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Effects of a rapid-resisted elliptical training program on motor, cognitive and neurobehavioral functioning in adults with chronic traumatic brain injury

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Abstract

This small clinical trial utilized a novel rehabilitation strategy, rapid-resisted elliptical training, in an effort to increase motor, and thereby cognitive, processing speed in ambulatory individuals with traumatic brain injury (TBI). As an initial step, multimodal functional abilities were quantified and compared in 12 ambulatory adults with and 12 without TBI. After the baseline assessment, the group with TBI participated in an intensive 8-week daily exercise program using an elliptical trainer and was reassessed after completion and at an 8-week follow-up. The focus of training was on achieving a fast movement speed, and once the target was reached, resistance to motion was increased in small increments to increase intensity of muscle activation. Primary outcomes were: High-Level Mobility Assessment Tool (HiMAT), instrumented balance tests, dual-task (DT) performance and neurobehavioral questionnaires. The group with TBI had poorer movement excursion during balance tests and poorer dual-task (DT) performance. After training, balance reaction times improved and were correlated with gains in the HiMAT and DT. Sleep quality also improved and was correlated with improved depression and learning. This study illustrates how brain injury can affect multiple linked aspects of functioning and provides preliminary evidence

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

that intensive rapid-resisted training has specific positive effects on dynamic balance and more generalized effects on sleep quality in TBI.

Keywords

Coordination; Motion; Cognition; TBI; Exercise

Introduction

Traumatic brain injury (TBI) is a significant and prevalent public health problem, with 3 million people, approximately 1.1 % of the US population, reported by the Centers for Disease Control living with a disability in one of more functional domains as a result of a TBI (Coronado et al. 2010). A recent study suggests that the true number who experience chronic residual effects event may be even higher (Dams-O'Connor et al. 2014). Although many with TBI “recover” to the point where they walk independently (Katz et al. 2004) and return to work, significant deficits in cognitive and emotional/behavioral functioning as well as higher-level motor functioning may persist (Basford et al. 2003). Of these, motor deficits have arguably been the least well studied in this population. Consequently, evidence supporting effectiveness of current motor rehabilitation strategies in TBI have been limited (Bland et al. 2011; Hellweg and Johannes 2008). Recent studies investigating intensive task-specific or functionally based mobility and balance training protocols have demonstrated some effectiveness in improving aspects of motor functioning directly related to the training in TBI (Katz-Leurer et al. 2009; Bisson et al. 2007; Ustinova et al. 2014; Peters et al. 2014) and have further associated postural gains with improvements in cerebellar microstructure (Drijkoningen et al. 2014).

Motor symptoms commonly reported in TBI include dizziness and fatigue which are difficult to detect on routine clinical examination. Some deficits may not emerge until individuals are challenged with a concurrent task, e.g., walking and talking. Objective, instrumented gait and balance tests and dual-task assessments are far more sensitive measures than physical examination alone in verifying and quantifying these subjective complaints (Basford et al. 2003; Kaufman et al. 2006). These measures could also be useful for exploring the coexistence of motor impairments with cognitive processing difficulties, depression, anxiety, sleep disorders and other neurobehavioral problems in TBI.

Greater understanding of the *multimodal* consequences of a brain injury and effects of motor training is of critical importance. Evidence from animal injury models has shown that even short bouts of exercise can decrease neuronal loss by reducing inhibition of myelin production that occurs post-injury (Chytrova et al. 2008) and both human and animal studies support its role in enhancing neuroplasticity through up-regulation of neurotrophic factors (Cotman and Berchtold 2002). In addition to direct physical and physiological effects, exercise has been shown to have positive effects on cognitive processing, memory and other neurobehavioral symptoms in multiple populations (Colcombe and Kramer 2003; Baker et al. 2010; Tanaka et al. 2009; Carruthers et al. 2014).

