Word Interference 1	−4.79 (1.28)***	−3.00 (2.34)	1 (.200)
Color–Word Interference 2	−2.92 (0.68)***	−0.69 (1.70)	1 (.687)
Color–Word Interference 3	−4.73 (3.57)	1.90 (4.73)	1 (.653)
Color–Word Interference 4	−9.62 (4.55)*	5.65 (6.02)	1 (.348)
IVA-CPT			
FSAQ	8.23 (8.06)	1.69 (9.98)	1 (.866)
AAQ	12.24 (7.21)†	4.67 (9.17)	1 (.610)
VAQ	−0.22 (8.48)	−4.22 (6.96)	1 (.940)
FSRCQ	7.67 (6.31)	−1.75 (7.50)	1 (.815)
ARCQ	13.15 (4.08)**	1.13 (5.71)	1 (.844)
VRCQ	1.08 (6.42)	−2.82 (7.76)	1 (.717)

Note. GEE = generalized estimating equation; SRC = standard rehabilitation care; IM = interactive metronome; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; WAIS-IV = Wechsler Adult Intelligence Scale–Fourth Edition; D-KEFS = Delis–Kaplan Executive Functioning System; IVA-CPT = Integrated Visual and Auditory Continuous Performance Test; FSAQ = Full Scale Attention Quotient; AAQ = Auditory Attention Quotient; VAQ = Visual Attention Quotient; FSRCQ = Full Scale Response Control Quotient; ARCQ = Auditory Response Control Quotient; VRCQ = Visual Response Control Quotient.
[a] Estimated marginal means based on original scale of raw values.
† Trend toward significance. * Significant at $p = .05$. ** Significant at $p = .025$. *** Significant at $p = .001$.

WAIS-IV Digit Span Backward and Letter–Number Sequencing, as well as D-KEFS Trail Making Condition 3). See Table 4 for details.

Of note, no significant group differences were observed for any IVA-CPT subscales, which are intended to be measures of sustained vigilance and response inhibition (IVA Attention and Response Control quotients, respectively; Tinius, 2003).

Discussion

Although this report concerns a preliminary analysis of results from an incomplete sample, these findings are promising, and awaiting resolution of administrative delays would postpone this report for more than a year. Therefore, we took this opportunity to share the preliminary findings as they exist at this time. Among soldiers treated with IM therapy in this study, there were some significant benefits measured by performance on well-defined cognitive tests, relative to those who received standard care without IM. Although the majority of individuals who sustain mTBIs recover fully without treatment, it is clear that some do not; and this may be of particular concern among those who have sustained more than one head injury, under potentially deadly circumstances (Brenner et al., 2010; Cooper et al., 2010; Cooper et al., 2011; Hartikainen et al., 2010; Luethcke et al., 2011; Roebuck-Spencer et al., 2012; Terrio, Nelson, Betthauser, Harwood, & Brenner, 2011; Vanderploeg et al., 2007; Zakzanis et al., 2011). It was a subset of this last group of individuals with whom this study was concerned. Our sample was referred from an Army community hospital for cognitive difficulties and postconcussive symptoms following blast-related mild-to-moderate TBI, irrespective of comorbid PTSD diagnosis. Given that the average time since injury for this sample was approximately twenty-nine months, spontaneous symptom resolution was unlikely. Although cognitive rehabilitation has been shown to be generally effective for moderate-to-severe TBI, we are aware of no other study demonstrating

Table 4
Adjusted Neuropsychological Test Performance Pairwise Mean Differences for Raw Scores and GEE Significance Levels at Posttreatment for IM Versus Pooled Baseline and IM Versus SRC

