Three-Dimensional Multiple Object Tracking and its Effects on Functional, Cognitive, and Biological Outcomes in TBI Survivors: A Patient-Oriented Study

By

Jamie Morrison
B.Sc., University of Victoria, 2023

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We acknowledge and respect the Lək̓ʷəŋən (Songhees and Xʷsepsəm/Esquimalt) Peoples on whose territory the university stands, and the Lək̓ʷəŋən and W̱SÁNEĆ Peoples whose historical relationships with the land continue to this day.

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Abstract

Traumatic brain injury (TBI) is a leading cause of disability worldwide; however, accessible interventions to support recovery at chronic time points are limited. Cognitive training is a promising therapeutic avenue due to its low cost and accessibility. Three-dimensional multiple object tracking (3D-MOT) is a visuospatial cognitive training task that engages working memory, distributed attention, and complex motion integration – functions that are commonly impacted after TBI. This study explored the effects of a five-week, at-home 3D-MOT intervention for moderate to severe TBI survivors. This research was conducted in a patient-oriented manner with the Victoria Brain Injury Society. Thirty participants were randomized into the intervention or control group. Estimation statistics were used to report mean differences, confidence intervals, and effect sizes, aligning with a patient-oriented approach to emphasize clinical relevance. Self-reported functional outcomes, neuropsychological assessments, and telomere length as a biomarker of aging were assessed at baseline, post-intervention, and one-month follow-up in the 20 participants who completed the study. The intervention group exhibited medium to large effect size improvements in daily life challenges, TBI symptom severity, perceived stress, attention as measured on the Digit Span Forward, and executive function as measured on the Verbal Fluency FAS Test, that persisted at follow-up. Improvements in short- and long-term verbal memory and retrieval, as measured by the California Verbal Learning Test – Second Edition, were observed at one-month follow-up, but not immediately post-intervention. No change in telomere length following 3D-MOT intervention was observed. Control participants did not show meaningful improvements on any of these outcomes. Participant feedback highlighted the acceptability and perceived benefit of 3D-MOT, supporting its potential to be used as a therapeutic tool for TBI recovery.

Keywords: Traumatic brain injury, Cognitive training, 3D-MOT, Patient oriented research

Table of Contents

List of Tables

List of Figures

List of Abbreviations

3D-MOT	Three-dimensional multiple object tracking
bp	Base pairs
CCT	Computerized cognitive training
CI	Confidence interval
Ct	Cycle threshold
CVLT-II	California Verbal Learning Test, 2nd edition
MMSE	Mini-Mental State Examination
MPAI-4	Mayo-Portland Adaptability Inventory, 4th edition
msTBI	Moderate to severe traumatic brain injury
NHST	Null hypothesis significance testing
NTC	No-template control
POR	Patient-oriented research
PSS	Perceived Stress Scale
SCAT-5	Sport Concussion Assessment Tool, 5th edition
SD	Standard deviation
SDMT	Symbol Digit Modalities Test
TBI	Traumatic brain injury
TMT-A	Trail Making Test A
TMT-B	Trail Making Test B
qPCR	Quantitative polymerase chain reaction
VBIS	Victoria Brain Injury Society

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Dedication

To my family, whose lives have been shaped by the effects of traumatic brain injury, and to all those navigating life after brain injury – you are seen, you are valued, and your experiences are the foundation of this work.

Chapter 1: Introduction

1.1 Overview and Prevalence of Traumatic Brain Injury

Traumatic brain injury (TBI) is a leading cause of disability worldwide, with an estimated 69 million individuals receiving a TBI each year (1). TBI can be defined as a bump, blow, or jolt to the head or body that results in the brain moving back and forth inside the skull (2,3). TBIs range in severity from mild to severe, with moderate to severe injuries involving longer periods of unconsciousness and disorientation (4). While mild TBIs, like concussions, receive more media attention, moderate to severe injuries account for one in five TBIs and are more likely to leave survivors with chronic, debilitating symptoms (5). It has been estimated that 57% of moderate to severe TBI (msTBI) survivors in the United States end up with moderate to severe disability. Furthermore, global outcomes often decline years after these msTBI injuries, as 39% of survivors have been found to have worse outcomes five years after injury compared to one- or two-year time points (6). These numbers are likely an underestimate due to the historical lack of knowledge surrounding TBI and standardized tools to assess outcomes (7). As msTBI is a prevalent injury and can result in drastic reduction in quality of life over chronic periods, there is a crucial need for ongoing research into accessible interventions to support recovery in this population (8).

1.2 Causes and Mechanisms of msTBI

Moderate to severe TBI can occur in numerous ways, but is most commonly a result of falls, motor vehicle accidents, sports-related injuries, and abuse or assault (9). The injury following TBI can be divided into a primary injury and a secondary injury. Primary injury refers to the initial mechanical damage to the brain that occurs, including hematoma, hemorrhage, and shearing or tearing of axons leading to diffuse axonal injury (10). Secondary injury in TBI refers to the damage occurring on a cellular level that can result in a neurometabolic cascade of events over longer periods of time, ultimately leading to short- and long-term symptoms.

After injury, the biomechanical force from TBI can result in mechanoporation of neuronal membranes, allowing ions to flow down their electrochemical gradients, disrupting the resting membrane potential of neurons. This disruption causes depolarization and subsequent neurotransmitter release. Excessive excitatory neurotransmitter release from damaged neurons can lead to excitotoxicity, which is suggested to damage the blood-brain barrier and cause cell death following TBI. Furthermore, in attempt to restore ionic gradients within neurons post-injury, the

Na^+/K^+-ATPase pump works in overdrive, which ultimately depletes intracellular ATP stores. Excessive intracellular calcium is also sequestered into mitochondria, which eventually disrupts mitochondrial functioning (10,11). These disruptions ultimately lead to an energy crisis and impaired cellular metabolism. A change in metabolic rate and altered cellular redox state can increase the generation of free radicals in the brain, leading to oxidative stress (12). Inflammation is another cellular mechanism that occurs during secondary injury in TBI. Immediately following injury, inflammation occurs through processes involving microglia, immune cells, cytokines, and inflammatory proteins. Inflammation early on may have beneficial effects in preventing further damage; however, studies suggest that inflammation can for persist years following TBI and may contribute to the long-term challenges survivors face (13,14).

1.3 Challenges Experienced by msTBI Survivors

1.3.1 Symptoms and Intersecting Challenges Following msTBI

A diverse array of symptoms within physical, cognitive, and behavioral domains can emerge following msTBI. Physical symptoms can include headaches, fatigue, visual disturbances, balance problems, dizziness, and challenges with sensory perception. Cognitive symptoms can include memory difficulties, attention challenges, slower processing, executive dysfunction, and communication challenges. Behavioral symptoms can include depression, anxiety, irritability, impulsivity, and emotional lability (15). As msTBI is an extremely heterogeneous injury, symptoms experienced by survivors and their duration can differ drastically. It has been hypothesized that TBI symptoms are related to mechanisms of secondary injury. For example, Giza and Hovda (2014) suggested that migraines, light sensitivity, and noise sensitivity are related to the ionic flux; cognitive challenges, slowed processing, and slowed reaction time are related to impaired neurotransmission and axonal injury; and the persistent impairments are related to cell death (11). While recovery from msTBI is possible, many individuals experience symptoms that can persist years post-injury (16).

Living with chronic symptoms of msTBI can drastically impair the quality of life for survivors. For example, TBI survivors are at a greater risk of facing intersecting challenges such as unemployment, being unhoused, mental health challenges, and incarceration (17–20). Social capacities can also be altered following msTBI for reasons such as survivors being more reliant on support to complete daily activities, or no longer possessing the same social skills and energy as

they did prior to injury (21). The multifactorial impact that msTBI can have on an individual's life, and the possible long-term effects on cognition, are reasons why it is of utmost importance to have accessible, research-based interventions for survivors during the recovery journey (22).

1.3.2 Lack of Resources for msTBI Recovery

Despite the prevalence of TBI, persistent symptoms, and the impairments in daily life functioning, survivor resources for chronic time points are lacking. Resources for survivors are prevalent in the acute time point, but survivors and their caregivers are often sent home with no resources for chronic recovery and support (23). A challenge with many existing therapies, especially those delivered by clinicians, is that they are inaccessible due to the cost associated with them (24). Furthermore, access to existing supports is even more limited in rural and underserved communities, which emphasizes the need to develop tools that can be used remotely (25).

TBI is increasingly recognized as a chronic condition, with functioning deteriorating over time in many survivors. Current literature emphasizes the need to develop effective rehabilitation programs for msTBI survivors that can allow for better outcomes at these chronic time points (26). Investigating accessible and scalable tools to improve functional and cognitive outcomes at chronic time points after msTBI is therefore essential.

1.4 Computerized Cognitive Training for TBI Recovery

Due to the lack of tools to aid with recovery after TBI and the burden these injuries can have on survivors, caregivers, and the healthcare system, research into accessible non-pharmacological interventions for TBI survivors is increasing (27). One form of non-pharmacological intervention that is growing in popularity amongst TBI research is computerized cognitive training (CCT). CCT encompasses a variety of mentally stimulating interventions accessed through technology that require input from a user and aim to improve functions through the concept of neuroplasticity (28,29). It is known that the adult brain is plastic, and appropriate stimuli can result in the rewiring and strengthening of synaptic connections (30). CCT interventions aim to repetitively engage the brain in tasks that may strengthen neuronal connections responsible for various cognitive functions and ideally translate to cognitive improvements in real life (29). In support of this hypothesis, Takeuchi et al. (2017) found computerized working memory training to elicit cerebral plasticity in brain regions including the

dorsolateral prefrontal cortex and anterior cingulate cortex – regions associated with executive functions and emotional regulation (31,32).

Cognitive improvements following CCT intervention have been demonstrated in various populations. A systematic review and meta-analysis of CCT in older adults with mild cognitive impairment or dementia found that such interventions can improve visual memory, verbal memory, and working memory (33). Alescio-Lautier et al. (2019) found improvements in global cognition, memory recall, and verbal fluency following 15 sessions of CCT in participants with Alzheimer's disease (34). Patients with schizophrenia demonstrated improvements in verbal learning, verbal memory, and cognitive control (35). Furthermore, a systematic review found improvements in working memory, processing speed, and attention following CCT in youth with brain tumors (36).

Beyond improvements in cognition, CCT studies have also found improved functional outcomes in populations. After CCT intervention, work ability and health perception status in breast cancer survivors was improved (37). Quality of life improvements following CCT have been seen in a variety of populations including older adults, people with Parkinson's disease, and people with vascular dementia (38–40). However, certain studies have found improvements in cognitive functions following CCT, but no improvements in functional outcomes – emphasizing the importance of evaluating both cognitive and functional outcomes when studying the efficacy of CCT interventions to understand whether they translate to real-world improvements for participants (37,41).

As msTBI often results in lasting cognitive challenges, CCT could be a beneficial therapeutic avenue for survivors. Research has found that neuroplastic changes can be elicited in whole-brain networks following cognitive training in people with TBI (42). There is also promise for CCT in reducing reported symptoms in military populations with mild TBI (43). Furthermore, improvements in cognitive and depressive symptoms, along with overall performance on a cognitive training composite were seen in individuals with mild TBI following CCT (28). Feasibility of at-home CCT in mild to severe TBI survivors at least six months post-injury has been evaluated and found that participants were able to engage in the intervention with minor reported symptoms (e.g., fatigue), and that remote support from the research team was appropriate (44). A recent systematic review of CCT randomized controlled trials suggests that this type of intervention can improve various cognitive domains and is safe for TBI survivors, making it a

promising rehabilitation strategy (45). Further research is required to understand whether CCT can be beneficial for msTBI survivors at a chronic time point.

1.5 Three-Dimensional Multiple Object Tracking (3D-MOT)

Three-dimensional multiple object tracking (3D-MOT) is a visuospatial CCT task that repetitively engages visual working memory, distributed attention, and complex motion integration. 3D-MOT can be accessed through NeuroTracker software on a tablet, computer, or television (46). The 3D-MOT task has users repetitively track spherical-shaped objects in space for a sustained period. Advantages of cognitive training with 3D-MOT include that it occurs in binocular 3D, which is suggested to be more representative of dynamic, real-world settings (47). Additionally, the tool has an adaptive algorithm, adjusting the task difficulty to an optimal level for the user at any given time.

3D-MOT has been studied in athlete populations as a cognitive training tool to enhance sports performance (46). Performance on tests of processing speed and attention improved in a group of volleyball players following 3D-MOT (48). Another study found that 3D-MOT intervention increased decision-making accuracy in soccer players, suggesting the transferability of this task into real-world settings (49).

3D-MOT has also been used among military populations, healthy adults, older adults, individuals with multiple sclerosis, and youth with mild TBI (46,47,50–52). Research has found 3D-MOT use in older adults with dementia and mild cognitive impairment to correlate with improved manual dexterity. This study highlighted the potential for 3D-MOT interventions to improve attention, executive function, and quality of life in older adults (51). Parsons et al. (2016) examined the effect of 3D-MOT on quantitative electroencephalograms in college students. Participants undergoing the 3D-MOT intervention improved on neuropsychological measures of attention, processing speed, and working memory, and also had increased frequency of gamma bands, which are thought to be associated with neuroplasticity (53). Tullo et al. (2018) found that 3D-MOT may help improve attention in youth with neurodevelopmental conditions, and that this tool can be feasible to implement in school settings (54). Furthermore, a pilot study has suggested 3D-MOT may be an acceptable intervention to support cognitive rehabilitation in individuals with multiple sclerosis (47).

3D-MOT is a tool that could be appropriate for msTBI survivors due to its low cost compared to traditional vision therapy and intensive rehabilitation programs, and its accessible nature as it can be completed in clinic or at home. This form of cognitive training is also not resource-intensive, as it does not require a clinician to administer, and does not have to be completed on a rigorous daily basis. As well, the 3D-MOT task is adaptive, in that it occurs at a speed that is optimally engaging for the user, which is beneficial for msTBI survivors who can have fluctuating cognitive abilities on a day-to-day basis (55). Recent research has suggested that 3D-MOT can be used in children with a history of mild TBI, suggesting its appropriateness for certain TBI populations (56,57).

Due to the potential of 3D-MOT to improve cognitive domains that can be affected long-term following msTBI and its accessible nature, this study will evaluate 3D-MOT as an intervention for msTBI survivors. Specifically, it will explore the efficacy of 10 3D-MOT sessions over five weeks in this population, as this training schedule is consistent with previous literature reporting cognitive improvements in adults (53).

1.6 Biological Aging and TBI

Alzheimer's Association puts msTBI survivors at a 2.3 to 4.5 times greater likelihood of later developing neurodegenerative diseases; however, limited information is available regarding interventions that can influence biological aging following msTBI (58). In recent years, research has focused on identifying biomarkers of the aging process (59). Telomeres are repetitive TTAGGG DNA sequences located at the ends of linear chromosomes that shorten with each cell cycle division over the lifespan (60). Due to this gradual shortening, telomere length is a widely studied biological marker of aging. Factors such as inflammation, chronic conditions, and perceived stress have been associated with shorter telomeres (61,62).

TBI may accelerate the process of biological aging through mechanisms such as chronic inflammation, oxidative stress, and dysregulation of the hypothalamic-pituitary-adrenal axis (63,64). Animal studies have found that repeated mild TBI results in shorter telomere length than non-TBI controls (65). In humans, shorter telomere length has been associated with increased symptom severity in adults with TBI (66). As a result, researchers have suggested that telomere length could act as a biomarker for managing clinical outcomes following TBI (67).

Recent literature suggests that telomere length can be maintained or even lengthen over time through beneficial lifestyle interventions. Individuals engaging in healthy behaviours (e.g., stress management, exercise, social support, diet) have demonstrated increased telomere length compared to controls (68–70). In one study, caregivers who engaged in aerobic exercise interventions demonstrated increased telomere length and reductions in perceived stress compared to controls (71).

Multidomain lifestyle interventions that include cognitive training have been shown to help maintain telomere length in older adults, and these results were associated with stronger cognitive outcomes (72). Cognitive training has also been shown to reduce perceived stress and symptoms in TBI survivors, which are factors associated with mechanisms that shorten telomeres, such as chronic inflammation (64,73,74). Pesce et al. (2017) even found evidence that a memory training intervention in healthy older adults could reduce pro-inflammatory cytokines and inflammation (75). Therefore, this study explores whether a 3D-MOT cognitive training intervention can influence telomere length in chronic msTBI survivors.

1.6 Patient-Oriented Research

Conducting research in a patient-oriented manner is crucial to ensure that outcomes investigated are relevant to the populations being studied. The overall goal of patient-oriented research (POR) is to produce findings that are meaningful to the study population and aimed at improving their health outcomes (76). POR involves including the perspectives of patients, caregivers, stakeholders, and clinicians when designing, conducting, and disseminating research (76,77). In conducting POR, it is essential to build trust with patient populations to encourage meaningful engagement. Trust-building processes will vary based on the specific population included in POR (78).

Mohatt et al. (2021) worked with patient-partners with msTBI to gain perspectives on how to successfully engage this population in clinical research studies. The three main themes identified were communication, preparation, and environment. Communication suggestions included offering instructions in multiple formats, allowing time for survivors to read materials at their own pace, and repeating information on multiple occasions. Preparation suggestions included sending materials and instructions in advance of meetings and providing meeting summaries. Environment suggestions included offering in-person meetings, having natural light in meeting rooms, and

providing a flexible schedule (79). These suggestions highlight important considerations and adaptations when conducting research with msTBI survivors.

This study aimed to conduct research in a patient-oriented manner by collaborating with a community partner organization that supports brain injury survivors and incorporating survivor input throughout the study process. In line with this approach, this study placed emphasis on self-reported functional outcomes in addition to cognitive outcomes, as is important to explore if the benefits of 3D-MOT translate into meaningful improvements in the lives of participants. To disseminate results in a way that emphasizes the magnitude and clinical relevance of change, rather than statistical significance, this study used estimation statistics to report mean differences, confidence intervals, and effect sizes. Further, participants who wished to do so had their voices amplified through the inclusion of quotes from semi-structured interviews following the study.

1.7 Study Rationale, Research Questions, and Hypotheses

As identified in the literature, there is a gap in available tools to help msTBI survivors improve their symptoms at chronic time points following injury. Effective therapeutic tools should be adaptive to the diverse cognitive abilities of survivors, low in cost, and accessible across different settings (e.g., in clinic, at home) (80). 3D-MOT is a cognitive training tool that could help address this gap; however, the exact domains it may help improve in msTBI survivors remain unclear. To explore whether 3D-MOT can improve outcomes at chronic time points in msTBI survivors, this patient-oriented study was designed with the Victoria Brain Injury Society. As it is important include measures that are relevant to survivors, this study explores a multitude of self-report measures, standardized neuropsychological assessments, and a biological marker of aging to obtain a well-rounded understanding of outcomes that may be improved following 3D-MOT.

This study will explore the following research questions:

1) Do msTBI survivors report improvements in perceived well-being following a 3D-MOT intervention?
2) Does cognitive performance improve in msTBI survivors following 3D-MOT, and if so, in which domains?
3) Is telomere length, a biological marker of aging, altered in msTBI survivors following a 3D-MOT intervention?

Based on the literature, this study hypothesizes the following:

1) Following the 3D-MOT intervention, msTBI survivors will demonstrate large effect size reductions in self-reported daily life challenges, perceived stress, and TBI symptoms.
2) Following 3D-MOT intervention, msTBI survivors will demonstrate large effect size improvements on standardized neuropsychological assessments.
3) Telomere length will increase in msTBI survivors following 3D-MOT intervention.