A symptom frequently reported in TBI is slowing of mental and/or motor reaction time or mental processing time. Slowed responsiveness could be a direct sign of poorer cortical connectivity across brain regions which may be a common mechanism that underlies deficits in balance, coordination, attention and cognitive processing, among others (Walker and Pickett 2007; Ghajar and Ivry 2008; McNamara et al. 2007). Sosnoff et al. (2008) noted an increased association between motor and cognitive functioning after brain injury, with mental reaction time, memory and balance difficulties most commonly associated in mild TBI. In a subsequent study, Broglio found the cognitive symptom of “feeling mentally foggy” to be significantly associated with motor reaction time (Broglio et al. 2009). Suggestion of a possible *causal* relationship was provided by an intervention study demonstrating improvements in movement and reaction time and scores on learning tasks after a single bout of exercise in a virtual reality environment (Grealy et al. 1999). Similarly, we hypothesized here that a novel rehabilitation paradigm, specifically fast-paced elliptical training involving all four extremities, would lead to improved motor reaction time with possible changes in cognitive processing speed as well. A small clinical trial with multimodal outcomes was designed to preliminarily test effectiveness of the intervention prior to its implementation in a larger controlled trial. Secondary hypotheses were that a sample of subjects with TBI who were released from medical or rehabilitative care would still demonstrate residual deficits in multiple domains compared to controls and that motor deficits would correlate with deficits in other aspects of functioning. We also predicted that gains from training would be maintained at follow-up. Based on these hypotheses, our specific objectives were to: (1) identify deficits in balance, mobility, cognitive and behavioral functioning in adults with TBI compared to adults without TBI; (2) interrelate deficits across functional domains; and (3) quantify effects of fast-paced motor training on motor performance, movement speed and reaction time, as well as cognitive processing and neurobehavioral functioning in ambulatory adults with TBI.

Methods

Participants

Thirty-three adults were screened for participation by the physician who performed the intake history and physical examination, 31 were enrolled, and of those, 24 completed the study: 12 (mean age 31.3 ± 9.4) with a diagnosis of TBI at least 6 months after injury and a comparison group of 12 healthy volunteers (HV; mean age 32.5 ± 9.3). The age range was 19–44 years with five females and seven males per group. Inclusion criteria for subjects were: (1) ability to walk independently and safely without assistance as determined by clinical observation and patient report of no instability or history of falling when walking; (2) sufficient attention and cognition to complete assessments as determined by the intake physician; and (3) capability to provide informed consent. All participants provided consent to participate in the study approved by our institutional review board. Exclusion criteria were: (1) the presence of an injury to any extremity, or other medical condition that would affect motor function or the ability to perform the exercise program; (2) currently receiving medical care or therapy for symptoms related to TBI; (3) contraindications to having an MRI; and (4) plans to change medication or therapy during the study period that could affect mood, cognition or motor function. Two participants with TBI were excluded due to

cardiovascular diagnoses, and two more enrolled but withdrew due to busy travel schedules. Five healthy volunteers were withdrawn because of abnormal balance scores (i.e., their scores were 2 standard deviations away from a normative mean, as provided by Neurocom; the manufacturer of the balance testing equipment). Table 1 lists the characteristics of participants with TBI.

Procedures

All participated in an initial assessment session. Only those with TBI followed a home-based exercise program for 8 weeks after the first assessment. The second assessment was done after training and the third was after an 8-week follow-up period during which they were no longer exercising. All assessments were performed at a major research hospital in Maryland.

Intervention

For this novel training paradigm, the exercise device was an elliptical trainer requiring coordinated reciprocal movements of legs and arms and which was provided to the participant and delivered to the home. The primary emphasis of training was on achieving and maintaining a consistent relatively rapid pace (40–80 RPM or a cadence of 80–160 steps/min) the entire training session and to gradually increase this throughout the program. Previous work by Buster et al. (2013) showed that the comfortable cadence on an elliptical for those with TBI was less than for an age-matched group of adults without TBI (TBI mean was 84 versus 98 steps/min in the comparison group) and that cadence was relatively more impaired on the elliptical than during walking in the group with TBI. The goal here for utilizing the elliptical was not simply to practice walking per se as it has been recommended for by Buster et al. (2013), but as a means to practice moving all four limbs in a fast coordinated manner to stimulate the sensory pathways from the spinal cord to the sensorimotor cortex and its intracortical connections.