Neuropsychological test	Mean difference (*SE*)[a]		IM–SRC *df* (Sidak *p*)[b]	Cohen's *d*[c]
	IM pooled baseline	IM–SRC		
RBANS indices				
Attention	12.13 (3.53)**	10.13 (5.57)	1 (0.248)	.511
Immediate Memory	19.11 (3.69)***	12.20 (4.44)**	1 (0.020)	.768
Delayed Memory	7.83 (3.48)	8.11 (4.20)	1 (0.198)	.527
Language	11.29 (2.27)***	5.16 (5.55)	1 (0.641)	.349
Visuospatial/Constructional	−2.38 (3.27)	0.24 (4.23)	1 (0.998)	.016
WAIS-IV subtests				
Digit Span Forward	0.56 (0.62)	0.84 (0.72)	1 (0.809)	.317
Digit Span Backward	1.89 (0.58)**	1.39 (0.78)	1 (0.267)	.593
Digit Sequencing	1.85 (0.63)**	1.43 (0.74)	1 (0.198)	.588
Letter–Number Sequencing	0.53 (0.93)	−0.69 (1.11)	1 (0.952)	−.189
Symbol Search	5.54 (1.28)***	3.29 (1.52)†	1 (0.061)	.478
Digit–Symbol Coding	13.34 (2.86)***	9.41 (3.84)†	1 (0.055)	.630
D-KEFS subtests				
Trail Making 1	−3.94 (1.35)**	−3.21 (1.95)	1 (0.345)	−.492
Trail Making 2	−8.98 (2.94)**	−4.62 (4.03)	1 (0.441)	−.435
Trail Making 3	−9.96 (2.26)***	−6.54 (3.46)	1 (0.215)	−.626
Trail Making 4	−3.88 (8.80)	1.17 (10.81)	1 (0.993)	.042
Trail Making 5	−9.51 (1.48)***	−4.70 (2.18)†	1 (0.060)	−.790
Color–Word Interference 1	−5.50 (0.84)***	−6.60 (1.16)***	1 (0.000)	−.804
Color–Word Interference 2	−3.29 (0.57)***	−3.36 (2.52)	1 (0.554)	−.631
Color–Word Interference 3	−6.24 (3.41)	−2.73 (3.83)	1 (0.725)	−.173
Color–Word Interference 4	−7.81 (4.41)	0.07 (5.85)	1 (1.000)	.004
IVA-CPT				
FSAQ	5.43 (8.47)	−.22 (11.19)	1 (1.000)	−.006
AAQ	12.49 (7.32)	2.96 (9.94)	1 (0.945)	.085
VAQ	−4.75 (9.83)	−2.74 (12.82)	1 (0.999)	−.071
FSRCQ	12.84 (3.65)**	7.26 (6.51)	1 (0.707)	.299
ARCQ	14.91 (3.55)***	5.77 (6.54)	1 (0.613)	.297
VRCQ	6.81 (3.86)	7.18 (7.10)	1 (0.776)	.284

Note. GEE analyses adjusted for the following subject-level covariates: age, education, severity of worst injury, number of blast exposures, posttraumatic stress disorder diagnosis, military occupational specialty, number of days between assessments, number of social work sessions, and number of speech therapy sessions received between assessments. GEE = generalized estimating equation; SRC = standard rehabilitation care; IM = interactive metronome; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; WAIS-IV = Wechsler Adult Intelligence Scale–Fourth Edition; D-KEFS = Delis–Kaplan Executive Functioning System; IVA-CPT = Integrated Visual and Auditory Continuous Performance Test; FSAQ = Full Scale Attention Quotient; AAQ = Auditory Attention Quotient; VAQ = Visual Attention Quotient; FSRCQ = Full Scale Response Control Quotient; ARCQ = Auditory Response Control Quotient; VRCQ = Visual Response Control Quotient.

[a] Estimated marginal means based on original scale of raw values. [b] Sequential Sidak adjustment for multiple comparisons was used for all analyses. [c] Cohen's *d* calculated using the posttreatment group IM–SRC differences in estimated marginal means with unadjusted posttreatment standard deviations for each group on each measure.

† Trend toward significance. * Significant at $p = .05$. ** Significant at $p = .025$. *** Significant at $p = .01$.

cognitive benefits for those with persisting chronic cognitive difficulties following one or more mild injuries.

Cognitive Functioning at Prerandomization

The primary indicator of preinjury intellectual functioning in this study battery was the WTAR. On this measure, the sample average was slightly above the normative value for the population average, indicating overall average range preinjury intellectual ability. In comparison to this reference point, the sample as a whole evidenced mild levels of cognitive difficulties at the prerandomization time point. We are aware of issues related to effort on testing with this population (Cooper et al., 2011). Though the TOMM has some limitations, it is generally regarded as an adequate effort measure, and a "failing" score on the TOMM was an exclusion criterion for participation in this study (Tombaugh, 1997). The observed decrements in relative performance were generally consistent with the participant's symptom self-reports and the severities of the injuries sustained, as documented in medical records.