Chapter 2: Methodology

2.1 Ethics Approval and Consent

Ethics approval for this study (Protocol #23-0350) was obtained from the University of Victoria Human Research Ethics Board in accordance with the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Appendix A). All participants were informed of the study's purpose, and written consent was obtained. Due to the nature of cognitive challenges that occur after brain injury, participants were sent a digital copy of the consent form to review at their own leisure, and a research team member verbally explained the consent form to participants in person. Prior to the study, a research team member consulted resources from the Victoria Brain Injury Society to increase accessibility of the consent form for participants. Alterations to the form included increasing font sizes and colour-coded headers (Appendix B). Participation in this study was completely voluntary at all time points, and this was emphasized to participants throughout the research process.

2.2 Victoria Brain Injury Society

This research was conducted in partnership with the Victoria Brain Injury Society (VBIS), aligning with a patient-oriented research approach. VBIS is a non-profit organization that has provided support, education, and advocacy to brain injury survivors and their families for over 40 years (Figure 2.1).

Staff members and brain injury survivors were consulted during the study design process to help this research meet the goals and needs of individuals with lived experience in the community being studied. Training materials were obtained from VBIS to ensure the research team was properly educated on important considerations for providing a trauma-informed and accessible research environment for TBI survivors.

Figure 2.1 The logo of the Victoria Brain Injury Society
VBIS is the community partner organization supporting this patient-oriented traumatic brain injury research study.

2.3 Participants

Participants with a self-reported history of msTBI who met the inclusion and exclusion criteria in Table 2.1 were recruited through VBIS, REACH BC, and flyers posted on community boards (Appendix C). This study did not require documented proof of an msTBI diagnosis due to several key considerations. First, recognition and diagnosis of TBI has grown over recent decades, but a historical lack of standardized diagnostic tools and TBI awareness has resulted in many injuries going unreported and undocumented (7). Additionally, individuals who experience polytrauma may not always receive a TBI diagnosis as acute care settings may prioritize treatment of visible or other life-threatening injuries at the time of admission (81,82). Finally, when consulting VBIS on the study design, it was determined that focusing solely on documented TBIs could bias the sample by excluding a large proportion of TBI survivors in the community, particularly those who experience barriers to accessing health care (83–85). Criteria for msTBI classification were based on the report by the National Academies of Sciences (2019) and the National Institute on Disability, Independent Living and Rehabilitation Research Traumatic Brain Injury Model System Centers research criteria (4,86). Participants were more than one-year post-TBI to minimize confounds from the natural TBI recovery process over time (87,88). Participants were also 19 years of age or older as this is the age of majority in British Columbia, and the demographic primarily served by VBIS. Participant inclusion and exclusion criteria can be found in Table 2.1.

Table 2.1 Inclusion and exclusion criteria for participants.

Inclusion criteria
1. A self-reported history of moderate to severe TBI defined by any one of the following: a. A loss of consciousness for > 30 minutes b. Posttraumatic amnesia for > 24 hours c. Glasgow Coma Scale score of 3-12
2. More than one year since the most recent TBI
3. Age ≥ 19 years
4. Willing to provide physician, health practitioner, or walk-in clinic information in case of incidental findings
Exclusion criteria
1. Diagnosis of any neurodegenerative disorder
2. Diagnosis of a visual impairment that could impede 3D-MOT training (e.g. colour blindness, monocular vision, blindness)
3. Participation in 3D-MOT training within the past year

An a priori power analysis was conducted for this study's primary outcome measure, the Mayo-Portland Adaptability Inventory-4 (MPAI-4), based on the initial statistical approach (analysis of variance: repeated measures, within-between interaction). Using Cohen's *f* for a medium effect size (Cohen's $f = 0.25$), alpha of 0.05, power of 0.80, and a correlation among repeated measures of 0.75, yielded a total required sample size of n = 16 (89). Based on this power analysis, a target sample size of n = 30 was chosen to account for potential attrition, which previous cognitive training studies have shown can occur at rates of approximately 30% in adults with TBI (90). Small sample sizes are common in intervention studies involving msTBI survivors as recruitment and retention can be inherently difficult due to the challenges that these injuries pose to participants (91,92). While sample size was determined based on null hypothesis significance testing, this study ultimately pivoted to estimation statistics for all analyses, as this approach is well-suited for analyzing small sample sizes and aligns with a patient-oriented approach.

2.4 Experimental Design

Data collection for this randomized pre-post intervention study occurred from December 2023 to January 2025 in Victoria, British Columbia, Canada. Individuals who expressed interest

in the study were scheduled for an intake appointment which took place over the phone or in person at the Victoria Brain Injury Society, depending on participant preference. Intakes involved assessing participant eligibility through inclusion and exclusion criteria, obtaining informed consent, and collecting demographic information. Participant intakes occurred on a rolling basis from December 2023 to October 2024. Self-report questionnaires, standardized neuropsychological assessments, and saliva collection occurred at baseline (T0), within one-week post-intervention (T1), and one month post-intervention (T2) (Figure 2.2). Upon completion of T0 data collection, participants were randomized into the 3D-MOT intervention or control group for five weeks. Simple randomization was conducted using Microsoft Excel (RANDBETWEEN(1,2)) to allocate participant numbers (TBI01-TBI30) to either group. Participants were assigned the next available participant number sequentially based on their order of enrollment. At the end of the study, all participants were given the opportunity to engage in a semi-structured interview to share their perspectives on the research process and suitability of 3D-MOT for brain injury survivors (Appendix D).

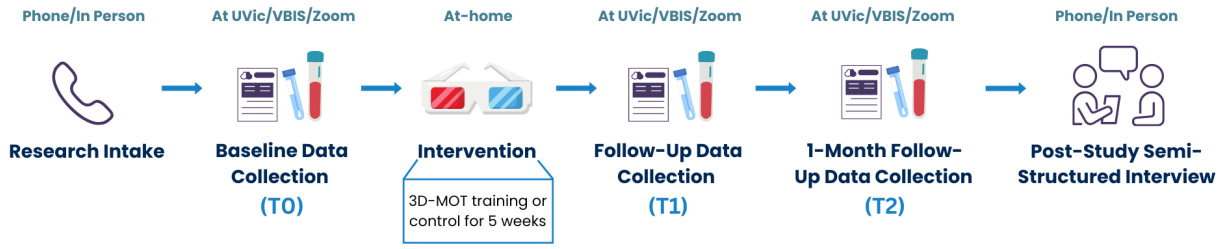

Figure 2.2 Overview of the study process for participants

2.5 3D-MOT Intervention

The intervention group underwent five weeks of cognitive training with 3D-MOT twice per week. Participants were asked to have at least one rest day between cognitive training days. NeuroTrackerX (Cognisens Athletics Inc., Montreal, QC, Canada) was the software used for 3D-MOT cognitive training. On each training day, participants completed three NeuroTrackerX "Core" sessions. Each Core session consisted of 20 trials of the 3D-MOT task, totaling 60 trials in a training day (Figure 2.3). NeuroTrackerX uses an adaptive staircase algorithm to adjust the speed of the targets based on previous trial performance (93). If the user correctly selects all four targets, the next trial will speed up by a factor of 0.05 log units. If any targets are incorrectly identified,

the next trial will slow down by a factor of 0.05 log units. NeuroTracker also provides the user with a "Speed Threshold" after each Core session, which is an arbitrary number representing the speed at which the user can successfully track all targets 50% of the time (94,95).

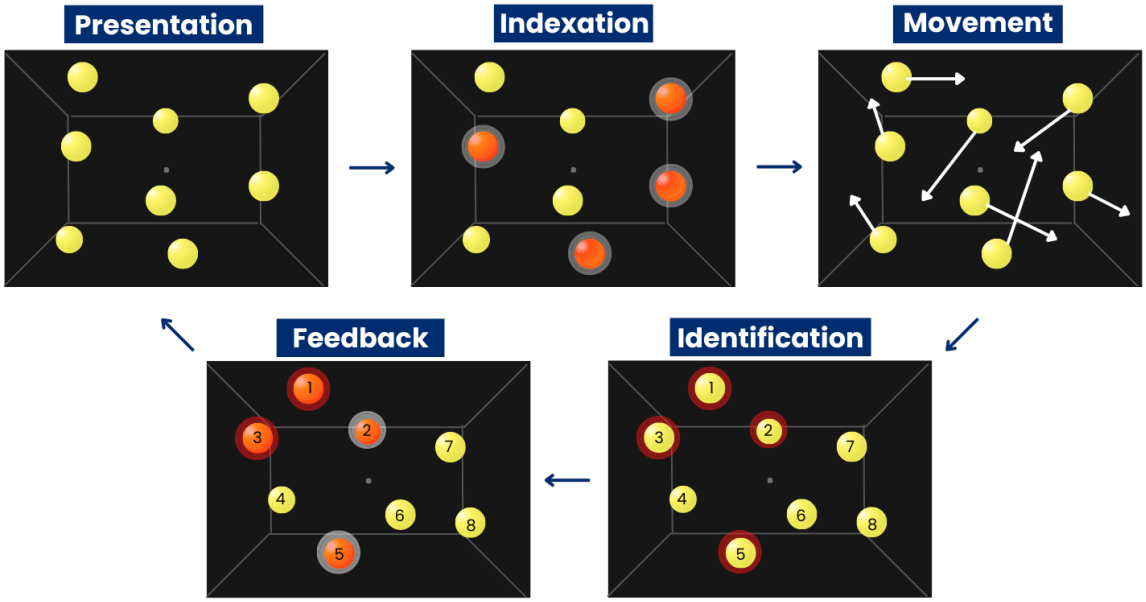

Figure 2.3 One trial of 3D-MOT on NeuroTrackerX software
Presentation: Eight yellow spheres appear on the screen. *Indexation*: Four of the eight spheres flash red to indicate to the participant that these are the targets. *Movement*: All eight spheres turn back to yellow and move around the screen in three-dimensional space for 8 seconds. *Identification*: The spheres stop moving, become numbered, and the participant selects the four spheres that were their initial targets. *Feedback*: The initial targets light up to provide the participant with feedback.

Participants received an initial overview of the cognitive training tool with a research team member and were provided with video and written instructions on how to use the software to ensure multiple modalities of explanation were accessible (Appendix E). Each participant received a pair of NeuroTrackerX anaglyph 3D glasses and was asked to complete the cognitive training from home on a laptop or computer monitor in a quiet setting. If participants did not have access to a computer or quiet space, VBIS loaned them a laptop and provided access to a private office space.

Participants were monitored through weekly phone or email check-ins with a research team member. During check-ins, research team members asked participants about their experience with the intervention and reminded them of their next training day. Team members were also available

to participants via phone or email from 8:00 am to 5:00 pm seven days a week, in case of any technology difficulties or questions.

The control group did not engage in 3D-MOT training. Instead, participants in this group were asked to obtain one hour of non-specific screen time per week (e.g., watching videos or movies) to mimic the screen time in the 3D-MOT group. Control participants also had weekly check-ins with a research team member and were prompted with questions about their week and experience in the study, with the aim of replicating the weekly social connection received by the intervention group. Following completion of the one-month follow-up (T2), all members of the control group were given the opportunity to try the 3D-MOT intervention to ensure they had access to potential benefits; however, this data was not collected.

2.6 Data Collection Tools

2.6.1 Self-Report Questionnaires

All self-report questionnaires were verbally administered by a research team member, who recorded participants' responses. The same team member conducted these questionnaires at baseline (T0), first follow-up (T1), and second follow-up (T2) for consistency. Daily life challenges, TBI symptoms, and perceived stress were all measured (Table 2.2).

Table 2.2 Self-report questionnaires administered to participants.

Questionnaire	Construct measured
Mayo-Portland Adaptability Inventory-4	Daily life challenges experienced
Sport Concussion Assessment Tool-5	TBI symptom severity Total number of TBI symptoms
Perceived Stress Scale	Perceived stress levels

2.6.1.1 Daily Life Challenges

The Mayo-Portland Adaptability Inventory-4 (MPAI-4) is a 30-item self-report measure that assesses perceived daily life challenges in TBI survivors. The MPAI-4 consists of three different subscales: the Ability Index (difficulties with physical, cognitive, and sensory abilities), the Adjustment Index (difficulties with emotional, interpersonal, and behavioral abilities), and the Participation Index (difficulties engaging in community and daily life activities).

This validated tool has been widely used in TBI research and offers meaningful insight into multiple domains of challenges that TBI survivors may face, making it well-suited for POR. The MPAI-4 is also recommended as a supplementary tool in moderate to severe TBI rehabilitation by the National Institute of Neurological Disorders and Stroke's (NINDS) Common Data Elements, and therefore was selected as the primary outcome measure for this study (96–98).

2.6.1.2 TBI Symptoms

The Sport Concussion Assessment Tool-5 (SCAT-5) is a self-report measure that has participants rate 22 concussion-related symptoms on a scale of 0 to 6, with 6 being the most severe. The SCAT-5 can provide insight into total number of TBI symptoms experienced (out of 22) and the severity of TBI symptoms experienced (out of 132). The SCAT-5 was chosen for this study as it is widely used as a self-report measure of symptoms in TBI research (99,100).

2.6.1.3 Perceived Stress

To evaluate participants' self-reported stress levels, the Perceived Stress Scale (PSS) was utilized. This assessment has participants rank 10 statements regarding personal feelings of stress on a Likert scale of 0 to 4. This assessment was chosen as it is a standard tool for measuring perceived stress, is quick to administer, and has been used in TBI research (101–104).

2.6.2 Standardized Neuropsychological Assessments

All neuropsychological assessments were administered by one trained clinical neuropsychology PhD student over Zoom in a 60-to-90-minute session (Table 2.3). Participants had the option of completing these assessments on a computer at-home or from a computer at VBIS. The neuropsychology student was blinded to participant group assignments.

Table 2.3 Standardized neuropsychological assessments administered to participants.

Assessment	Domain assessed
California Verbal Learning Test - Second Edition	Verbal learning and memory
Digit Span Task	Attention and working memory
Mini Mental State Examination	Global cognitive functions
Symbol Digit Modalities Test	Attention and processing speed
Trail Making Test A and B	Processing speed
Verbal Fluency FAS and Animals	Verbal fluency

2.6.2.1 California Verbal Learning Test

The California Verbal Learning Test - Second Edition (CVLT-II) is a neuropsychological assessment that evaluates verbal learning and memory. In this test, participants are presented with 16 words, each belonging to one of four semantic categories. These words are presented to the participant for five immediate recall trials. Participants are presented with an interference list, which involves a new set of words and then are tested on short-delay free and cued recall. After a period of 20 minutes, participants are tested on long-delay free and cued recall, followed by a yes or no word recognition trial (105). Cued recall provides participants with category-based cues.

Alternate forms of the CVLT-II were used so that participants received one set of words at baseline, a different set at T1, and the original set again at T2. The CVLT-II was chosen for this study as it has been widely used as a measure of verbal memory in TBI research (106). This study evaluated the sum of correctly recalled words from trials 1-5 as a measure of learning, short-delay free and cued recall as a measure of short-term verbal memory and retrieval, long-delay free and cued recall as a measure of longer-term verbal memory and retrieval (107,108).

2.6.2.2 Digit Span Task

The Digit Span Task is a subtest of the Wechsler Adult Intelligence Scale – Fourth Edition and is highly recommended by the NINDS Common Data Elements for moderate to severe TBI rehabilitation studies evaluating attention and working memory. This study evaluated the Total Digit Span Score, Digit Span Forward, Digit Span Backward, and Digit Span Sequencing components.

Digit Span Forward requires participants to recall numerical sequences of increasing lengths in the same order presented to them. This test primarily a measures simple auditory attention and short-term memory (109). Digit Span Backward asks participants to repeat numerical sequences of increasing lengths in the opposite order presented to them, and is considered a measure of working memory (110). Digit Span Sequencing requires participants to repeat numerical sequences of increasing lengths in ascending order, and is suggested to be a measure of working memory and cognitive flexibility (111).

All Digit Span scores represent the total number of correct sequences recalled. The Total Digit Span score is a sum of the Forward, Backward, and Sequencing raw scores.

2.6.2.3 Mini Mental State Examination

The Mini-Mental State Examination (MMSE) is a global measure of cognition commonly involved in diagnosing cognitive impairment. The MMSE involves tasks that evaluate orientation in time and place, learning and recall of three words, attention and calculation, and language abilities. Based on performance on these tasks, participants receive a total score out of 30, which was used in analysis for this study (112,113). The MMSE was chosen for this study as it one of the most commonly used tool for evaluating global cognition in individuals with neurological conditions (114).

2.6.2.4 Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT) is used as a measure of attention and processing speed. The oral version of the SDMT was used in this study. This test presents participants with nine abstract symbols and a corresponding number to each symbol. Participants are presented with a list of symbols and are asked to say aloud the correct number associated with each symbol. The SDMT score represents the number of correct responses in a 90-second period (115). The SDMT was chosen for this study as it is highly recommended by the NINDS Common Data Elements as a tool for measuring processing speed in neurorehabilitation research (98).

2.6.2.5 Trail Making Test A and B

The Trail Making Test A (TMT-A) primarily measures processing speed, while the Trail Making Test B (TMT-B) assesses both processing speed and executive function. The oral version

of the Trail Making Test was used in this study. In the TMT-A, participants are asked to count aloud from 1 to 25 as fast as they can. The TMT-B has participants alternate between numbers and letters as fast as they can, beginning with 1, A, 2, B, 3, C until they reach 13 (116,117). The score reported for both TMT-A and TMT-B is the total time in seconds taken to complete the task. The Trail Making Test was chosen for this study as it is recommended by the NINDS Common Data Elements as a basic measure for evaluating psychomotor speed and executive functions in moderate to severe traumatic brain injury rehabilitation (118).

2.6.2.6 Verbal Fluency Test

The Verbal Fluency Test is used as a measure of executive function. Two components of the Verbal Fluency test were included in this study: the FAS and Animals tests. The Verbal Fluency FAS test has participants list as many words as possible beginning with the letters F, A, and S, with one minute per letter. Participants must avoid proper nouns and words with the same root but different suffixes. The total FAS score is the sum of words listed across all three letter trials. The FAS test evaluates phonemic fluency as a measure of executive function. In the Verbal Fluency Animals test, participants list as many unique animal names as possible in one minute. The Animals test evaluates semantic fluency as a measure of executive function and semantic memory (119–121). The score on the Verbal Fluency Animals test represents the number of correct animal names generated in one minute. The Verbal Fluency test was chosen for this study as it is recommended by the NINDS Common Data Elements as a supplementary measure for TBI research and has been widely used in TBI studies (98,122).

2.6.3 Saliva Sample Collection

All saliva sample collections occurred at the University of Victoria Medical Sciences Building in an appropriate room for medical procedures. Saliva samples were collected using the DNA Genotek OCR-100 OraCollect™ Sample Collection Kit (Figure 2.4). To minimize sample contamination, participants were asked to refrain from eating or drinking for at least 45 minutes prior to the appointment. Participants were instructed to swab the outside of their lower gums back and forth 10 times on both sides, following the DNA Genotek collection instructions. Saliva swabs were stored at room temperature until DNA extraction for telomere length analysis.