Mild resistance to leg motion was provided initially and progressively increased once they were able to maintain the target pace on average the entire exercise session. The resistance was mainly added to increase the level of muscle activation and thereby the intensity of sensory input to the spinal pathways. Participants were encouraged to maintain a smooth fast rhythm but not to exceed a moderate intensity (i.e., be able to talk easily while exercising). While we did not track heart rate during this study, we purposely aimed to keep the exertion level lower than that needed to reach a target heart rate that would be considered aerobic. All participants were instructed to exercise 5 days a week for 30 min, for 8 weeks. All recorded the length, average speed and resistance of each session on a paper log. Participants were monitored by phone the first week and every 2 weeks thereafter, progressing as advised. For example, if the patient could maintain their target cadence for 15 min and not exceed a low–moderate exertion level, then RPM increased by 5. In 2 weeks, if they were still able to handle that increased RPM, then resistance was increased by 1. Additionally, a sensor was attached to an elliptical pedal to record usage. Participants were instructed to not let anyone else use the device. When the device was returned, compliance data were downloaded from the sensor.

Outcome measures

Primary outcome measures of balance, mobility and cognitive/behavioral functioning were, respectively, *reaction time and movement excursion* during the limits of stability (LOS) test and *latency of response* during the motor control test (MCT) (NeuroCom SMART EquiTest®); the *High-Level Mobility Assessment Tool (HiMAT)*; (Williams et al. 2006); and the *Hamilton Depression Inventory (HAM-D)*. These were chosen as primary measures because they were expected to be sensitive to the type of intervention proposed in this study which focused on fast reciprocal coordination training. The LOS and MCT are standardized Neurocom balance tests that evaluate different aspects of balance control. The main difference between the LOS and the MCT is that the first provides information regarding voluntary control of balance for safe and independent everyday function (e.g., postural transitions, reaching for objects while standing), whereas the MCT provides information regarding automatic control of balance as a reaction to unexpected external disturbances (e.g., slipping and tripping). Secondary measures included: (1) additional balance measures from the LOS and Sensory Organization Test (SOT), which is another standardized NeuroCom balance test and provides information regarding sensory control balance (somatosensory, visual and vestibular); (2) temporal–spatial gait parameters including velocity, cadence, step length and elliptical cadence; (3) dual-task (DT) performance during word generation starting with a specific letter and subtraction tasks counting backwards by 3 s; (4) neuropsychological assessments including the Hopkins Verbal Learning Test-Revised (HVLt-R), finger tapping test (FTT), Pittsburgh Sleep Quality Index (PSQI); (5) other emotional/behavioral assessments including Beck Anxiety Inventory (BAI); and (6) PTSD Checklist-Civilian Version (PCL-C); (Blake et al. 1995). Examiners were not blinded; however, data from previous assessments were not available when collecting and/or processing each session's data to minimize bias.

Statistical analysis

Power analyses were based on historical data (Katz et al. 2004) showing improvement in LOS reaction time and MCT response latency after training. Given the within-subjects design and effect sizes reported, a sample size of 10 was determined sufficient to yield >80 % power to detect a small clinical effect ($d = 0.20$) in each. Normally, distributed data were analyzed with unpaired *t* tests to compare control versus TBI groups, and paired *t* tests to compare outcomes for the group with TBI before and training and at follow-up. Nonparametric tests were used for non-normally distributed data. A two-way analysis of variance (ANOVA) was used to compare single- versus dual-task performance before and after exercise. Pearson product–moment correlation was used for cross-domain associations between pretest measures within the TBI cohort and between change scores for the variables showing a significant difference after training with other measures within and across domains ($\alpha = 0.05$ for all tests).

Results

For objective 1, group differences were found in balance performance, specifically the LOS test, with those with TBI having more limited endpoint excursion in backwards and left directions expressed as a percent of their predicted limit (backwards: TBI = 71.6 ± 25.6 , HV

= 89.3 ± 11.4 , $p = 0.042$; left: TBI = 37.0 ± 18.8 , HV = 49.6 ± 12.5 , $p = 0.037$). They also had poorer dual-task performance, calculated as a cost function relative to single-task performance, on both motor and cognitive tasks during word generation ($p = 0.047$ and 0.045 , respectively), lower scores on HVLT-R total recall and higher scores (increased symptoms) on the PCL-C and HAM-D (HVLT-R: TBI = 39.63 ± 11.13 , HV = 53.18 ± 8.17 , $p = 0.004$; PCL-C: TBI = 30.1 ± 12.4 , HV = 9.6 ± 3.3 , $p = 0.02$, HAM-D: TBI = 4.90 ± 5.37 , HV = 1.08 ± 1.88 , $p = 0.04$). No other test scores or gait measures were different between groups.