In general, neurocognitive test scores fell less than 1 *SD* below expected levels of performance in this sample. This is consistent with other reports on changes in cognitive functioning following mTBI (Bogdanova & Verfaellie, 2012; Ozen & Fernandes, 2012; Roebuck-Spencer et al., 2012). Also consistent with previous reports, this generally lower-than-expected performance was con-

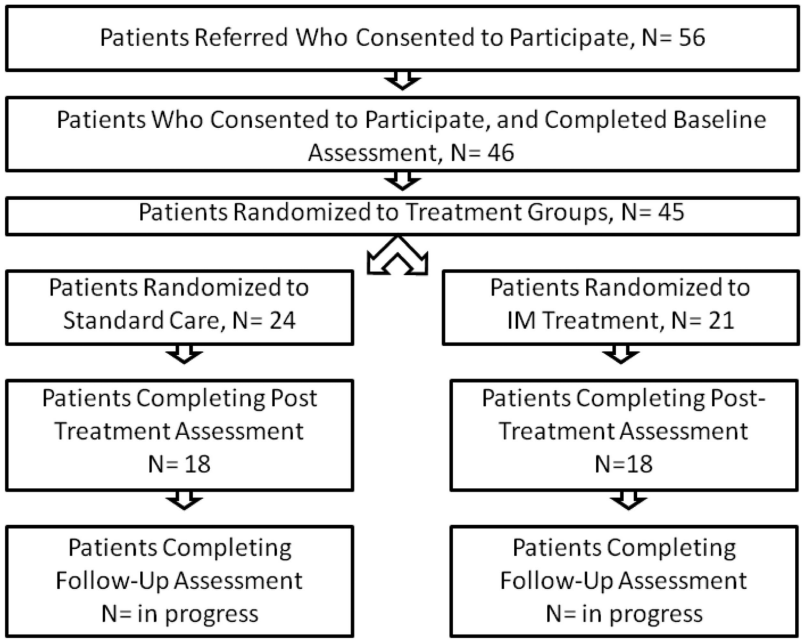

Figure 1. Participant flow. IM = interactive metronome.

sistent across several functional domains, with few exceptions. More pronounced decrements in performance were observed in tasks requiring attention switching. This is evident in prerandomization performance on the WAIS-IV Digit–Symbol Coding subtest, which requires either constant reference to information kept in working memory, or physical switching between the coding key and the individual items (Larson, Farrer, & Clayson, 2011; Nelson et al., 2009). Increased task complexity and cognitive flexibility also resulted in decreased performance in the D-KEFS Color–Word Interference Trial 4, which requires inhibition of the prepotent response on some items, and rule set switching to provide the prepotent response on others (Bagiella et al., 2010).

A similar decrement in performance was present in tasks requiring sustained vigilance and behavioral inhibition, as in the IVA-CPT, which is an integrated visual and auditory go–no go task of approximately 20 min in duration, in which all of the subscale averages for the group are below the expected level (normative average is 100; Tinius, 2003). This finding is also consistent with previous literature that has reported on this test (Tinius, 2003). Less dramatic, but notable decreases in average scores for the sample were present in the majority of RBANS indices, with the exception of the Visuospatial/Constructional Index, on which the sample scored in the expected range (see Figure 2), consistent with apparent sparing of visuospatial functioning also evidenced by D-KEFS Trail Making performance near or at the expected range across the five trials (see Table 2).

Treatment Effects

Several measures showed statistically significant, or borderline significant changes (trends), with clinically meaningful magnitudes in the IM treatment group relative to the SRC group at Time 2. Principally, the RBANS Immediate Memory index showed a meaningful increase that brought the average scores for those in the IM group to within the expected range in relation to their preinjury intellectual functioning. This finding is in the context of the prerandomization means being somewhat (though not significantly) lower for that group.

Other tests showed meaningful magnitudes of change, though they failed to reach statistical significance in this small sample. Estimated gains of 10 and eight points on Attention and Delayed Memory indices suggest possibly promising effects on cognition among those receiving IM therapy. WAIS-IV Digit–Symbol Coding and Symbol Search subtests showed borderline significant improvement, again, with impressive associated effect sizes (d = .630 and d = .478, respectively) as did motor speed and planning, in D-KEFS Trail Making Condition 5 (d = .790). We also noted that small effect sizes, which may prove functionally important in support of other cognitive processes, were also evidenced. For instance, Digit Span Backward (d = .593) and Letter–Number Sequencing (d = .588) both failed to reach statistical significance in this sample, but indicate possible differential improvements in working memory, which supports a wide range of other complex cognitive functions.