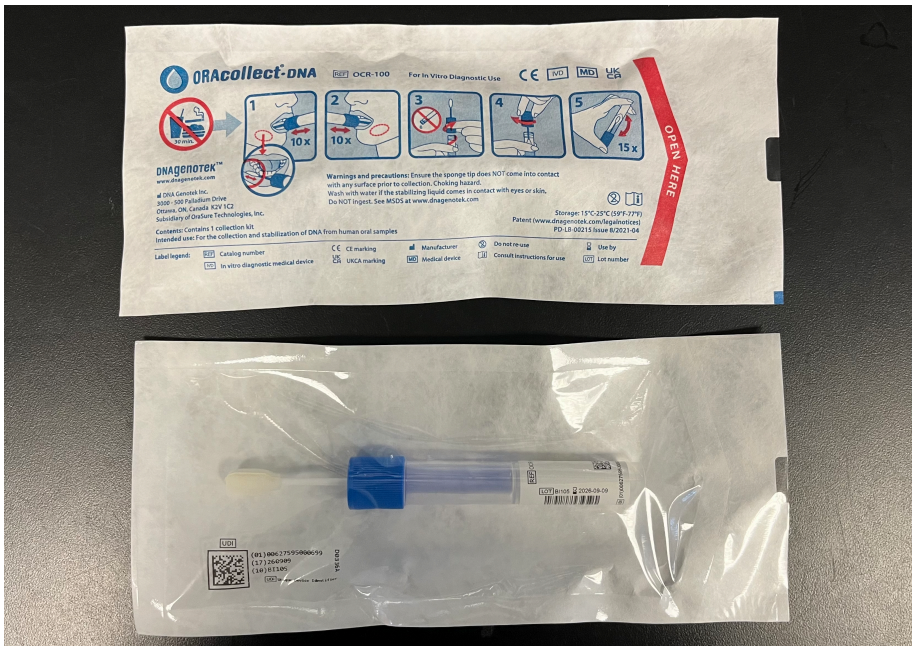

Figure 2.4 DNA Genotek OCR-100 OraCollect™ Sample Collection Kit

2.7 Telomere Length Analysis

2.7.1 DNA Extraction

DNA extraction was performed according to the DNA Genotek prepIT™-L2P protocol for manual DNA extraction. Saliva swabs were incubated in a water bath at 50 ºC for 1 hour. At a work surface cleaned with RNaseZap™ wipes and distilled water, 500 µL of the saliva sample was transferred to a 1.5 mL microcentrifuge tube and 20 µL of prepIT™-L2P was added and mixed by vortexing. Samples were incubated on ice for 10 minutes, then centrifuged at 15,000 x *g* for 5 minutes at room temperature. The supernatant was collected and transferred to a new microcentrifuge tube, and the pellet was discarded. Next, 600 µL of 100% ethanol was added to the sample, mixed by inversion 10 times, and allowed to incubate at room temperature for 10 minutes for DNA precipitation. Samples were centrifuged at 15,000 x *g* for two minutes and the supernatant was removed and discarded. The pellet was washed with 250 µL of 70% ethanol and let to stand for one minute. Ethanol was completely removed and 100 µL of TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH 8.0) was added as the DNA storage solution and vortexed for 5 seconds. Samples were incubated at 50 ºC for 1 hour with vortexing every 10 minutes to ensure rehydration of DNA. DNA concentration was quantified using the Thermo Fisher Scientific

NanoDrop 1000, and samples were diluted with TE buffer to a concentration of 20 ng/µL in preparation for telomere length analysis with quantitative polymerase chain reaction.

2.7.2 Quantitative Polymerase Chain Reaction

Quantitative polymerase chain reaction (qPCR) was conducted for both telomeres and a single copy reference gene (36B4), with all samples run in duplicate. All qPCR was performed at the University of Victoria Health Core.

A 96-well plate was prepared with master mix in each sample well. Each well contained 19 µL of master mix, comprised of Fast SYBR™ Green Master Mix, DEPC-treated nuclease-free water, forward primer, and reverse primer. In each well of master mix, 1 µL of DNA sample was added, resulting in a total volume of 20 µL. One no-template control (NTC) well was included on each plate to ensure reagents were not contaminated. In the NTC well, 19 µL of master mix was combined with 1 µL of DEPC-treated nuclease-free water instead of the DNA sample. The specific volumes of reagents for telomere and 36B4 qPCR were based on Cawthon (2002) and are found in Table 2.4 (123).

Table 2.4 Volumes of reagents per well in telomere and 36B4 qPCR.

Telomere qPCR		36B4 qPCR	
Reagent	Amount per well	Reagent	Amount per well
Fast SYBR™ Green	10.00 µL	Fast SYBR™ Green	10.00 µL
DEPC-treated water	6.66 µL	DEPC-treated water	7.40 µL
Telomere forward primer	0.54 µL of 10 µM	36B4 forward primer	0.60 µL of 10 µM
Telomere reverse primer	1.80 µL of 10 µM	36B4 reverse primer	1.00 µL of 10 µM
DNA sample	1.00 µL	DNA sample	1.00 µL

Four 96-well plates were used to run qPCR for all samples in this study. A QIAGEN QIAQuant qPCR thermocycler was used for amplification. The cycling parameters for the telomere and 36B4 qPCR are shown in Tables 2.5 and 2.6, respectively. The QIAGEN software provided cycle threshold (Ct) values for each sample, which were used in analysis. Melting curves were generated from the software to ensure that amplification of non-specific products was not occurring (124). Amplification and melting curves are found in Appendix F.

Table 2.5 qPCR cycling parameters for telomere sequence amplification.

qPCR cycle stage	Temperature	Time	Cycles
Enzyme activation	95ºC	10 minutes	
Denaturation	95ºC	15 seconds	x40
Annealing and extension	60ºC	2 minutes	
Melt curve	50ºC to 90ºC	15 seconds	

Table 2.6 qPCR cycling parameters for 36B4 single copy gene amplification.

qPCR cycle stage	Temperature	Time	Cycles
Enzyme activation	95ºC	10 minutes	
Denaturation	95ºC	15 seconds	x40
Annealing and extension	58ºC	2 minutes	
Melt curve	50ºC to 90ºC	15 seconds	

2.7.3 Estimated Telomere Length Analysis

Estimated telomere length analyses was conducted according to the method described by Cawthon (2002). The single copy reference gene (36B4) was used to compare the quantity of telomere repeats to a consistent amount of genomic DNA, controlling for differences in the amount of DNA present between samples. The linear regression equation $[2^{Ct(telomere)} / 2^{Ct(36B4)}]^{-1} = -2^{-\Delta Ct}$ determined by Cawthon (2002), approximates the telomere to single copy gene (T/S) ratio. Average Ct values were calculated from the duplicate samples. The average telomere Ct was subtracted from the average 36B4 Ct to obtain the ΔCt, which was used in the linear regression equation to calculate the T/S ratio. To convert the T/S ratio into estimated telomere length in base pairs (bp), the equation $y = 1910.5x + 4157$ was used, with x equalling the T/S ratio and y equalling telomere length in base pairs (123,125,126).

2.8 Semi-Structured Interviews

To gain participant perspectives, a semi-structured interview was developed with VBIS. This interview consisted of a set list of 6 open-ended questions specific to participants in the intervention group and 7 open-ended questions for all participants. Upon completion of T2 data collection, participants were given the opportunity to complete the semi-structured interview with

a research team member. This study will present the results from the intervention-specific questions. Semi-structured interview questions are presented in Table 2.7.

Table 2.7 Intervention group semi-structured interview questions.

Questions
How was your experience with the NeuroTracker intervention?
What did you like about the NeuroTracker intervention?
What did you not like about the NeuroTracker intervention?
Do you believe NeuroTracker provided you with any benefits?
Would you recommend NeuroTracker to other brain injury survivors?
Is there anything you would change about the NeuroTracker intervention?

2.9 Statistical Analyses

This study was powered for a repeated-measures, within-between analysis of variance (ANOVA) for the primary outcome measure (MPAI-4). However, it was decided that ANOVA was not the most appropriate method of analysis due to unequal sample sizes across time points, small overall sample sizes, and violations of normality assumptions for some outcome measures. Therefore, to report the data in a more informative and clinically relevant manner, estimation statistics with bootstrapping was chosen as the primary analysis method.

Classic null hypothesis significance testing (NHST) with p-values has several drawbacks. When it comes to using NHST, it encourages dichotomous thinking – where a result is either statistically significant or not. This "black or white" way of interpretation may not be suitable in clinical settings, where meaningful improvements in patient well-being do not always reach statistical significance (127). Furthermore, there are challenges with NHST when it comes to replication. If a given study is replicated, even under near-identical conditions, p-values have been shown to fluctuate. This fluctuation can be attributed to p-values being highly sensitive to small changes in sample sizes and variations in random sampling, leading to challenges with reproducibility in science (128,129).

To avoid the limitations of NHST and provide a more stable and representative picture of the dataset, this study utilized estimation statistics to report mean differences, confidence intervals, and effect sizes within groups. Confidence intervals provide insight toward the extent of uncertainty of the mean differences reported (130). Effect sizes provide information regarding the magnitude of difference and can be used to infer the practical significance of a finding, supporting

a patient-oriented research approach (131,132). Figure 2.5 explains the key elements in the paired mean difference figures displayed throughout the results section.

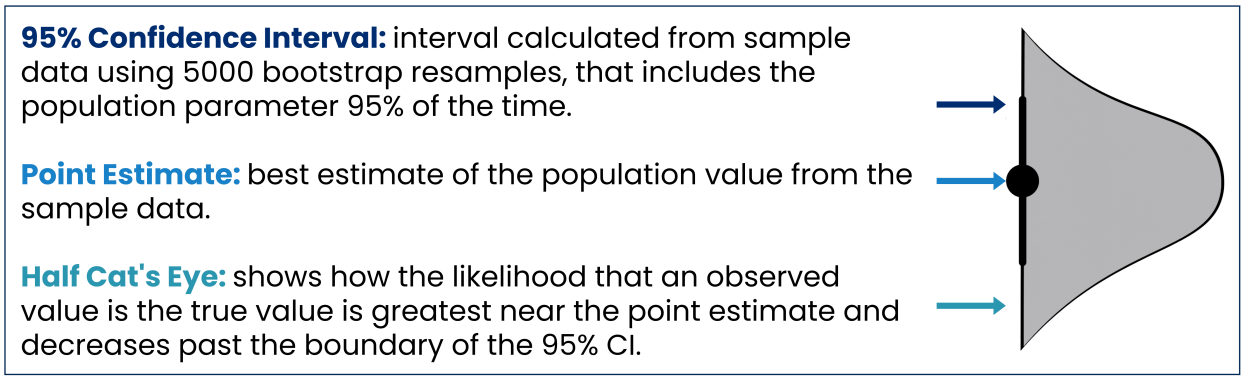

Figure 2.5 Elements of estimation plots
Description of the 95% confidence interval, point estimate, and sample distribution displayed for the paired mean difference figures in the results section.

Between-group analyses for the 3D-MOT intervention and control groups were conducted for comparison of baseline demographic variables, T0 outcome measures, T1 outcome measures, and T2 outcome measures. Between-group analyses were performed with student's t-tests after using Levine's test to confirm equal variances. Non-normally distributed data, as determined by a p-value of less than 0.05 from the Shapiro-Wilk test, was analysed using the Mann-Whitney U test.

All analyses were performed using RStudio software (version 2024.12.1+563). The packages used in analysis and data visualization were dabestr, ggplot2, and tidyverse (133–135). Mean values and standard deviation for all outcome measures are reported as Mean ± SD. The 95% confidence intervals (CIs) for mean differences were estimated using 5000 bootstrap resamples and were bias-corrected and accelerated. Effect sizes are reported as Hedges' g, to account for the bias in Cohen's d that can occur when working with small sample sizes (136,137). The 95% CIs for effect sizes were also estimated using 5000 bootstrap resamples and were bias-corrected and accelerated. Based on Cohen's (1988) conventional guidelines, mean differences associated with medium to large effect sizes (Hedges' $g \geq 0.5$) are highlighted in this study as having the potential for clinical relevance (Table 2.8) (138).

Table 2.8 Hedges' g effect size classifications used in this study.

Hedges' g value	Effect size classification
$g < 0.2$	Negligible effect
$0.2 \leq g < 0.5$	Small effect
$0.5 \leq g < 0.8$	Medium effect
$g \geq 0.8$	Large effect

Note. Values are adapted from Cohen (1988).

Chapter 3: Results

3.1 Participant Recruitment and Retention

A total of 31 participants completed intake appointments for this study. Of these 31 participants, one individual dropped out prior to completing baseline data collection (T0) due to non-responsiveness to study communication. The remaining 30 participants completed baseline data collection. Ten participants were lost to follow-up (T1), with seven of these individuals from the 3D-MOT intervention group and three from the control group. Reasons for attrition in the intervention group included scheduling conflicts (n = 3), TBI symptom exacerbation (n = 2), perceived intervention-related stress (n = 1), and non-responsiveness to study communication (n = 1). Attrition from the control group was attributed to non-responsiveness to study communication (n = 2) and a mid-study diagnosis of a neurodegenerative disorder (n = 1). Twenty participants returned for the first (T1) and second follow-ups (T2), however one participant from the intervention group and one participant from the control group did not complete the T2 neuropsychological assessments due to illness (n = 1) and discomfort with the assessment process (n = 1), respectively (Figure 3.1).

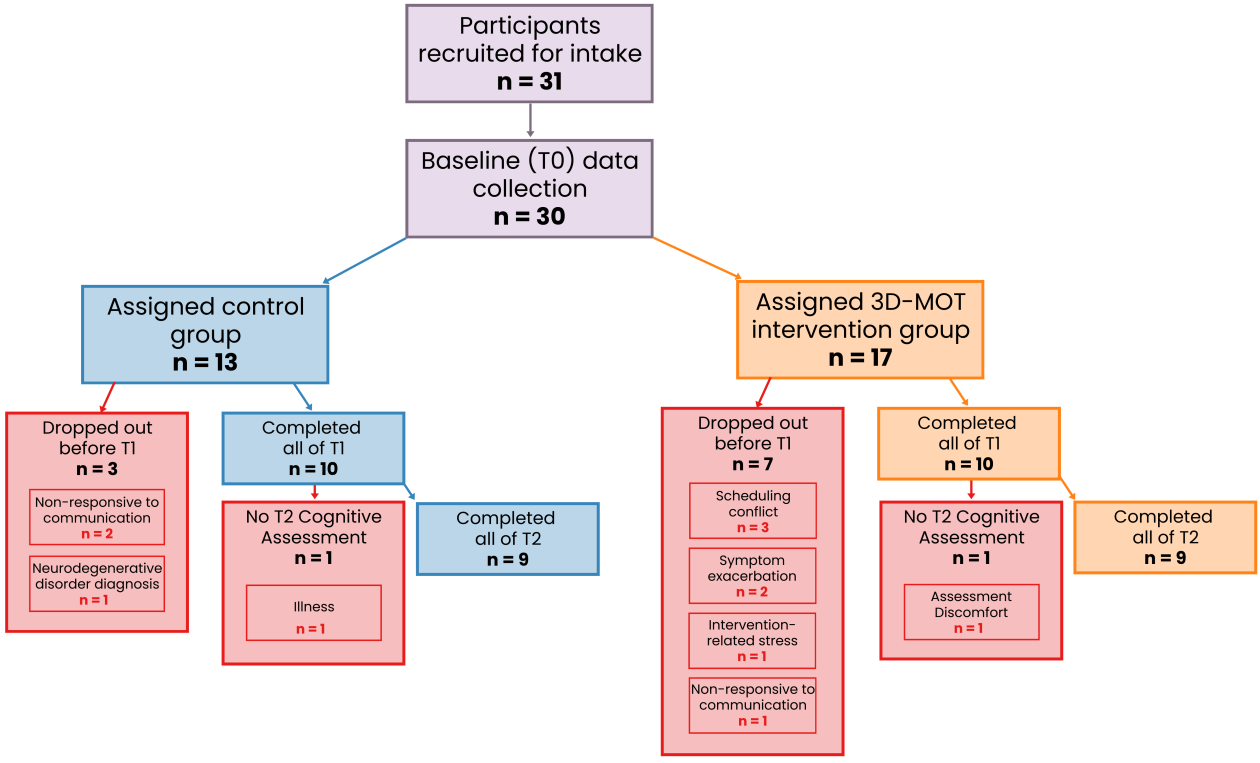

Figure 3.1 Flow diagram illustrating participant recruitment and retention

For this pre-post intervention study, data was analyzed from the 20 participants who completed the T0 and T1 data collection. Table 3.1 outlines the demographics of these participants.

Table 3.1 Demographic characteristics of study participants by group.

Variable	Control (n = 10)	3D-MOT (n = 10)	p-value
Categorical variables			
Biological sex	Female (n = 3), Male (n = 7)	Female (n = 4), Male (n = 6)	
Gender identity	Cisgender (n = 9), Transgender (n = 1)	Cisgender (n = 9), Transgender (n = 1)	
Ethnicity	White (n = 9), Latin American (n = 1)	White (n = 9), Indigenous (n = 1)	
Mechanism of msTBI	12 total msTBIs Assault (n = 4), Fall (n = 2), MVA (n = 5), Other (n = 1)	16 total msTBIs Assault (n = 4), Fall (n = 5), MVA (n = 5), Other (n = 2)	
Continuous variables (Mean ± SD)			
Age	56.3 ± 20.4	57.2 ± 12.7	p = 0.907
Years of education	12.8 ± 1.3	13.9 ± 2.0	p = 0.151
Hours of physical activity per week	5.6 ± 3.8	7.6 ± 8.6	p = 1.000
Number of social engagements per week	1.8 ± 2.0	5.2 ± 3.5	**p = 0.036**
Number of TBIs (any severity)	4.2 ± 3.8	4.3 ± 6.4	p = 0.937
Number of msTBIs	1.2 ± 0.4	1.6 ± 1.0	p = 0.322
Years since msTBI	21.1 ± 17.0	16.1 ± 18.3	p = 0.344

Note. P-values are calculated from independent samples t-tests or Mann-Whitney U tests, depending on data normality. P-values < 0.05 are bolded.

3.2 The Effect of 3D-MOT on Self-Reported Outcomes in msTBI Survivors

3.2.1 Perceived Daily Life Challenges After 3D-MOT

Following the 3D-MOT intervention, participants reported fewer total daily life challenges on the MPAI-4 at T1 (Mean = 30.6 ± 15.7) compared to baseline (Mean = 50.7 ± 21.2), with a mean difference of -20.1 (95% CI [-36.2, -4.7]) and a large effect size (Hedges' g = -0.94, 95% CI [-1.64, -0.49]). In the control group, daily life challenges slightly decreased from baseline (Mean = 43.5 ± 22.9) to T1 (Mean = 38.1 ± 24.9), with a mean difference of -5.4 (95% CI [-24.9, 14.3]) and a small effect size (Hedges' g = -0.20, 95% CI [-0.56, -0.02]).

One-month post-intervention, participants reported fewer daily life challenges at T2 (Mean = 32.1 ± 19.1) compared to baseline, with a mean difference of -18.6 (95% CI [-35.4, -1.4]; permutation p = 0.064) and a large effect size (Hedges' g = -0.84, 95% CI [-1.64 -0.45]). The control group's daily life challenges at T2 (Mean = 42.4 ± 24.4) did not differ meaningfully from baseline, with a mean difference of -1.1 (95% CI [-22.1, 17.2]) and a negligible effect size (Hedges' g = -0.04, 95% CI [-0.24, 0.14]) (Figure 3.2).

No significant between-group differences in MPAI-4 total daily life challenges were observed at T0, T1, or T2 (Table 3.3).