The second objective was to explore relationships among domains in TBI. Strong links were identified between voluntary motor behaviors and cognitive and emotional measures at pretest. Interestingly, maximal and endpoint movement excursions during the LOS test had the strongest and most consistent relationships to both cognitive and emotional measures such that greater excursion forward was related to higher scores in verbal learning (HVLT-R total recall, $r = 0.74$, $p = 0.008$; HVLT-R delayed recall $r = 0.81$, $p = 0.003$), and greater excursion to the right was related to fewer depressive symptoms ($r = -0.63$, $p = 0.04$). Slower walking velocity was related to higher depression scores ($r = -0.65$, $p = 0.03$). Slower finger tapping rate, another speed-related voluntary motor task, was also related to higher depression scores ($r = -0.72$, $p = 0.04$) and poorer sleep quality ($r = -0.75$, $p = 0.048$). Finally, poorer dual-task performance, which utilizes both cognitive and motor brain resources, showed a strong relationship to higher anxiety ($r = 0.71$, $p = 0.02$).

The third and primary objective was to determine the effects of exercise on functioning in TBI. All subjects with TBI returned for the post-exercise assessment, but one subject was notably distraught at that assessment and had difficulty complying with the testing. Since her measured exercise compliance was less than 20 % and post-training data were considered unreliable due to her emotional state, we did not include her data in the post-intervention analyses. One other subject was not able to return for the follow-up assessment.

Exercise compliance as a group differed between the paper logs and sensor data and also varied widely across subjects, with more training sessions reported as completed (97.5 %) than recorded by the sensor (78 %). One subject did not return the log sheet and in another the sensor failed. Except for the subject noted above, mean compliance indicated by the sensor was greater than 80 %. The elliptical cadence training target of 80 steps/min was achieved by all subjects with a mean minimum cadence during training of 85.6 steps/min and maximum of 118.2.

Several motor outcomes improved after training. The MCT composite latency score and LOS reaction time backwards test were lower after training (faster reactions) with no change during follow-up. The only change in balance during follow-up was increased LOS forward endpoint excursion (EPE-F) (posttest 81.6 ± 13.4 , follow-up 91.3 ± 13.5 , $p = 0.001$). No changes were observed for secondary motor outcome measures (SOT, dual tasking, gait measures and elliptical cadence).

Table 2 shows mean values before and after training and corresponding p values. Figure 1 demonstrates individual changes in (MCT) and (LOS) reaction time. Note the direction of

improvement in balance is mainly positive. The HiMAT did not change as a result of training or during follow-up. However, individual improvement on the HiMAT was strongly related to a better MCT composite score ($r = -0.83$; $p = 0.02$) which in turn was strongly correlated with improved DT walking performance during word generation ($r = 0.78$; $p = 0.02$).

While the HAM-D did not improve after training, improvements were seen for the Pittsburgh Sleep Quality Index (PSQI), with a similar but nonsignificant trend for the Beck Anxiety Inventory (BAI). No changes were seen in other cognitive and emotional/behavioral measures after training or at follow-up. However, improvement on the PSQI was related to improved HAM-D scores ($r = 0.69$; $p = 0.04$) and higher HVLT-R delayed recall scores ($r = 0.70$; $p = 0.03$).

In cross-domain relationships, change in elliptical cadence after training was directly related to changes in total recall scores on the HVLT-R ($r = 0.72$; $p = 0.03$) suggesting a link between motor outcomes and short-term memory. HiMAT change scores were inversely related to changes on the PCL-C, such that improvements in mobility were related to lessening of PTSD symptoms ($r = -0.83$; $p = 0.01$). Greater gains in LOS excursion were related to lessening of anxiety ($r = -0.71$; $p = 0.02$) and depression ($r = -0.82$; $p < 0.01$).