Of note, no significant effects were observed on IVA performance. This suggests that "attention" is not a unitary construct, and that sustained attention may require different mechanisms than momentary cognitive control and working memory access required for Digit Span Backward and Digit–Symbol Coding tasks, which are closely related components of the RBANS Attention index, all of which evidenced treatment effects in the medium effect size range. Previous work in the area of specialized attention networks that subsume different types of attention has suggested this is likely (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). Alternatively, it could be that this test is actually measuring some

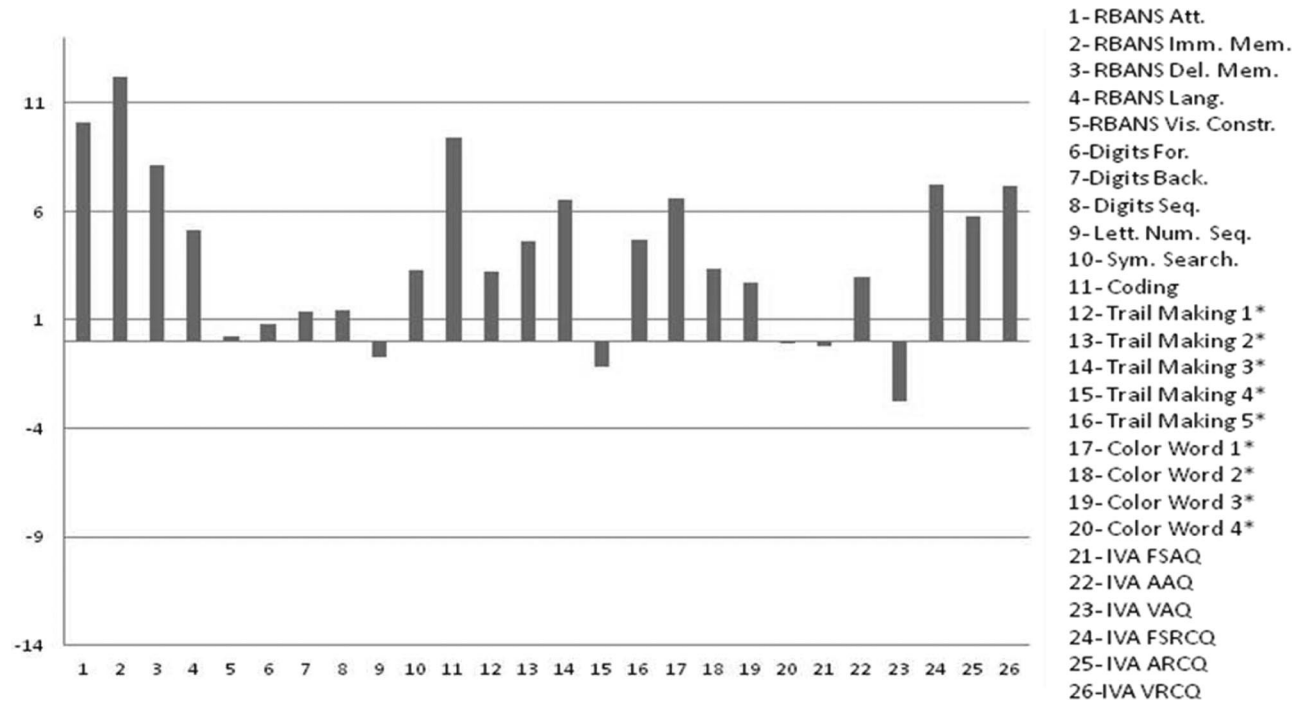

Figure 2. Posttreatment mean differences (IM – SRC) of estimated marginal means for cognitive measures. IM = interactive metronome; SRC = standard rehabilitation care; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; Att. = Attention; Imm. Mem. = Immediate Memory; Del. Mem. = Delayed Memory; Lang. = Language; Vis. Constr. = Visuospatial/Constructional; For. = Forward; Back. = Backward; Seq. = Sequencing; Lett. Num. Seq. = Letter–Number Sequencing; Sym. = Symbol; Coding = Digit–Symbol Coding; WAIS-IV = Wechsler Adult Intelligence Scale–Fourth Edition; D-KEFS = Delis–Kaplan Executive Functioning System; IVA = Integrated Visual and Auditory Continuous Performance Test; FSAQ = Full Scale Attention Quotient; AAQ = Auditory Attention Quotient; VAQ = Visual Attention Quotient; FSRCQ = Full Scale Response Control Quotient; ARCQ = Auditory Response Control Quotient; VRCQ = Visual Response Control Quotient. * Time-to-completion scored test: order of subtraction reversed to be consistent with scaling of other measures.