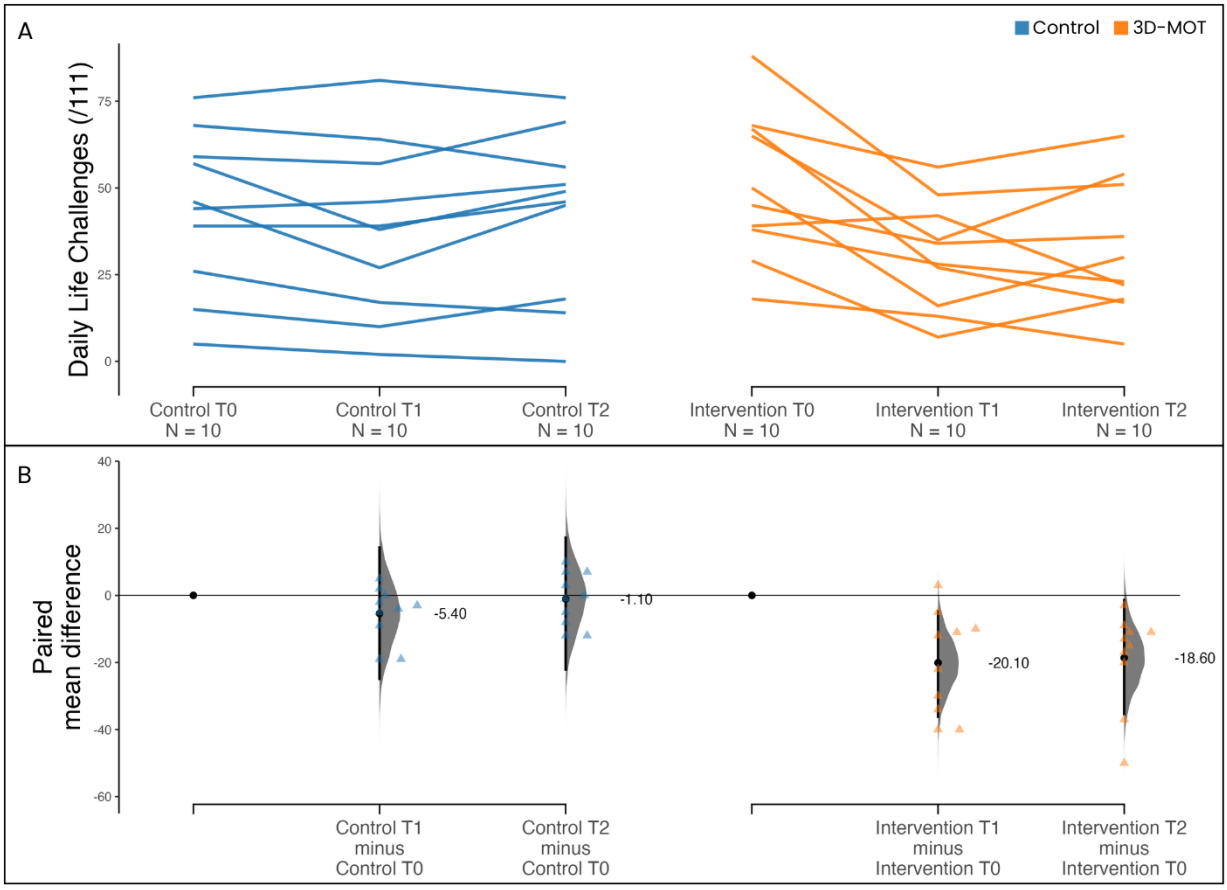

Figure 3.2 Reported daily life challenges on the MPAI-4 following 3D-MOT
(A) Reported daily life challenges in msTBI survivors on the MPAI-4 from the 10 control participants and 10 3D-MOT intervention participants assessed at baseline (T0), follow-up (T1), and one-month follow-up (T2). (B) Paired mean differences in MPAI-4 daily life challenges for the control group and the 3D-MOT intervention group, with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples. Negative mean difference values indicate a decrease in daily life challenges.

Breaking down the MPAI-4 into its subscales, the intervention group had a reduction in ability challenges at T1 (Mean = 15.2 ± 7.7) compared to baseline (Mean = 24.6 ± 8.8), with a mean difference of -9.4 (95% CI [-16.3, -2.5]) and a large effect size (Hedges' g = -1.03, 95% CI [-1.96, -0.46]). The control group had no meaningful change in ability challenges at T1 (Mean = 16.7 ± 9.4) compared to baseline (Mean = 18.4 ± 9.0), with a mean difference of -1.7 (95% CI [-9.3, 5.9]) and a negligible effect size (Hedges' g = -0.17, 95% CI [-0.49, 0.05]).

The intervention group had reductions in their reported ability challenges one-month post-intervention at T2 (Mean = 16.4 ± 11.3) compared to baseline, with a mean difference of -8.2 (95% CI [-16.6, 0.3]) and a medium effect size (Hedges' g = -0.71, 95% CI [-1.40, -0.19]). The control group's ability challenges at T2 (Mean = 16.7 ± 10.3) did not differ meaningfully from baseline,

with a mean difference of -1.7 (95% CI [-9.7, 6.1]) and a negligible effect size (Hedges' g = -0.16, 95% CI [-0.52, 0.23]) (Figure 3.3).

No significant between-group differences in MPAI-4 ability challenges were observed at T0, T1, or T2 (Table 3.3).

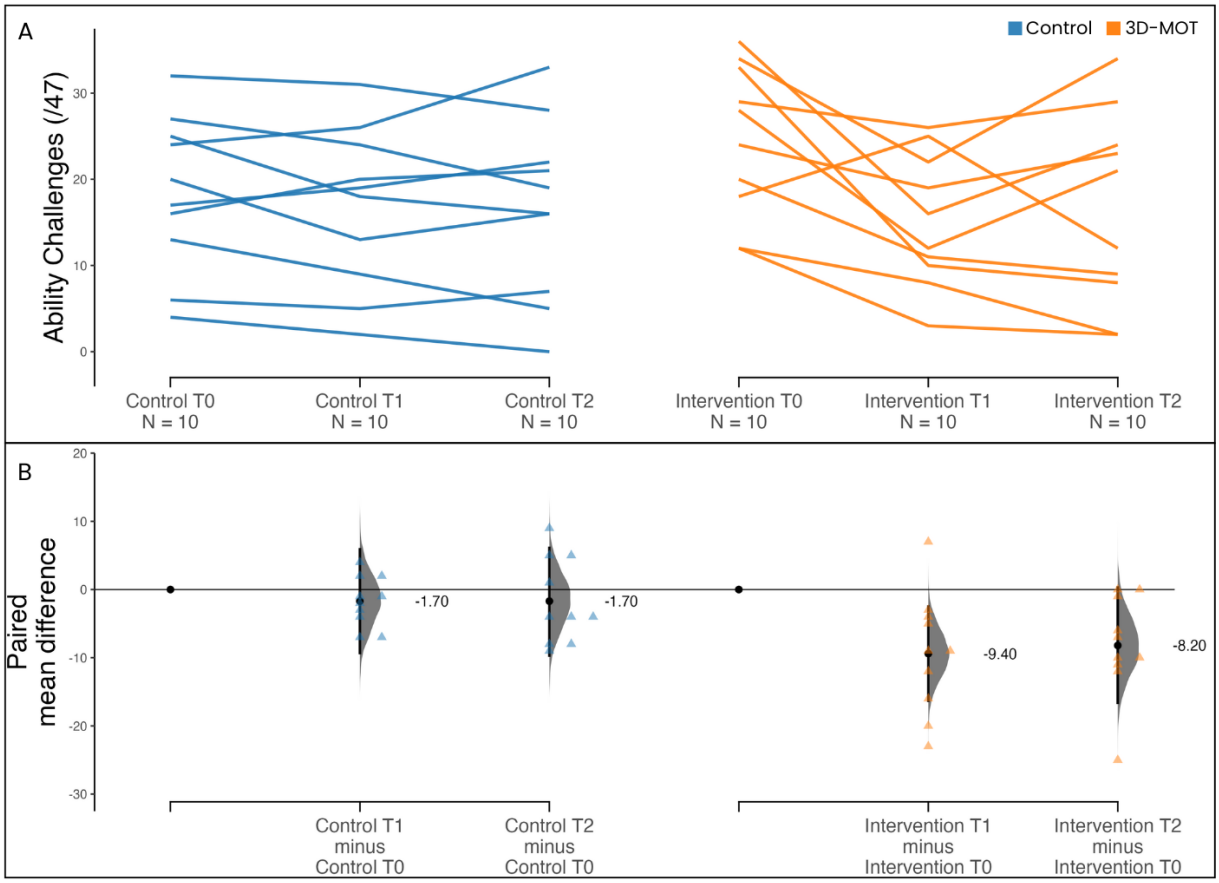

Figure 3.3 Reported ability challenges on the MPAI-4 following 3D-MOT
(A) Reported ability challenges in msTBI survivors on the MPAI-4 from the 10 control participants and 10 3D-MOT intervention participants assessed at baseline (T0), follow-up (T1), and one-month follow-up (T2). The ability challenges subscale evaluates difficulties with physical, cognitive, and sensory abilities. (B) Paired mean differences in MPAI-4 ability challenges for the control group and the 3D-MOT intervention group, with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples. Negative mean difference values indicate a decrease in ability challenges.

As for the adjustment MPAI-4 subscale, participants in the 3D-MOT intervention group had reductions in adjustment challenges at T1 (Mean = 13.0 ± 9.0) compared to baseline (Mean = 21.1 ± 10.4), with a mean difference of -8.1 (95% CI [-16.7, 0.1]) and a medium effect size (Hedges' g = -0.74, 95% CI [-1.24, -0.35]). The control group had a slight reduction in MPAI-4 adjustment challenges at T1 (Mean = 18.2 ± 12.4) compared to baseline (Mean = 21.9 ± 11.5),

with a mean difference of -3.7 (95% CI [-13.3, 6.6]) and a small effect size (Hedges' g = -0.30, 95% CI [-0.52, -0.03]).

One-month post-intervention, participants were still reporting reductions in adjustment challenges at T2 (Mean = 13.2 ± 8.8) compared to baseline, with a mean difference of -7.9 (95% CI [-16.1, 0.0]) and a medium effect size (Hedges' g = -0.74, 95% CI [-1.63, -0.37]). The control group reported adjustment challenges at T2 (Mean = 22.4 ± 12.0) that did not differ meaningfully from baseline, with a mean difference of 0.5 (95% CI [-10.1, 9.5]) and a negligible effect size (Hedges' g = 0.04, 95% CI [-0.12, 0.20]) (Figure 3.4).

No significant between-group differences in MPAI-4 adjustment challenges were observed at T0, T1, or T2 (Table 3.3).

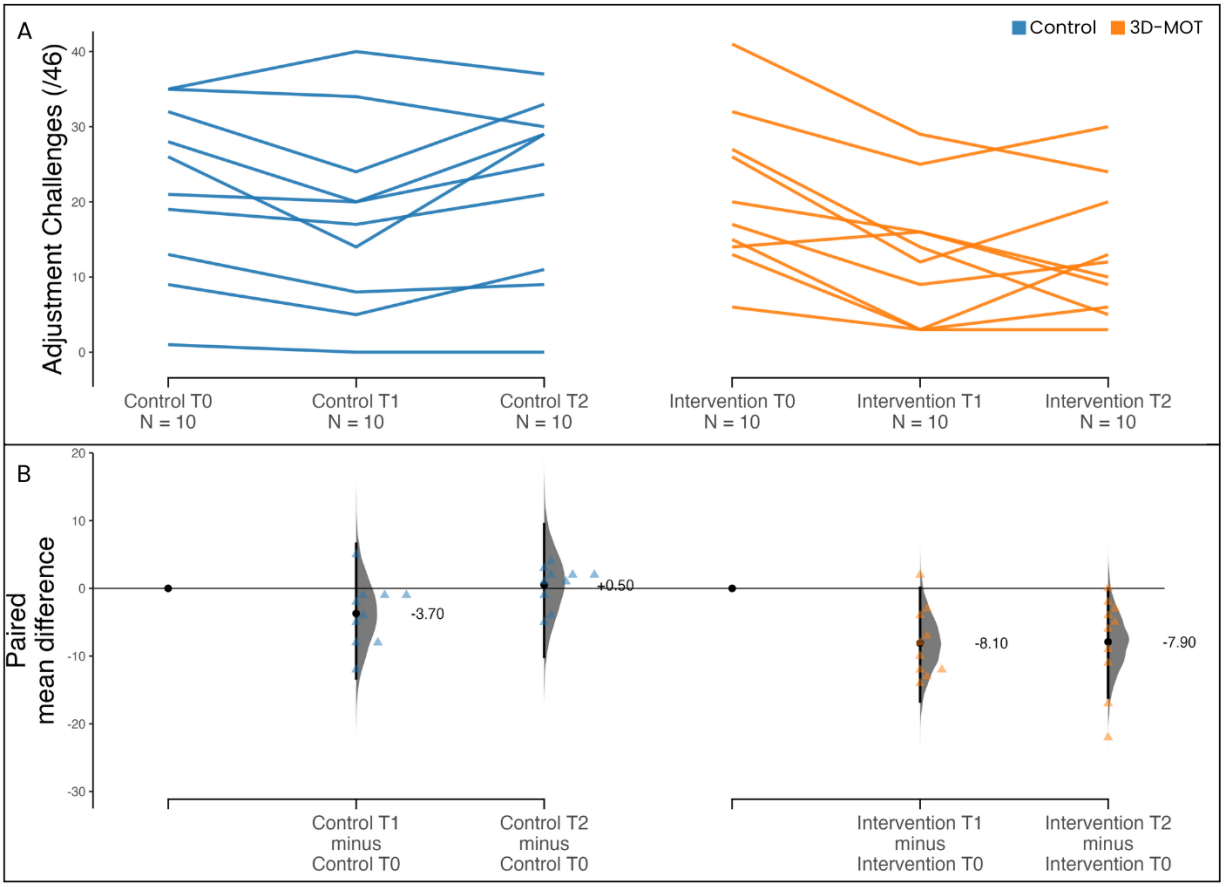

Figure 3.4 Reported adjustment challenges on the MPAI-4 following 3D-MOT
(A) Reported adjustment challenges in msTBI survivors on the MPAI-4 from the 10 control participants and 10 3D-MOT intervention participants assessed at baseline (T0), follow-up (T1), and one-month follow-up (T2). The adjustment challenges subscale evaluates difficulties with emotional, interpersonal, and behavioral domains. (B) Paired mean differences in MPAI-4 adjustment challenges for the control group and the 3D-MOT intervention group, with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples. Negative mean difference values indicate a decrease in adjustment challenges.

On the MPAI-4 participation subscale, the intervention group reported reduced participation challenges at T1 (Mean = 6.9 ± 5.0) compared to baseline (Mean = 10.5 ± 7.0), with a mean difference of -3.6 (95% CI [-8.8, 1.5]) and a medium effect size (Hedges' g = -0.52, 95% CI [-1.24, -0.04]). The control group had no meaningful change in participation challenges at T1 (Mean = 8.5 ± 7.6) compared to baseline (Mean = 10.0 ± 6.9), with a mean difference of -1.5 (95% CI [-7.3, 4.7]) and a negligible effect size (Hedges' g = -0.18, 95% CI [-0.65, 0.02]).

One-month post-intervention, participants reported reduced participation challenges at T2 (Mean = 5.9 ± 4.6) compared to baseline, with a mean difference of -4.6 (95% CI [-9.6, 0.4]) and a medium effect size (Hedges' g = -0.68, 95% CI [-1.44, -0.18]). The control group reported

participation challenges with no meaningful difference from baseline to T2 (Mean = 9.8 ± 7.4), with a mean difference of -0.2 (95% CI [-6.0, 5.9]) and a negligible effect size (Hedges' *g* = -0.03, 95% CI [-0.34, 0.14]) (Figure 3.5).

No significant between-group differences in MPAI-4 participation challenges were observed at T0, T1, or T2 (Table 3.3).

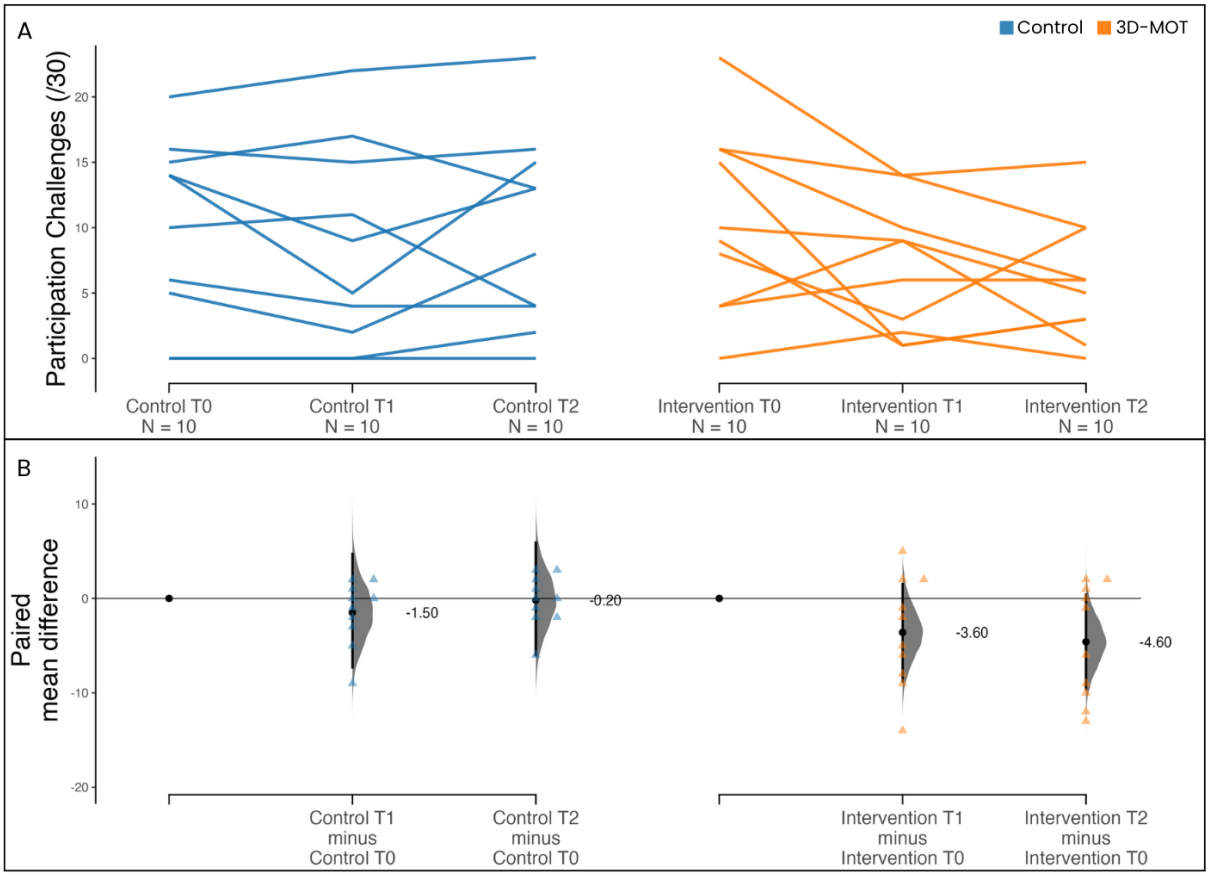

Figure 3.5 Reported participation challenges on the MPAI-4 following 3D-MOT
(A) Reported participation challenges in msTBI survivors on the MPAI-4 from the 10 control participants and 10 3D-MOT intervention participants assessed at baseline (T0), follow-up (T1), and one-month follow-up (T2). The participation challenges subscale evaluates difficulties engaging with community and daily life activities. (B) Paired mean differences in MPAI-4 participation challenges for the control group and the 3D-MOT intervention group, with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples. Negative mean difference values indicate a decrease in participation challenges.