Discussion

TBI is a heterogeneous group of disorders of varying etiology, severity, presentation, and prognosis. In this study, we enrolled individuals no longer receiving medical or therapeutic care and functioning well based on routine clinical tests. We utilized measures intended to challenge their capabilities to identify more subtle subclinical residual deficits. All were volunteers, so our sample may have been biased toward those who were still experiencing difficulties and therefore seeking additional interventions. With respect to baseline motor function, only balance performance measures were worse in the sample with TBI. Gait speed did not differ between groups, consistent with previous reports. Mobility limitations only seem to emerge when challenged with more complex functional tasks that involve higher-level skills and coordination or when sharing resources with cognitive domains (e.g., dual-task performance). This is relevant to everyday life which often involves the performance of several activities at the same time, each requiring brain resources that, if limited, deficiencies may emerge. Several emotional and cognitive impairments were also identified in the group with TBI.

The exercise program focused primarily on increasing the speed of reciprocal movements with the goal of improving motor reaction time through changes in brain pathways. The elliptical cadence utilized in this study would not be considered particularly fast for adults without TBI who may be exercising on the elliptical at a pace and resistance level high enough for aerobic conditioning, but the initial cadence was similar to that reported previously in TBI and did increase significantly throughout the training. The intervention did improve voluntary and automatic balance reactions in this small group of individuals with TBI. In fact, the only balance improvements were related to the speed of responses, with no improvement in excursion which was noted to be deficient at the onset. This suggests that

the speed of motor processing had improved as a task-specific effect of training. Those who showed faster automatic balance reactions after the training also tended to walk and talk faster and to perform higher mobility tasks faster. These associations further suggest that improvements in motor processing speed have the potential to translate into direct functional improvements.

We further examined and found associations among change scores across functional domains in the group with TBI; e.g., an association was found between higher balance scores and less depressive symptoms that may have been spurious given the multiple comparisons made. However, the finding of several, and in many cases moderately strong, associations across domains preliminarily supports possible multimodal effects that warrant further study. Multiple studies in diverse populations have evaluated the effect of exercise on depressive symptoms with a recent Cochrane review that identified 39 RCTs, 35 of which compared exercise to a control intervention, concluding that exercise was moderately more effective in reducing depression than control although the most robust trials suggested that the effect may be small (Cooney et al. 2013).

The lack of improvement in DT after intervention is similar to the literature, which shows that dual-task performance only improves if the intervention is specific to the testing paradigm; e.g., a small study in individuals with brain injury found improvements in walking and talking following specific training involving walking and talking (Evans et al. 2009). Another study in the elderly compared single- versus dual-task balance and walking training and found improvements in dual tasking only in those who practiced dual tasking, not in those who practiced each task in isolation (Silsupadol et al. 2009). Interestingly, a recent study in recreational athletes found no benefits of dual-task over single-task training on balance or complex attention (Ingriselli et al. 2013); however, these findings warrant replication in neurologically impaired and elderly populations. Finger tapping speed did not improve, but may be related to the fact the movement speed was not trained distally. Gait temporal-spatial parameters also did not improve, but this cohort already had a gait speed within normal prior to exercising so ceiling effects were likely.

Exercise has well-known generalized benefits on sleep and emotional health as well as on cognitive functions such as memory (Ingriselli et al. 2013; Newman and Motta 2007). Sleep did improve here and was correlated with positive changes in the HAM-D and HVLTD-DR. While it is encouraging that some positive benefits were found from this short training protocol in an already fairly high functioning group and we anticipate that benefits would continue to accumulate with continued exercise, a larger trial is clearly warranted. No significant functional decline or adverse effects were noted after training or at follow-up, so these results support recommendations for regular enhanced physical activity in those with TBI (Wise et al. 2012). Exercise is now being advocated earlier in rehabilitation and may potentially have greater benefit as well as neuroplastic effects, but clear guidelines still need to be established so that neural recovery is enhanced rather than disrupted (Griesbach 2011). Although potential neuroplastic effects of exercise were not addressed here, we hope to glean further insights through analysis of functional brain imaging data also collected pre- and post-training as part of this study.

Limitations

Limitations are the inclusion of multiple outcomes due to the exploratory nature, the relatively short training duration, small sample and the lack of a control group that did not exercise, although we would not typically expect those with chronic TBI to improve in function so long after injury. Because this was a pilot study on a novel intervention, we chose to study a broad range of outcomes and to not correct for multiple comparisons here so as not to miss any possible, albeit small, effects across domains that should be included as outcome measures in a future more focused trial if these data were found to be promising.