"integrated" form of attention, as the scale title suggests (Tinius, 2003), and that this sustained, or integrated, process is somewhat more difficult to affect through rehabilitation efforts. This topic certainly warrants further investigation.

Strengths and Limitations

Among the strengths of this investigation is the nature of the intervention being evaluated. Because IM is largely computer-based and -administered, standardization of the treatment protocol under investigation was greatly facilitated. All participants in the IM group received the same program of sessions, with the same number of repetitions, the same levels of feedback, and the same degree of interpersonal contact. This situation would be extremely difficult to replicate with therapist-intensive modes of rehabilitation interventions.

Another strength related to the treatment delivery is that it was provided in a highly ecologically valid manner. Participants randomized to IM treatment underwent their training sessions in a fully functioning rehabilitation gym, with other injured service members performing other rehabilitation exercises all around them. Service delivery was purposely integrated into the functioning rehabilitation services clinic to more closely resemble circumstances that may be present in real-world implementation of the intervention. The Defense and Veterans Brain Injury Center has a limited number of sites that are integrated into functioning brain injury treatment clinics, embedded within the Army Medical Command. Due to this association, we were provided with the support of the chain of command, access to potential participants, and space within an Army hospital facility where treatments were provided.

Given the proportion of participants in each group who had a comorbid diagnosis of PTSD (n = 7, or 38% of each group), it must be considered that IM training may have had some effect on emotional functioning, and thereby potentially affected cognition. In the initial randomized trial of IM among children with ADHD, emotional regulation was noted as an outcome showing a significant treatment effect (Shaffer et al., 2001). Regrettably, emotional functioning was not directly measured immediately posttreatment as a focus of our study.

Another potential limitation of our design is that participants in the experimental group attended 15 more clinical appointments than those in the standard of care group. IM therapy is very

labor-intensive for the patient, and it is possible that improved self-efficacy resulting from this expenditure of effort plays some role in perceived improvements.

The principal limitation of this study is due to its implementation as a pilot study aimed at determining the feasibility of delivering this intervention to a military population, within the military medical environment, and to estimate the probable effect size of the intervention in this population with this type of injury history. Because this was a pilot study, the sample was too small to detect even medium-sized effects, of which there appeared to be several. Also, power calculations did not account for attrition; therefore, although the projected sample of 25 participants in each group was nearly met for recruitment at the time of this report, it proved insufficient with the observed drop-out rate of about 20% in the SRC group and about 15% in the IM group. It should be noted, however, that only two subjects from the treatment group dropped out of the study during the treatment phase, one due to hospitalization for suicidal ideation, and one due to life issues who was lost to follow up. In the standard of care group, there were seven subjects who dropped, only two of whom were due to deployment or change of duty assignment. This may indicate that the active treatment regimen was well tolerated.

Another limitation of our study is that the assessments at Time 2 were not conducted by an independent psychometrist who was blind to the treatment condition of participants. Indeed, in behavioral intervention randomized controlled trials, participants themselves are aware of their condition assignment, which can affect their confidence, emotional response to the testing situation, and a host of other factors. Every effort was made to reduce any bias stemming from this awareness, including provision of consultation to clinical providers for treatment options for those in the SRC group. However, the fact remains that posttreatment assessments were not conducted in a blinded fashion.

Another limitation of this trial is due to the logistics of the intervention. We were unable to standardize the intensity of the treatment across all participants receiving IM because of scheduling limitations present in working with an active duty population, many of whom were not on "light duty" designations, and still had full responsibilities of their jobs. Although the target treatment intensity was a 1-hr session, 3 days a week, for a duration of 35 days, in practice, the mean duration of the treatment phase for the IM group was 54 days, with significant variability in adherence to this schedule due to factors over which the investigators had no control. However, the principle aim of this study was to determine the effects of IM therapy on cognitive recovery, not to establish a dose–response relationship between recovery and intensity and duration of treatment sessions. Nor was this investigation aimed at determining the effects of single versus multiple concussions on cognition. Such studies may prove fruitful avenues of future research, but would differ from the current investigation significantly in both sample size and design characteristics.