3.2.2 Perceived TBI Symptoms After 3D-MOT

Intervention participants reported reduced TBI symptom severity on the SCAT-5 at T1 (Mean = 37.1 ± 23.2) compared to baseline (Mean = 63.5 ± 33.3), with a mean difference of -26.4 (95% CI [-48.4, -0.4]) and a medium effect size (Hedges' *g* = -0.76, 95% CI [-2.08, -0.32]). The

control group had no meaningful reductions in TBI symptom severity at T1 (Mean = 53.8 ± 32.9) compared to baseline (Mean = 57.8 ± 28.5), with a mean difference of –4.0 (95% CI [-30.7, 20.2]) and a negligible effect size (Hedges' *g* = -0.11, 95% CI [-0.29, 0.16]).

One-month post-intervention, participants continued to report reductions in TBI symptom severity at T2 (Mean = 42.8 ± 22.8) compared to baseline, with a mean difference of -20.7 (95% CI [-41.9, 5.0]) and a medium effect size (Hedges' *g* = -0.63, 95% CI [-1.66, -0.10]). The control group had minor reductions in TBI symptom severity at T2 (Mean = 51.4 ± 29.7) compared to baseline, with a mean difference of -6.4 (95% CI [-30.4, 18.1]) and a small effect size (Hedges' *g* = -0.20, 95% CI [-0.59, 0.02]) (Figure 3.6).

No significant between-group differences in TBI symptom severity were observed at T0, T1, or T2 (Table 3.3).

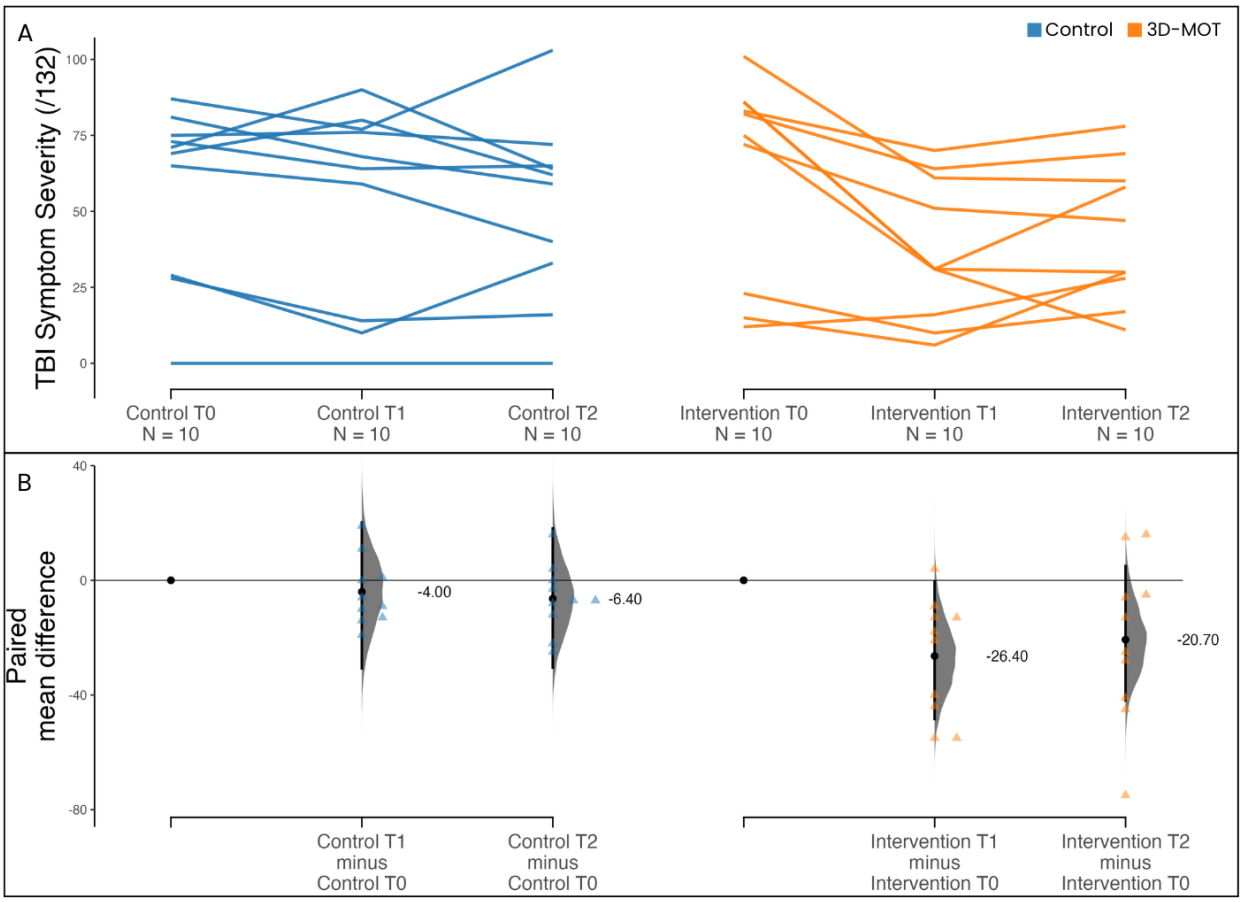

Figure 3.6 Reported SCAT-5 TBI symptom severity following 3D-MOT
(A) TBI symptom severity reported by msTBI survivors on the SCAT-5 from the 10 control participants and 10 3D-MOT intervention participants assessed at baseline (T0), follow-up (T1), and one-month follow-up (T2). Participants rated 22 symptoms from 0-6, with 6 being the most severe. (B) Paired mean differences in SCAT-5 symptom severity for the control group and the 3D-MOT intervention group, with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples. Negative mean difference values indicate a decrease in symptom severity.

For total number of TBI symptoms on the SCAT-5, participants in the intervention group reported slight reductions at T1 (Mean = 14.3 ± 6.2) compared to baseline (Mean = 16.8 ± 6.6), with a mean difference of -2.5 (95% CI [-7.6, 3.0]) and a small effect size (Hedges' g = -0.36, 95% CI [-1.03, 0.01]). The control group had no meaningful change in total TBI symptoms at T1 (Mean = 15.7 ± 7.7) compared to baseline (Mean = 17.2 ± 6.7), with a mean difference of -1.5 (95% CI [-7.6, 4.2]) and a negligible effect size (Hedges' g = -0.19, 95% CI [-0.81, 0.04]).

One-month post-intervention, participants had no meaningful change in total TBI symptoms at T2 (Mean = 16.0 ± 5.1) compared to baseline, with a mean difference of -0.8 (95% CI [-5.2, 4.5]) and a negligible effect size (Hedges' g = -0.12, 95% CI [-0.79, 0.37]). The control

group also had no meaningful change in total TBI symptoms at T2 (Mean = 17.4 ± 6.9) compared to baseline, with a mean difference of 0.2 (95% CI [-5.8, 5.4]) and a negligible effect size (Hedges' *g* = 0.03, 95% CI [-0.02, 0.36]) (Figure 3.7).

No significant between-group differences in total TBI symptoms were observed at T0, T1, or T2 (Table 3.3).

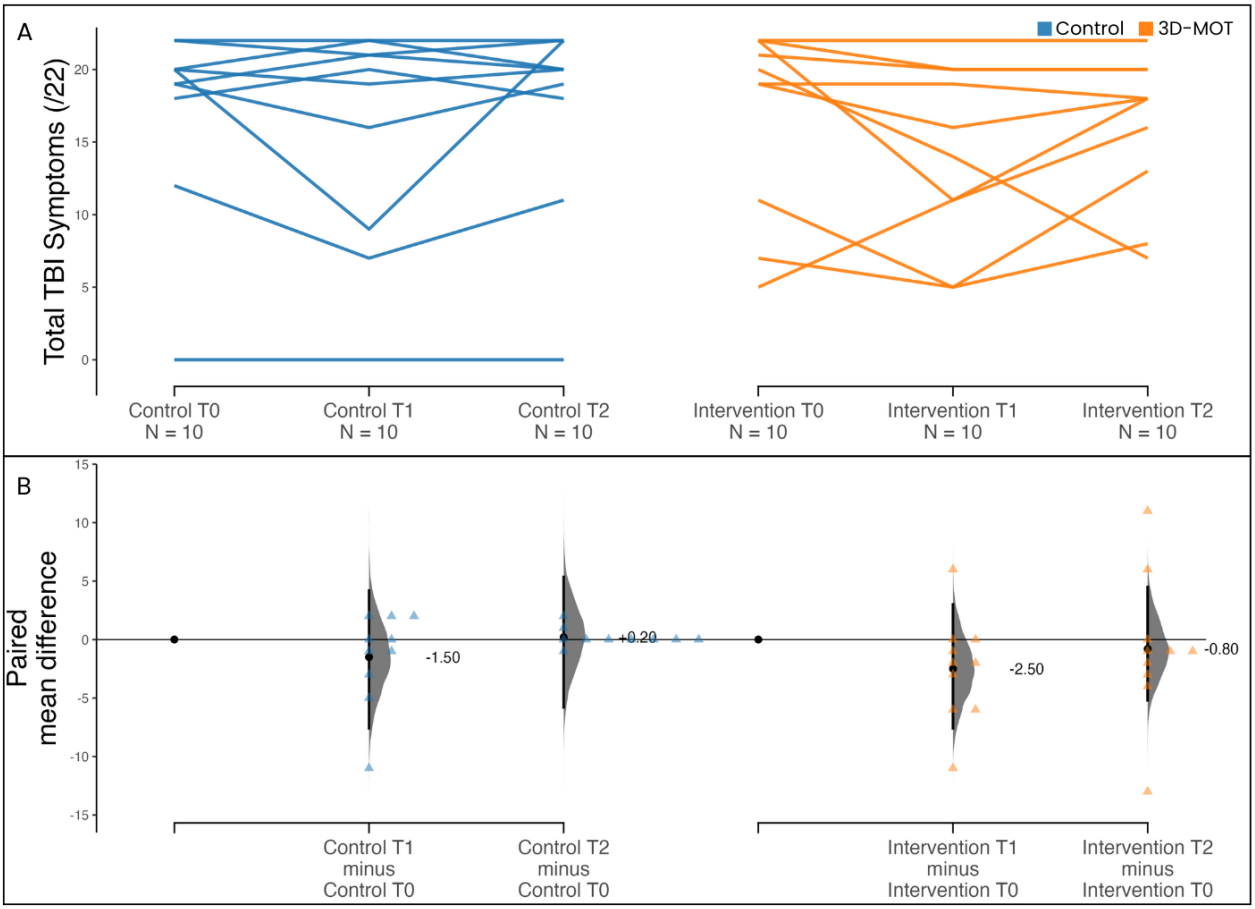

Figure 3.7 Total reported TBI symptoms on the SCAT-5 following 3D-MOT
(A) Number of reported TBI symptoms by msTBI survivors on the SCAT-5 from the 10 control participants and 10 3D-MOT intervention participants assessed at baseline (T0), follow-up (T1), and one-month follow-up (T2). (B) Paired mean differences in the number of SCAT-5 symptoms for the control group and the 3D-MOT intervention group, with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples. Negative mean difference values indicate a decrease in number of symptoms.

3.2.3 Perceived Stress After 3D-MOT

Participants reported reduced perceived stress after 3D-MOT intervention at T1 (Mean = 12.4 ± 8.7) compared to baseline (Mean = 18.2 ± 8.1), with a mean difference of -5.8 (95% CI [-

12.5, 1.5]) and medium effect size (Hedges' g = -0.63, 95% CI [-1.28, -0.19]). The control group had no meaningful change in perceived stress at T1 (Mean = 17.5 ± 9.3) compared to baseline (Mean = 19.4 ± 7.0), with a mean difference of -1.9 (95% CI [-8.9, 4.8]) and negligible effect size (Hedges' g = -0.19, 95% CI [-0.77, 0.06]).

One-month post-intervention, participants continued to report reduced perceived stress at T2 (Mean = 11.0 ± 6.9) compared to baseline, with a mean difference of -7.2 (95% CI [-13.1, -0.7]) and large effect size (Hedges' g = -0.87, 95% CI [-1.65, -0.45]). The control group reported minor reductions in perceived stress at T2 (Mean = 16.6 ± 7.2) compared to baseline, with a mean difference of -2.8 (95% CI [-9.3, 2.4]) and small effect size (Hedges' g = -0.36, 95% CI [-0.87, 0.09]) (Figure 3.8). A summary of findings for the self-reported outcomes in this study are presented in Table 3.2.

No significant between-group differences in perceived stress were observed at T0, T1, or T2 (Table 3.3).

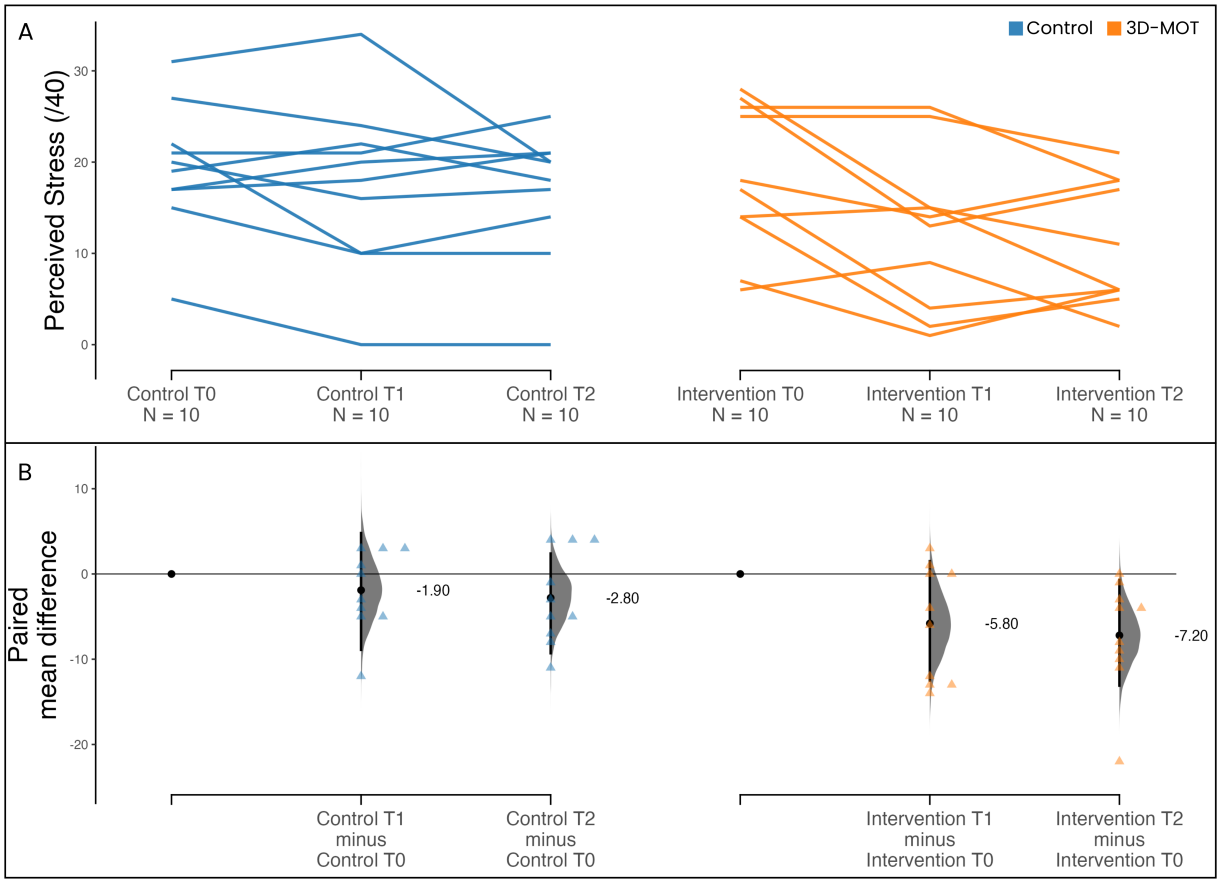

Figure 3.8 Reported stress on the PSS following 3D-MOT
(A) Perceived stress reported by msTBI survivors on the PSS from the 10 control participants and 10 3D-MOT intervention participants assessed at baseline (T0), follow-up (T1), and one-month follow-up (T2). Participants ranked 10 statements about stressors on a Likert scale from 0 to 4. (B) Paired mean differences in PSS scores for the control group and the 3D-MOT intervention group, with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples. Negative mean difference values indicate a decrease in perceived stress.

Table 3.2 Summary of results for self-reported outcomes in msTBI survivors.

Assessment	Group	Comparison	Mean difference	95% CI	Hedges' *g*
MPAI-4 daily life challenges	3D-MOT intervention	T0 vs T1	-20.1	[-36.2, -4.7]	**-0.94**
		T0 vs T2	-18.6	[-35.4, -1.4]	**-0.84**
	Control	T0 vs T1	-5.4	[-24.9, 14.3]	-0.20
		T0 vs T2	-1.1	[-22.1, 17.2]	-0.04
MPAI-4 ability challenges	3D-MOT intervention	T0 vs T1	-9.4	[-16.3, -2.5]	**-1.03**
		T0 vs T2	-8.2	[-16.6, 0.3]	**-0.71**
	Control	T0 vs T1	-1.7	[-9.3, 5.9]	-0.17
		T0 vs T2	-1.7	[-9.7, 6.1]	-0.16
MPAI-4 adjustment challenges	3D-MOT intervention	T0 vs T1	-8.1	[-16.7, 0.1]	**-0.74**
		T0 vs T2	-7.9	[-16.1, 0.0]	**-0.74**
	Control	T0 vs T1	-3.7	[-13.3, 6.6]	-0.30
		T0 vs T2	0.5	[-10.1, 9.5]	0.04
MPAI-4 participation challenges	3D-MOT intervention	T0 vs T1	-3.6	**[**-8.8, 1.5]	**-0.52**
		T0 vs T2	-4.6	[-9.6, 0.4]	**-0.68**
	Control	T0 vs T1	-1.5	[-7.3, 4.7]	-0.18
		T0 vs T2	-0.2	[-6.0, 5.9]	-0.03
SCAT-5 symptom severity	3D-MOT intervention	T0 vs T1	-26.4	[-48.4, -0.4]	**-0.76**
		T0 vs T2	-20.7	[-41.9, 5.0]	**-0.63**
	Control	T0 vs T1	–4.0	[-30.7, 20.2]	-0.11
		T0 vs T2	-6.4	[-30.4, 18.1]	-0.20
SCAT-5 total symptoms	3D-MOT intervention	T0 vs T1	-2.5	[-7.6, 3.0]	-0.36
		T0 vs T2	-0.8	[-5.2, 4.5]	-0.12
	Control	T0 vs T1	-1.5	[-7.6, 4.2]	-0.19
		T0 vs T2	0.2	[-5.8, 5.4]	0.03
PSS perceived stress	3D-MOT intervention	T0 vs T1	-5.8	[-12.5, 1.5]	**-0.63**
		T0 vs T2	-7.2	[-13.1, -0.7]	**-0.87**
	Control	T0 vs T1	-1.9	[-8.9, 4.8]	-0.19
		T0 vs T2	-2.8	[-9.3, 2.4]	-0.36

Note. Medium and large effect sizes ($|g| \geq 0.5$) are bolded.

Table 3.3 Between-group comparisons of self-reported outcome measures.