Conclusions

This study corroborated previous findings of interrelationships among deficits across multiple functional domains in chronic TBI. Perhaps of even greater import, change scores across domains after training were strongly related. Task specificity of the speed-focused training was seen by positive changes in balance reaction time with no change in impaired excursion. This is the first training study to our knowledge focused specifically on movement speed in TBI, and positive effects here warrant further examination in larger and longer controlled trials. These results further support the importance of moderate (likely below the target heart rate needed to be considered aerobic) exercise in acute and chronic TBI even for those with minimal motor involvement because of its potential wide-ranging effects on neuroprotection and neural recovery as well as multi-domain functional deficits in TBI.

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Fig. 1.

Individual changes from pretest to posttest on the motor control test (MCT) and **b** limits of stability reaction time backwards (LOS RT-B). Note that the values decrease from pretest to posttest for the majority of the subjects, indicating positive changes, specifically in a shorter latency of response in milliseconds and **b** a faster voluntary reaction time in seconds.

Table 1

Demographics of the participants with TBI

Age at recruitment	Gender	Age at TBI	Type of injury
35	F	22	Penetrating gunshot wound
29	F	15	Closed head injury skiing
23	M	<1	Closed head injury grandfather clock
44	F	43	MVA
23	M	16	MVA
44	M	21	MVA
35	M	34	Closed head injury bike
19	M	17	MVA
35	F	34	Closed head injury assault
27	M	26	Closed head injury fall
19	M	18	Closed head injury fall
43	F	40	Closed head injury bike

Table 2

Pre- and post-training means and standard deviations for balance, mobility and neuropsychological measures with respective *p* values in group with TBI

Variable	N	Pretest	Posttest	<i>p</i>
<i>Balance</i>				
LOS (RT-B)	10	0.9 ± 0.3	0.8 ± 0.2	0.03
LOS (RT-C)	10	1.0 ± 0.3	0.9 ± 0.3	0.11
LOS (MVL-C)	11	4.0 ± 2.2	4.4 ± 2.4	0.27
LOS (EPE-C)	11	66.5 ± 18.6	70.3 ± 15.0	0.28
LOS (MXE-C)	11	78.5 ± 16.0	81.6 ± 14.2	0.31
MCT (COMP)	9	145.8 ± 17.2	135.6 ± 14.4	0.001
<i>Dual tasking</i>				
ST COG (W)	10	9.50 ± 2.1	9.20 ± 1.7	0.08
ST COG (N)	10	9.7 ± 2.0	10.4 ± 3.2	0.51
ST MOT	10	15.6 ± 2.27	15.4 ± 1.46	0.66
DT COG (W)	10	6.8 ± 2.6	7.3 ± 2.1	0.62
DT COG (N)	10	10.3 ± 3.2	9.7 ± 2.5	0.21
DT MOT (W)	10	18.8 ± 4.6	17.7 ± 2.8	0.22
DT MOT (N)	10	17.7 ± 4.0	17.0 ± 2.2	0.3
<i>Mobility</i>				
HiMAT	9	35.7 ± 7.4	34.3 ± 7.8	0.18
Cadence	11	111.6 ± 8.8	113.1 ± 8.4	0.46
Velocity	11	1.3 ± 0.3	1.3 ± 0.2	0.5
Step length	11	0.7 ± 0.1	0.7 ± 0.1	0.58
Reaction time	11	1.0 ± 0.2	1.0 ± 0.3	0.3
<i>Neuropsychological</i>				
HVLT-R (TR)	11	39.6 ± 11.14	42.0 ± 17.3	0.48
HVLT-R (DR)	11	40.0 ± 13.6	38.6 ± 22.3	0.72
HVLT-R (RET)	11	46.0 ± 11.1	45.8 ± 12.3	0.96
HVLT-R (RDI)	11	41.8 ± 15.1	43.9 ± 13.1	0.72
DOM FTT	8	43.5 ± 5.3	41.8 ± 8.7	0.28
NON FTT	7	41.7 ± 6.2	40.4 ± 7.4	0.47
BAI	11	7.3 ± 9.7	5.6 ± 7.3	0.09
PSQI	11	5.2 ± 3.3	3.5 ± 3.5	0.04
PCL-C	11	30.1 ± 12.4	25.5 ± 10.0	0.14
HAM-D	11	4.9 ± 5.4	3.4 ± 5.0	0.35