Finally, an issue of potential relevance to mechanisms underlying the observed effects is that we did not formally assess our participants for history of ADHD or history of depressive disorder. Although it is unlikely that the observed prerandomization differences from expected cognitive functioning are accounted for by unreported or undiagnosed ADHD or depression that may have existed prior to injury, there is likely some base rate of this disorder among service members, and we did not formally assess its possible role in their observed cognitive functioning.

In light of the above limitations, and, to some extent, even the strengths, the generalizability of the findings presented here may be imperfect. It may be, as has been suggested in the literature, that blast-related brain injuries represent a distinct form of TBI. If this is the case, the effectiveness of the intervention in individuals with other mechanisms of injury may differ from that observed with these participants. There may also be limitations on age, in that our sample is of a somewhat narrow age range, and the findings may not be generalizable to children or to those of advancing age. Our sample was also composed entirely of men, and although it is unlikely that there are sex differences in neuroplasticity, we cannot comment on the appropriateness of this treatment for women.

Future Directions for Research

Future research on this intervention could focus on its implementation with a larger sample, to more accurately assess effect sizes, and to evaluate its applicability to other populations with cognitive difficulties due to injury, illness, or even unintended side effects of other drug treatments (e.g., chemotherapy side effects). A key question that we were unable to address in the current sample concerns the effect of treatment intensity (i.e., number of sessions per week) on outcomes. There is currently no empirically supported intensity or duration for treatment with IM. The training schedule and duration in this study was based on recommendations from the manufacturers, and appeared sound from a neurobiological, theoretical standpoint. However, more work could be done to determine what optimal training intensity may be. As expected, all participants in the treatment group improved their response times to the metronome beat over all exercises. A further analysis of the slope of performance improvement may inform dose–response and treatment-intensity parameters. However, that analysis would likely require a larger sample size, and should be designed using a different experimental paradigm.

As indicated in the introduction, we hypothesized that the observed treatment effects would not be due solely to the factors outlined in the limitations above, and that there would be real neurophysiological changes that likely underlie a portion of the cognitive improvements we observed. Analyses of electrocortical data collected immediately after the assessment sessions (same day) as part of this investigation are currently underway, and findings will be reported later. Sponheim et al. (2011) reported evidence of disrupted cortical functional connectivity following blast-related brain injury, and we hypothesize that the processes involved in IM training are very dependent on integration across a number of functional connectivity networks. Continuing efforts in the analysis of the physiological data will be directed toward evaluation of changes in functional connectivity following IM treatment.

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(*Appendix follows*)

Appendix

Standardized Interactive Metronome Intervention Exercise Schedule by Session Number

S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15
Pre LFA	SFT	SFT	SFT	SFT	SFT	SFT	SFT	SFT	SFT	SFT	SFT	SFT	SFT	SFT
	BH-500	BH-500	BT-400	BT-400	BH-500	Mid LFA	RH/LT-200	BT-200	BH-1,500	RH/LT-1,000	BH-2,000	BH-2,000	BH-2,000	BT-300
SFT	BT-300	BT-400	BH-1,000	BH-1,200			LH/RT-200	BH-2,000						BHeels-300
BH-200*					BT-1,000	BHeels-200								
BH-300	RH-300	RH/LT-500				LT-200	BHeels-200							BH-1,000
	LH-300					RT-200	BH-1,500			BT-500				
BT-300	BT-300	LH/RT-500	RH/LT-400	BRTL T-100	BLTR T-100	BH-1,000			RH-300	BHeels-500				
LH-300	RT-300	LH-300	LH/RT-300	BLTR T-100	BRTL T-100									
				BHeels-200	RH/LH-300	BT-200			BHeels-300					Post LFA
	LT-300	BHeels-200	RH-300	BT-300					BT-300	LH-400	BHeels-400	RH/LT-200	LH/RT-200	
							LH-200	BHeels-200				LH/RT-200	RH/LT-200	

Note. S = session; LFA = Long-Form Assessment (30 repetitions of all 13 exercises with no guide sounds); SFT = Short-Form Test (54 repetitions both hands, without guide sounds followed by 54 repetitions both hands with guide sounds); BH = both hands; BT = both toes; LH = left hand; RH = right hand, LT = left toe; RT = right toe; BHeels = both heels; LHeel = left heel; RHeel = right heel; BRTLT = balance on right foot and tap left toe; BLTRT = balance on left foot and tap right toe.

* No guide sounds.

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