Assessment	T0 comparison p-value	T1 comparison p-value	T2 comparison p-value
MPAI-4 daily life challenges	0.474	0.431	0.307
MPAI-4 ability challenges	0.138	0.700	0.951
MPAI-4 adjustment challenges	0.872	0.299	0.066
MPAI-4 participation challenges	0.874	0.587	0.173
SCAT-5 symptom severity	0.364	0.185	0.478
SCAT-5 total symptoms	0.878	0.425	0.205
PSS perceived stress	0.727	0.221	0.091

Note. P-values are calculated from independent samples t-tests or Mann-Whitney U tests, depending on data normality.

3.3. The Effect of 3D-MOT on Cognitive Function in msTBI Survivors

3.3.1 California Verbal Learning Test: Verbal Learning and Memory

Evaluating total words recalled across Trials 1-5 in the CVLT-II, intervention participants had no meaningful change at T1 (Mean = 51.7 ± 12.3) compared to baseline (Mean = 51.6 ± 12.7), with a mean difference of 0.1 (95% CI [-10.7, 10.3]) and a negligible effect size (Hedges' g = 0.01, 95% CI [-0.19, 0.41]). Control participants had a minor reduction in total words recalled at T1 (Mean = 42.9 ± 11.4) compared to baseline (Mean = 47.1 ± 11.9), with a mean difference of -4.2 (95% CI [-13.7, 5.7]) and a small effect size (Hedges' g = -0.33, 95% CI [-0.81, 0.02]).

One-month post-intervention, the nine participants who completed the assessment had a minor increase in total words recalled at T2 (Mean = 59.1 ± 12.9) compared to baseline (Mean = 53.1 ± 12.5), with a mean difference of 6.0 (95% CI [-5.8, 16.1]) and a small effect size (Hedges' g = 0.42, 95% CI [-0.19, 0.41]). The nine participants in the control group showed no meaningful change in total words recalled at T2 (Mean = 48.6 ± 7.3) compared to baseline (Mean = 49.9 ± 8.5), with a mean difference of -1.3 (95% CI [-8.9, 5.1]) and a negligible effect size (Hedges' g = -0.15, 95% CI [-1.09, 0.41]) (Figure 3.9).

No significant between-group differences in CVLT-II Trials 1-5 scores were observed at T0 or T1, however a significant difference was observed at T2 (p = 0.049) (Table 3.5).

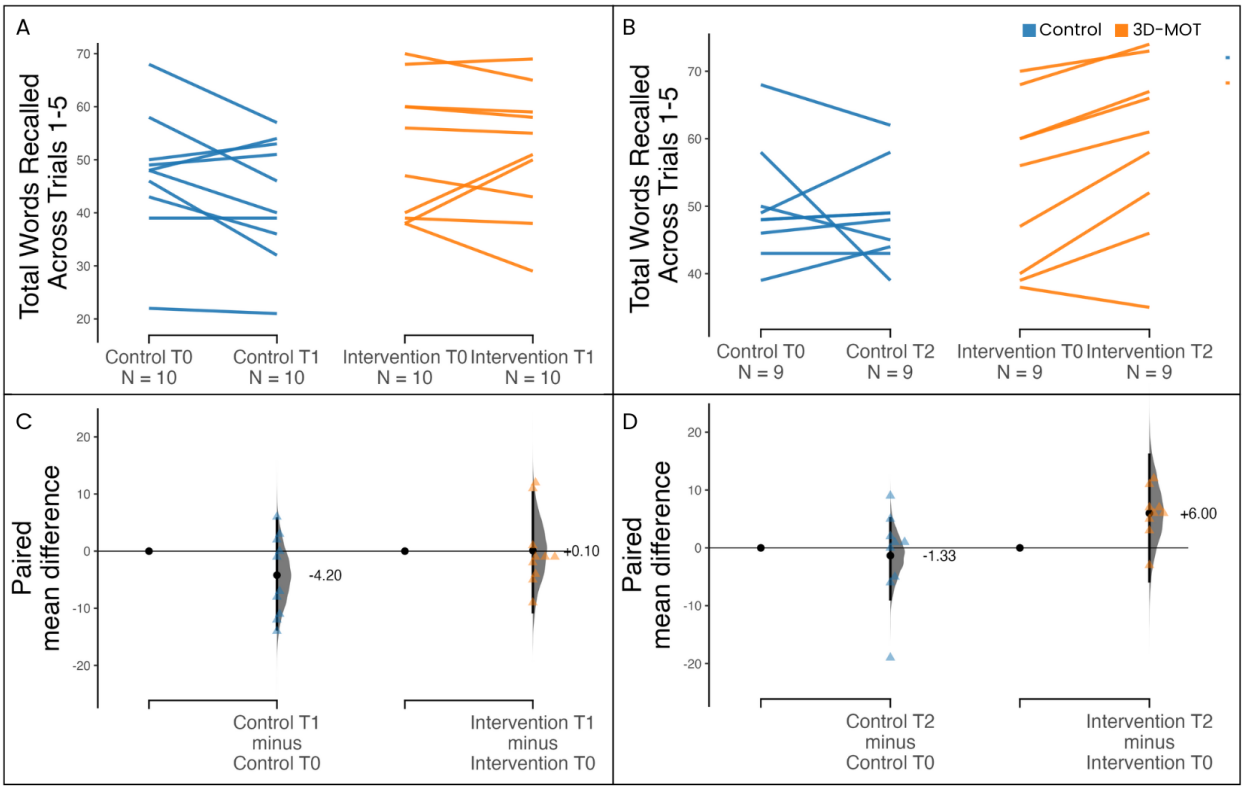

Figure 3.9 Performance on CVLT-II Trials 1-5 following 3D-MOT
(A, B) Total words recalled across Trials 1-5 of the CVLT-II by 10 control and 10 3D-MOT intervention participants with msTBI assessed at baseline (T0) and follow-up (T1) (Panel A), and by nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). (C, D) Paired mean differences of CVLT-II Trials 1-5 scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

For short-delay free recall on the CVLT-II, intervention participants had a minor increase in performance at T1 (Mean = 11.0 ± 4.2) compared to baseline (Mean = 10.1 ± 3.6), with a mean difference of 0.9 (95% CI [-2.4, 4.2]) and a small effect size (Hedges' *g* = 0.20, 95% CI [-0.12, 0.51]). The control group had a small reduction in CVLT-II short-delay free recall at T1 (Mean = 8.8 ± 3.6) compared to baseline (Mean = 9.7 ± 3.1), with a mean difference of -0.9 (95% CI [-3.8, 1.7]) and a small effect size (Hedges' *g* = -0.24, 95% CI [-0.81, 0.31]).

The nine participants who completed the one-month post-intervention assessment demonstrated improvements in CVLT-II short-delay free recall at T2 (Mean = 12.9 ± 2.9) compared to baseline (Mean = 10.7 ± 3.3), with a mean difference of 2.2 (95% CI [-0.6, 4.8]) and a medium effect size (Hedges' *g* = 0.65, 95% CI [0.28, 1.40]). The nine control participants had no meaningful change in CVLT-II short-delay free recall at T2 (Mean = 10.4 ± 1.6) compared to

baseline (Mean = 10.2 ± 2.8), with a mean difference of 0.2 (95% CI [-1.8, 2.1]) and a negligible effect size (Hedges' g = 0.09, 95% CI [-0.44, 1.03]) (Figure 3.10).

No significant between-group differences in CVLT-II short-delay free recall scores were observed at T0 or T1, however a significant difference was observed at T2 (p = 0.039) (Table 3.5).

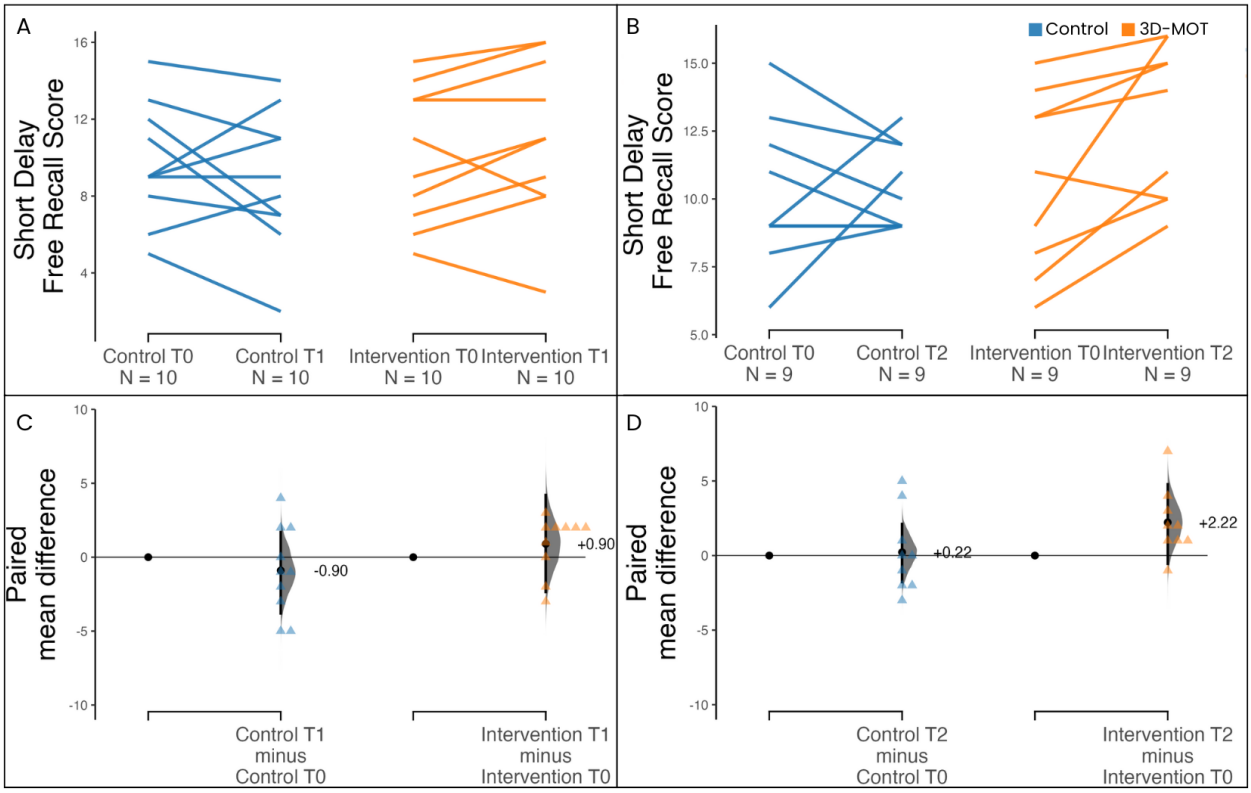

Figure 3.10 Performance on CVLT-II short-delay free recall following 3D-MOT
(A, B) CVLT-II short-delay free recall scores in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and the nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). Scores reflect the number of words correctly recalled out of 16. (C, D) Paired mean differences of CVLT-II short-delay free recall scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

For short-delay cued recall on the CVLT-II, intervention participants had a slight improvement in scores at T1 (Mean = 12.5 ± 3.7) compared to baseline (Mean = 11.1 ± 3.8), with a mean difference of 1.4 (95% CI [-1.8, 4.4]) and a small effect size (Hedges' g = 0.34, 95% CI [-0.09, 0.84]). The control group had no meaningful difference in CVLT-II short-delay cued recall at T1 (Mean = 10.4 ± 3.2) compared to baseline (Mean = 10.8 ± 3.0), with a mean difference of -0.4 (95% CI [-3.1, 2.0]) and a negligible effect size (Hedges' g = -0.12, 95% CI [-0.59, 0.34]).

The nine participants who completed the one-month post-intervention assessment demonstrated improvements in CVLT-II short-delay cued recall at T2 (Mean = 13.7 ± 2.4) compared to baseline (Mean = 11.7 ± 3.5), with a mean difference of 2.0 (95% CI [-0.7, 4.6]) and a medium effect size (Hedges' *g* = 0.55, 95% CI [0.20, 1.30]). The nine control participants had no meaningful change in CVLT-II short-delay cued recall at T2 (Mean = 11.7 ± 2.4) compared to baseline (Mean = 11.4 ± 2.4), with a mean difference of 0.2 (95% CI [-2.0, 2.1]) and a negligible effect size (Hedges' *g* = 0.08, 95% CI [-0.47, 0.73]) (Figure 3.11).

No significant between-group differences in CVLT-II short-delay cued recall scores were observed at T0, T1, or T2 (Table 3.5).

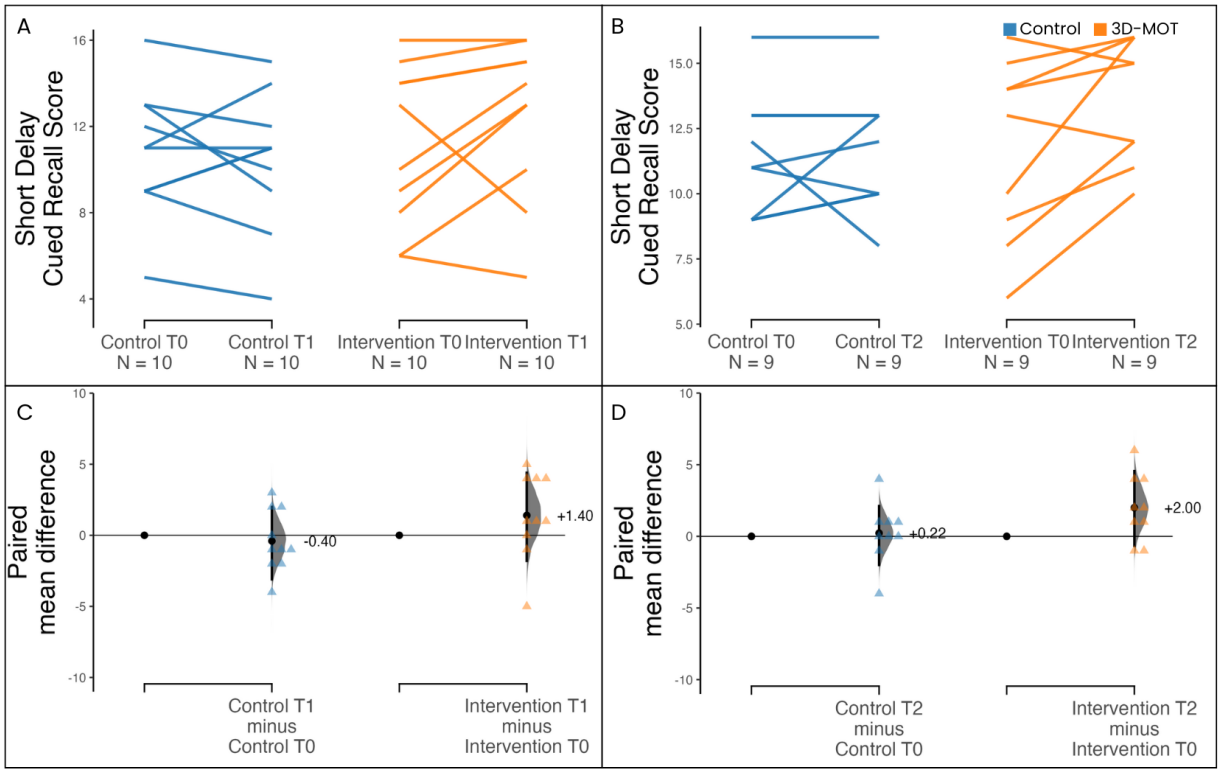

Figure 3.11 Performance on CVLT-II short-delay cued recall following 3D-MOT
(A, B) CVLT-II short-delay cued recall scores in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). Scores reflect the number of words correctly recalled out of 16. (C, D) Paired mean differences of CVLT-II short-delay cued recall scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

For long-delay free recall on the CVLT-II, intervention participants had no meaningful change at T1 (Mean = 11.3 ± 4.2) compared to baseline (Mean = 10.6 ± 3.6), with a mean difference of 0.7 (95% CI [-2.8, 3.8]) and a negligible effect size (Hedges' *g* = 0.16, 95% CI [-0.14, 0.58]). The control group had a slight reduction in the CVLT-II long-delay free recall score at T1 (Mean = 8.9 ± 3.8) compared to baseline (Mean = 9.8 ± 3.3), with a mean difference of -0.9 (95% CI [-4.0, 1.8]) and a small effect size (Hedges' *g* = -0.23, 95% CI [-0.76, 0.00]).

The nine participants who completed the one-month post-intervention assessment demonstrated improvements in CVLT-II long-delay free recall at T2 (Mean = 13.2 ± 2.7) compared to baseline (Mean = 11.2 ± 3.2), with a mean difference of 2.0 (95% CI [-0.9, 4.3]) and a medium effect size (Hedges' *g* = 0.59, 95% CI [0.14, 1.38]). The nine control participants had no meaningful change at T2 (Mean = 10.7 ± 2.6) compared to baseline (Mean = 10.4 ± 2.7), with a mean difference of 0.2 (95% CI [-2.2, 2.4]) and a negligible effect size (Hedges' *g* = 0.07, 95% CI [-0.23, 0.63]) (Figure 3.12).

No significant between-group differences in CVLT-II long-delay free recall scores were observed at T0, T1, or T2 (Table 3.5).

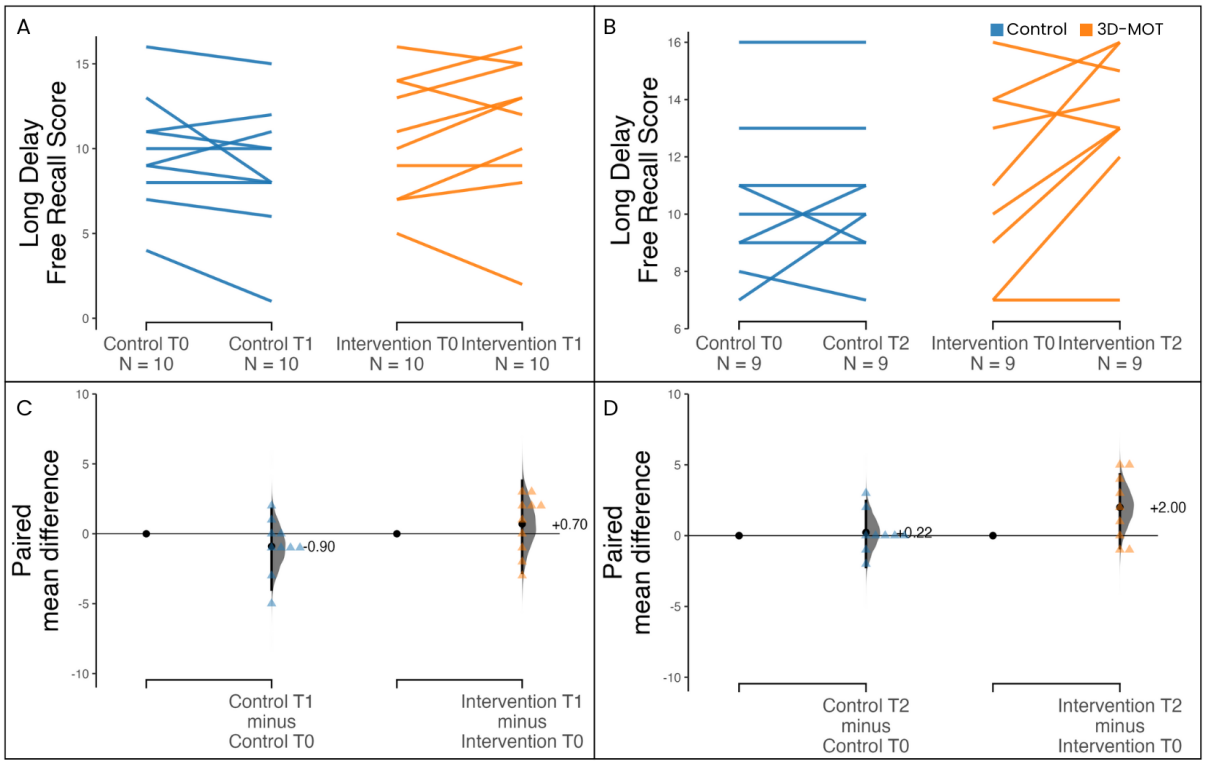

Figure 3.12 Performance on CVLT-II long-delay free recall following 3D-MOT
(A, B) CVLT-II long-delay free recall scores in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). Scores reflect the number of words correctly recalled out of 16. (C, D) Paired mean differences of CVLT-II long-delay free recall scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

For long-delay cued recall on the CVLT-II, intervention participants had a small improvement at T1 (Mean = 11.6 ± 4.1) compared to baseline (Mean = 9.7 ± 4.8), with a mean difference of 1.9 (95% CI [-1.9, 5.6]) and a small effect size (Hedges' g = 0.39, 95% CI [-0.11, 1.22]). The control group had no meaningful difference in CVLT-II long-delay cued recall at T1 (Mean = 10.0 ± 3.0) compared to baseline (Mean = 9.8 ± 3.5), with a mean difference of 0.2 (95% CI [-2.5, 2.8]) and a negligible effect size (Hedges' g = 0.05, 95% CI [-0.45, 0.43]).

The nine participants who completed the one-month post-intervention assessment demonstrated improvements in CVLT-II long-delay cued recall at T2 (Mean = 13.7 ± 2.4) compared to baseline (Mean = 10.2 ± 4.7), with a mean difference of 3.4 (95% CI [0.6, 7.2]) and a large effect size (Hedges' g = 0.81, 95% CI [0.27, 1.46]). The nine control participants had a small improvement in CVLT-II long-delay cued recall at T2 (Mean = 11.8 ± 3.0) compared to

baseline (Mean = 10.4 ± 3.1), with a mean difference of 1.3 (95% CI [-1.7, 3.7]) and a small effect size (Hedges' g = 0.40, 95% CI [0.02, 1.11]) (Figure 3.13). A summary of results for verbal learning and memory, as measured through the CVLT-II, is displayed in Table 3.4.

No significant between-group differences in CVLT-II long-delay cued recall scores were observed at T0, T1, or T2 (Table 3.5).

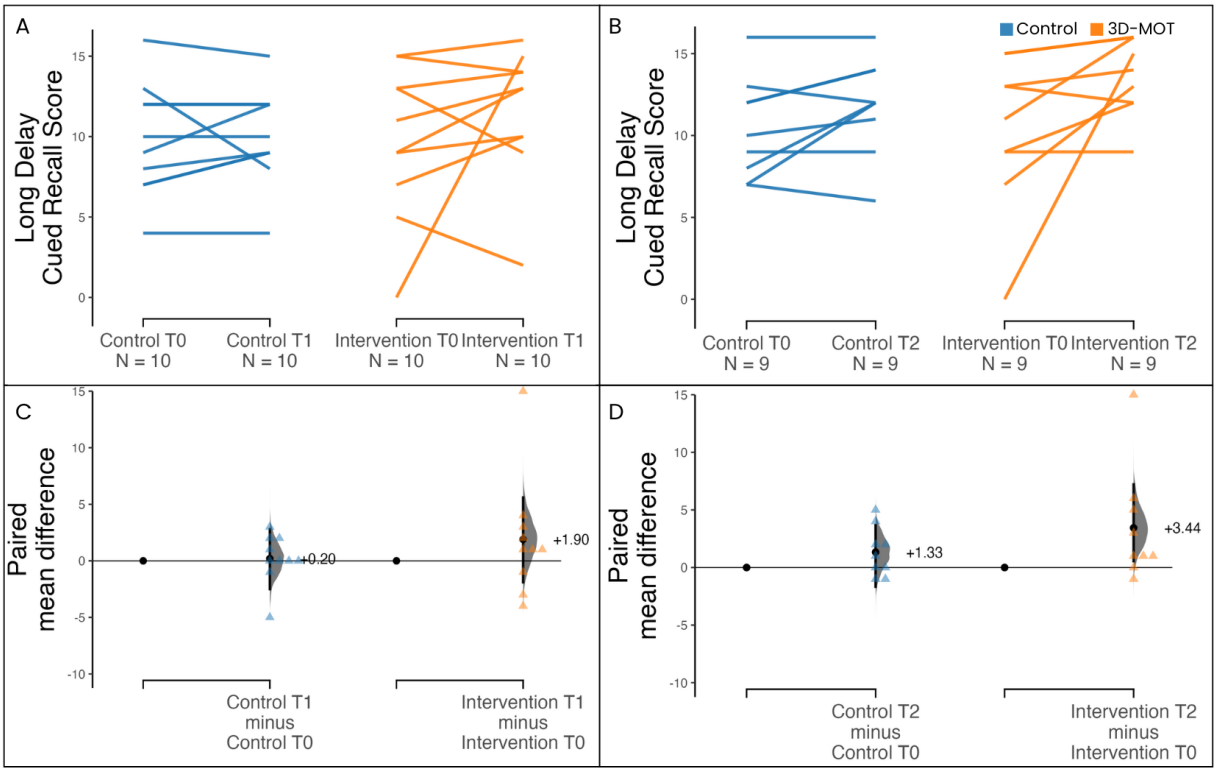

Figure 3.13 Performance on CVLT-II long-delay cued recall following 3D-MOT
(A, B) CVLT-II long-delay cued recall scores in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). Scores reflect the number of words correctly recalled out of 16. (C, D) Paired mean differences of CVLT-II long-delay cued recall scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

Table 3.4 Summary of results for the CVLT-II outcomes in msTBI survivors.

Assessment	Group	Comparison	Mean difference	95% CI	Hedges' g
California Verbal Learning Test trials 1-5 score	3D-MOT intervention	T0 vs T1	0.1	[-10.7, 10.3]	0.01
		T0 vs T2	6.0	[-5.8, 16.1]	0.42
	Control	T0 vs T1	-4.2	[-13.7, 5.7]	-0.33
		T0 vs T2	-1.3	[-8.9, 5.1]	-0.15
California Verbal Learning Test short-delay free recall	3D-MOT intervention	T0 vs T1	0.9	[-2.4, 4.2]	0.20
		T0 vs T2	2.2	[-0.6, 4.8]	**0.65**
	Control	T0 vs T1	-0.9	[-3.8, 1.7]	-0.24
		T0 vs T2	0.2	[-1.8, 2.1]	0.09
California Verbal Learning Test short-delay cued recall	3D-MOT intervention	T0 vs T1	1.4	[-1.8, 4.4]	0.34
		T0 vs T2	2.0	[-0.7, 4.6]	**0.55**
	Control	T0 vs T1	-0.4	[-3.1, 2.0]	-0.12
		T0 vs T2	0.2	[-2.0, 2.1]	0.08
California Verbal Learning Test long-delay free recall	3D-MOT intervention	T0 vs T1	0.7	[-2.8, 3.8]	0.16
		T0 vs T2	2.0	[-0.9, 4.3]	**0.59**
	Control	T0 vs T1	-0.9	[-4.0, 1.8]	-0.23
		T0 vs T2	0.2	[-2.2, 2.4]	0.07
California Verbal Learning Test long-delay cued recall	3D-MOT intervention	T0 vs T1	1.9	[-1.9, 5.6]	0.39
		T0 vs T2	3.4	[0.6, 7.2]	**0.81**
	Control	T0 vs T1	0.2	[-2.5, 2.8]	0.05
		T0 vs T2	1.3	[-1.7, 3.7]	0.40

Note. Medium and large effect sizes ($|g| \geq 0.5$) are bolded.

Table 3.5 Between-group comparisons of CVLT-II scores.

Assessment	T0 comparison p-value	T1 comparison p-value	T2 comparison p-value
CVLT-II trials 1-5 score	0.425	0.114	**0.049**
CVLT-II short-delay free recall	0.792	0.222	**0.039**
CVLT-II short-delay cued recall	0.846	0.191	0.096
CVLT-II long-delay free recall	0.612	0.196	0.059
CVLT-II long-delay cued recall	0.958	0.331	0.155

Note. P-values are calculated from independent samples t-tests or Mann-Whitney U tests, depending on data normality. P-values < 0.05 are bolded.

3.3.2 Digit Span Task: Attention and Working Memory

Following 3D-MOT intervention, participants had slightly higher Digit Span Total scores at T1 (Mean = 27.9 ± 3.1) compared to baseline (Mean = 26.2 ± 3.5), with a mean difference of 1.7 (95% CI [-1.0, 4.5]) and a small effect size (Hedges' g = 0.46, 95% CI [-0.04, 0.94]). The control group's total scores at T1 (Mean = 28.2 ± 4.2) were not meaningfully different from

baseline (Mean = 28.8 ± 4.6), with a mean difference of -0.6 (95% CI [-4.3, 2.9]) and a negligible effect size (Hedges' g = -0.12, 95% CI [-0.67, 0.58]).

The nine participants who completed the one-month post-intervention neuropsychological assessment had higher Digit Span Total scores at T2 (Mean = 27.4 ± 3.7) compared to their baseline (Mean = 25.6 ± 3.1), with a mean difference of 1.9 (95% CI [-1.0, 5.0]) and a medium effect size (Hedges' g = 0.50, 95% CI [-0.10, 1.11]). The nine control participants showed minimal change at T2 (Mean = 29.6 ± 4.8) compared to their baseline (Mean = 29.2 ± 4.6), with a mean difference of 0.3 (95% CI [-4.1, 4.2]) and a negligible effect size (Hedges' g = 0.06, 95% CI [-0.32, 0.94]) (Figure 3.14).

No significant between-group differences in Digit Span Total scores were observed at T0, T1, or T2 (Table 3.7).

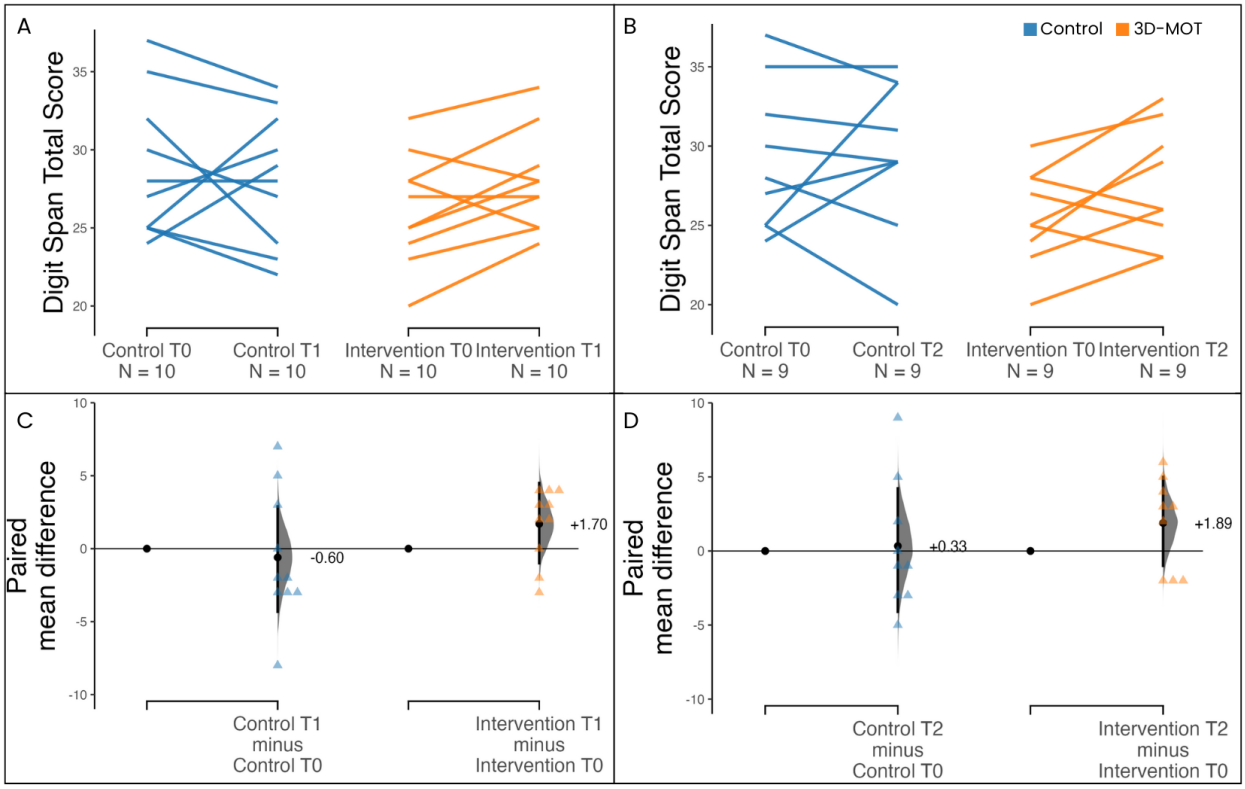

Figure 3.14 Digit Span Total scores following 3D-MOT
(A, B) Digit Span Total scores in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). (C, D) Paired mean differences in Digit Span Total scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

On the Digit Span Forward test, intervention participants had higher scores at T1 (Mean = 10.3 ± 1.6) compared to baseline (Mean = 9.1 ± 1.4), with a mean difference of 1.2 (95% CI [0.0, 2.5]) and a medium effect size (Hedges' *g* = 0.72, 95% CI [0.20, 1.40]). Control participants had no meaningful change in Digit Span Forward scores at T1 (Mean = 10.8 ± 2.4) compared to baseline (Mean = 11.3 ± 2.4), with a mean difference of -0.5 (95% CI [-2.5, 1.5]) and a negligible effect size (Hedges' *g* = -0.19, 95% CI [-0.81, 0.16]).

The nine participants who completed the one-month post-intervention neuropsychological assessment had higher Digit Span Forward scores at T2 (Mean = 9.8 ± 1.5) compared to baseline (Mean = 8.9 ± 1.3), with a mean difference of 0.9 (95% [CI -0.2, 2.1]) and a medium effect size (Hedges' *g* = 0.58, 95% CI [0.00, 1.33]). The nine control participants had lower Digit Span Forward scores at T2 (Mean = 10.7 ± 2.1) compared to baseline (Mean = 11.7 ± 2.2), with a mean difference of -1.0 (95% CI [-3.0, 0.9]) and a small effect size (Hedges' *g* = -0.41, 95% CI [-0.98, -0.11]) (Figure 3.15).

A significant between-group difference in Digit Span Forward scores was observed at T0 (p = 0.022). No significant between-group differences were observed at T1 or T2 (Table 3.7).

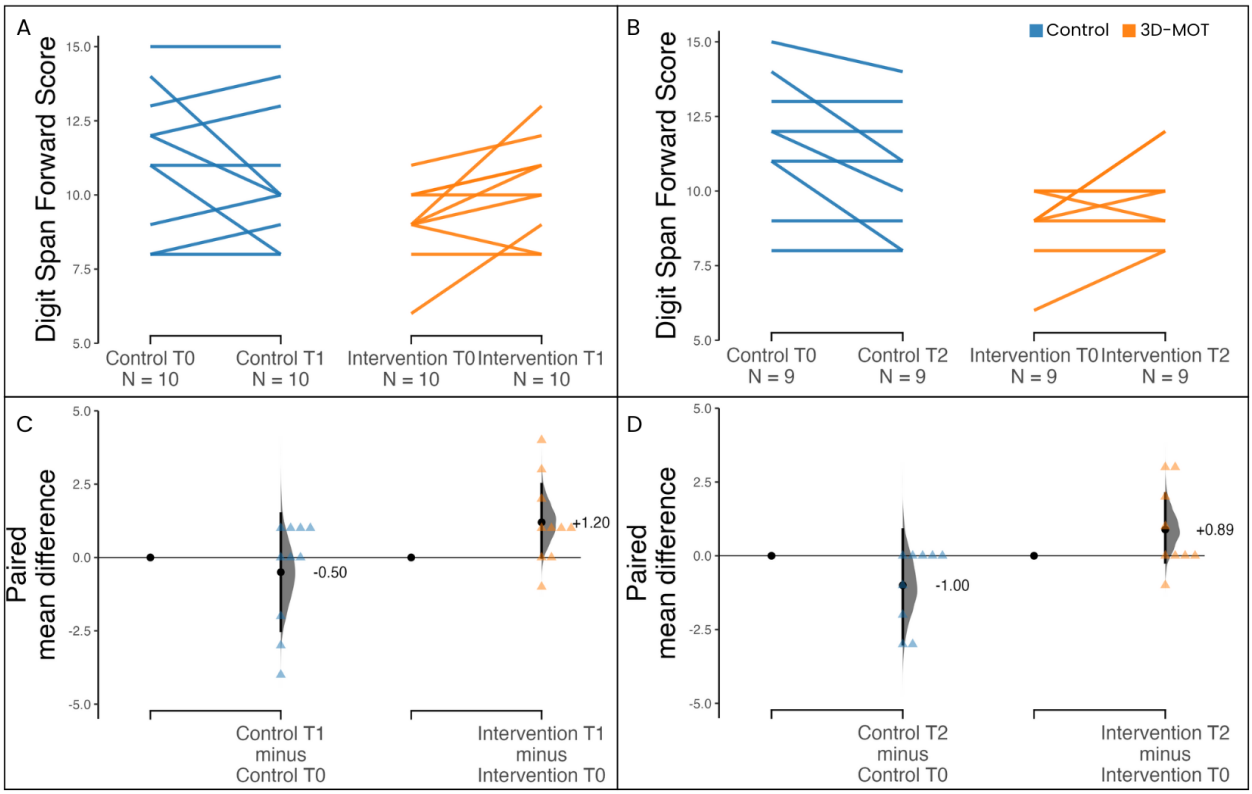

Figure 3.15 Performance on the Digit Span Forward test following 3D-MOT
(A, B) Digit Span Forward scores in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). Scores represent the total number of correct sequences recalled. (C, D) Paired mean differences in Digit Span Forward scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

On the Digit Span Backward test, intervention participants had the same average score at T1 (Mean = 9.0 ± 1.8) as at baseline (Mean = 9.0 ± 2.2), with a mean difference of 0.0 (95% CI [-2.0, 1.4]) and no measurable effect (Hedges' g = 0.00, 95% CI [-0.73, 0.55]). Control participants had slightly higher Digit Span Backward scores at T1 (Mean = 9.2 ± 1.8) compared to baseline (Mean = 8.7 ± 2.5), with a mean difference of 0.5 (95% CI [-1.7, 2.0]) and a small effect size (Hedges' g = 0.21, 95% CI [-0.51, 1.25]).

The nine participants who completed the one-month post-intervention neuropsychological assessment had no meaningful difference between their Digit Span Backward scores at T2 (Mean = 8.8 ± 1.8) and baseline (Mean = 8.6 ± 1.7), with a mean difference of 0.2 (95% CI [-1.2, 1.9]) and a negligible effect size (Hedges' g = 0.11, 95% CI [-0.85, 0.88]). The nine control participants had higher Digit Span Backward scores at T2 (Mean = 10.0 ± 1.9) compared to their baseline

(Mean = 8.7 ± 2.7), with a mean difference of 1.3 (95% CI [-1.3, 3.0]) and a medium effect size (Hedges' g = 0.50, 95% CI [0.00, 1.69]) (Figure 3.16).

No significant between-group differences in Digit Span Backward scores were observed at T0, T1, or T2 (Table 3.7).

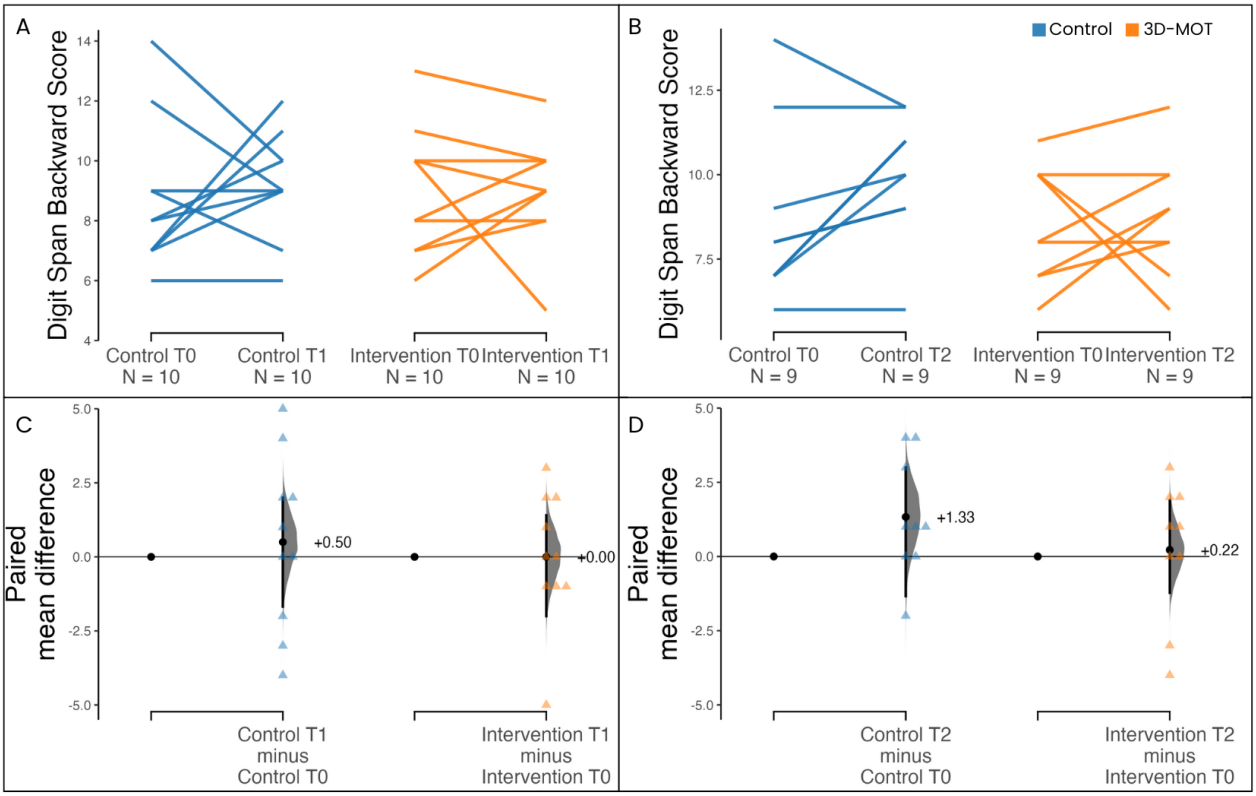

Figure 3.16 Performance on the Digit Span Backward test following 3D-MOT
(A, B) Digit Span Backward scores in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and in nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). Scores represent the total number of correct sequences recalled. (C, D) Paired mean differences in Digit Span Backward scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

On the Digit Span Sequencing test, intervention participants had slightly higher scores at T1 (Mean = 8.6 ± 1.2) compared to baseline (Mean = 8.1 ± 1.0), with a mean difference of 0.5 (95% CI [-0.5, 1.4]) and a small effect size (Hedges' g = 0.42, 95% CI [-0.46, 1.12]). Control participants had slightly lower Digit Span Sequencing scores at T1 (Mean = 8.2 ± 1.7) compared to baseline (Mean = 8.8 ± 1.8), with a mean difference of -0.6 (95% CI [-2.2, 0.7]) and a small effect size (Hedges' g = -0.32, 95% CI [-1.12, 0.67]).

The nine participants who completed the one-month post-intervention neuropsychological assessment had slightly higher Digit Span Sequencing scores at T2 (Mean = 8.9 ± 2.7) compared to their baseline (Mean = 8.1 ± 1.1), with a mean difference of 0.8 (95% CI [-0.9, 2.2]) and a small effect size (Hedges' g = 0.36, 95% CI [-0.63, 1.03]). The nine control participants had no meaningful change in Digit Span Sequencing scores at T2 (Mean = 8.9 ± 1.4) compared to baseline (Mean = 8.9 ± 1.8), with a mean difference of 0.0 (95% CI [-1.6, 1.3]) and no measurable effect (Hedges' g = 0.00, 95% CI [-1.00, 1.12]) (Figure 3.17).

No significant between-group differences in Digit Span Sequencing scores were observed at T0, T1, or T2 (Table 3.7).

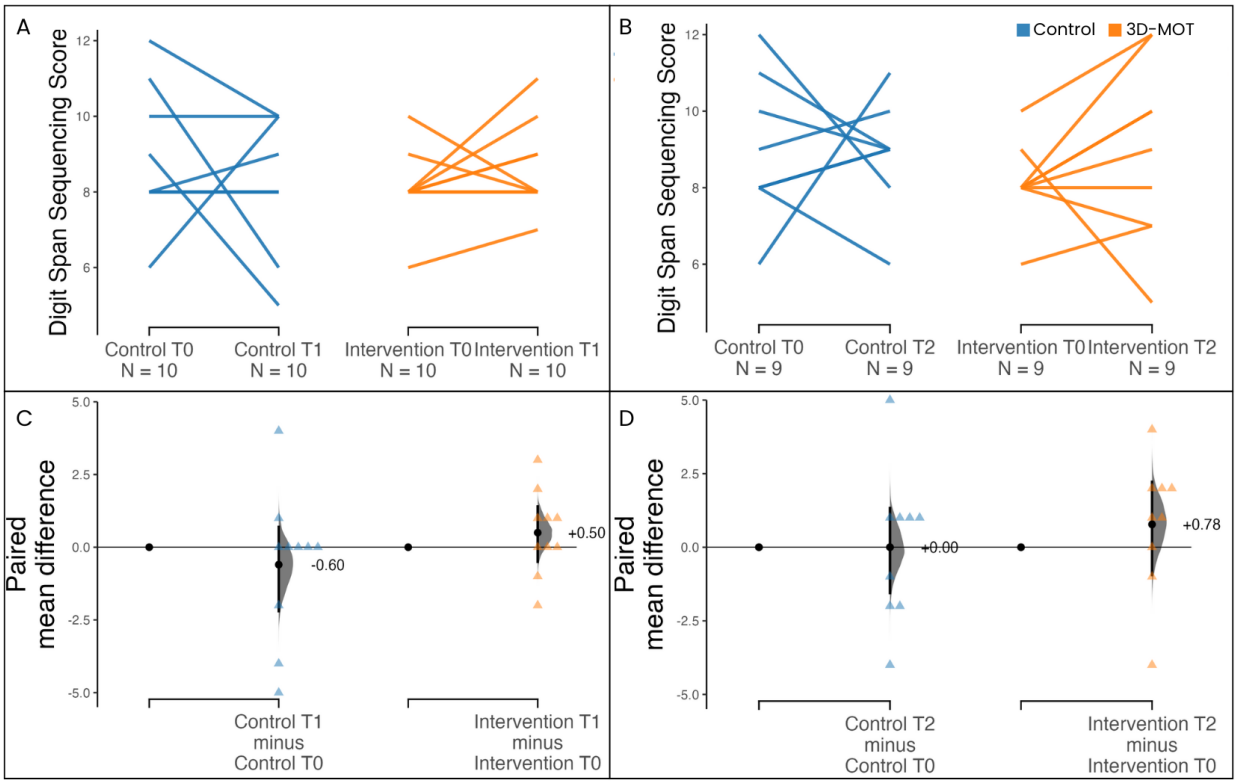

Figure 3.17 Performance on the Digit Span Sequencing test following 3D-MOT
(A, B) Digit Span Sequencing scores in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and in nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). Scores represent the total number of correct sequences recalled. (C, D) Paired mean differences of Digit Span Sequencing scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

3.3.3 Mini Mental State Examination: Global Cognitive Function

On the MMSE, intervention participants had no meaningful change at T1 (Mean = 28.4 ± 1.4) compared to baseline (Mean = 28.4 ± 1.7), with a mean difference of 0.0 (95% CI [–1.3, 1.2]) and no measurable effect (Hedges' g = 0.00, 95% CI [-0.97, 0.43]). Control participants had a minor reduction in MMSE score at T1 (Mean = 26.9 ± 2.6) compared to baseline (Mean = 27.6 ± 2.1), with a mean difference of -0.7 (95% CI [-2.9, 1.1]) and a small effect size (Hedges' g = -0.25, 95% CI [-0.57, -0.08]).

The nine participants who completed the one-month post-intervention neuropsychological assessment had no meaningful change on their MMSE scores at T2 (Mean = 28.6 ± 1.7) compared to baseline (Mean = 28.4 ± 1.7), with a mean difference of 0.1 (95% CI [-1.6, 1.4]) and a negligible effect size (Hedges' g = 0.06, 95% CI [-0.33, 0.85]). The nine control participants had no meaningful change on their MMSE scores at T2 (Mean = 27.8 ± 2.1) compared to baseline (Mean = 28.0 ± 1.8), with a mean difference of -0.2 (95% CI [-2.0, 1.4]) and a negligible effect size (Hedges' g = -0.10, 95% CI [-0.83, 0.48]) (Figure 3.18).

No significant between-group differences in MMSE scores were observed at T0, T1, or T2 (Table 3.7).

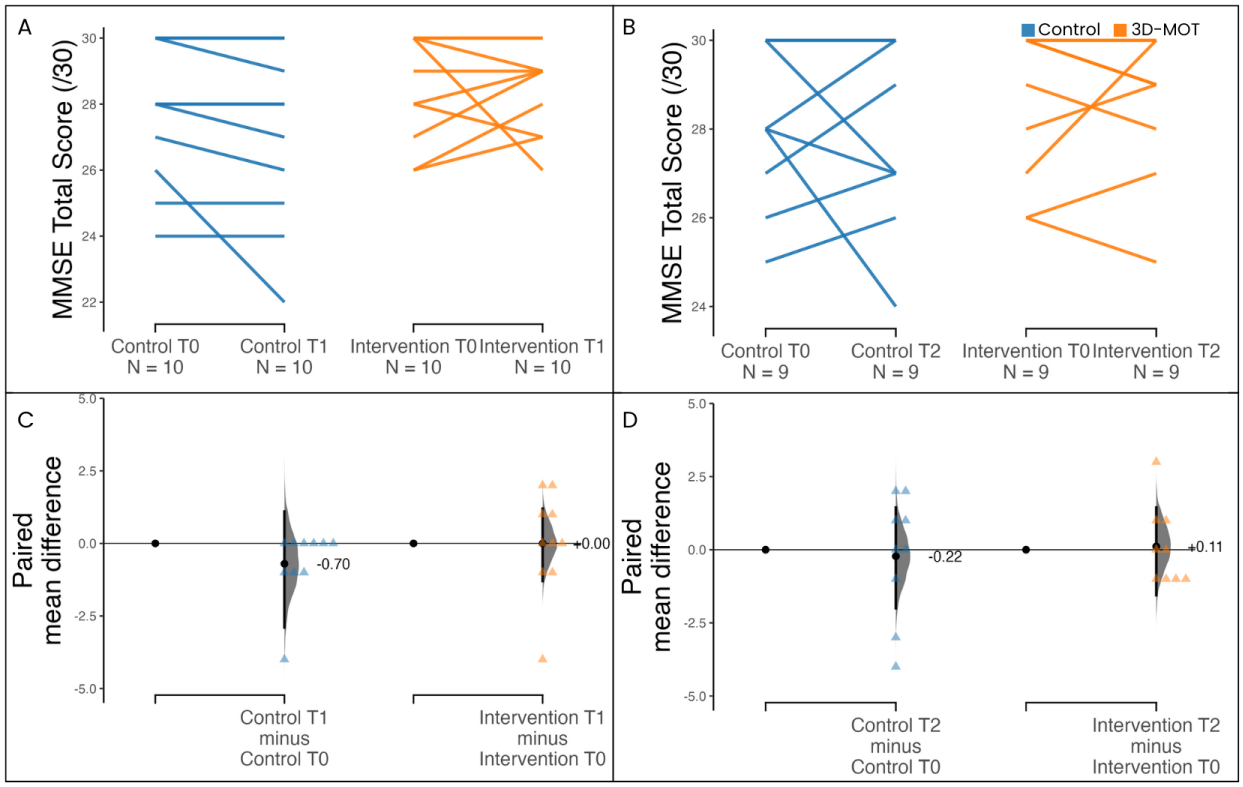

Figure 3.18 Performance on the MMSE following 3D-MOT
(A, B) MMSE scores in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). (C, D) Paired mean differences in MMSE scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

3.3.4 Symbol Digit Modalities Test: Attention and Processing Speed

For the SDMT, two control participants at T1 did not finish the test due to technological difficulties, resulting in no scores at this time point. Therefore, the control baseline and T1 comparison was conducted with the eight participants who did complete the SDMT.

On the SDMT, intervention participants had no meaningful difference in the number of correct responses at T1 (Mean = 45.5 ± 12.2) compared to baseline (Mean = 43.8 ± 11.2), with a mean difference of 1.7 (95% CI [-8.4, 11.0]) and a negligible effect size (Hedges' g = 0.13, 95% CI [-0.30, 0.55]). Control participants had a minor increase in correct SDMT responses at T1 (Mean = 42.8 ± 11.3) compared to baseline (Mean = 38.5 ± 12.6), with a mean difference of 4.3 (95% CI [-6.8, 14.8]) and a small effect size (Hedges' g = 0.31, 95% CI [0.06, 0.92]).

The nine participants who completed the one-month post-intervention neuropsychological assessment had no meaningful change in their number of SDMT correct responses at T2 (Mean = 46.0 ± 11.7) compared to baseline (Mean = 45.2 ± 10.9), with a mean difference of 0.8 (95% CI [-9.3, 10.1]) and a negligible effect size (Hedges' g = 0.06, 95% CI [-0.38, 0.53]). The nine control participants had more correct SDMT responses at T2 (Mean = 44.0 ± 10.4) compared to baseline (Mean = 37.1 ± 12.5), with a mean difference of 6.9 (95% CI [-3.2, 16.4]) and a medium effect size (Hedges' g = 0.53, 95% CI [0.16, 1.14]) (Figure 3.19).

No significant between-group differences in SDMT scores were observed at T0, T1, or T2 (Table 3.7).

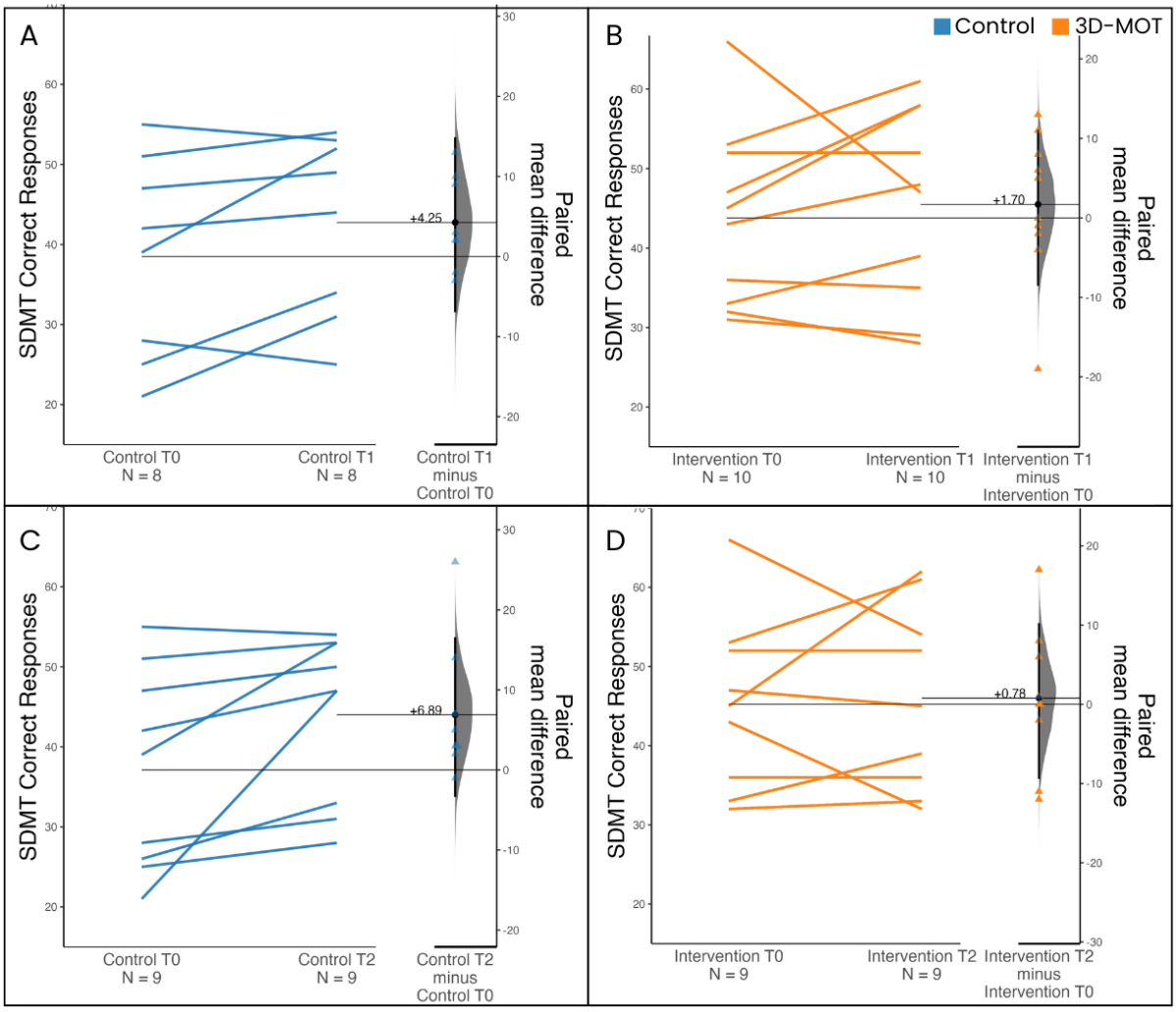

Figure 3.19 Performance on the SDMT following 3D-MOT
SDMT correct responses in 8 control participants (Panel A) and 10 3D-MOT intervention participants (Panel B) with msTBI, assessed at baseline (T0) and follow-up (T1), and the nine control (Panel C) and nine 3D-MOT intervention (Panel D) participants assessed at the one-month follow-up (T2). Paired mean differences of SDMT correct responses in the control group and 3D-MOT intervention group at T1 versus baseline (Panels A, B) and T2 versus baseline (Panels C, D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

3.3.5 Trail Making Tests: Executive Function and Processing Speed

On the Trail Making Test A, intervention participants took slightly longer to complete the task at T1 (Mean = 7.2 ± 1.3 seconds) compared to baseline (Mean = 6.9 ± 1.4 seconds), with a mean difference of 0.3 (95% CI [-1.0, 1.2]) and a small effect size (Hedges' g = 0.20, 95% CI [-0.40, 1.04]). Control participants took slightly longer to complete the Trail Making Test A at T1 (Mean = 8.1 ± 2.0 seconds) compared to baseline (Mean = 7.6 ± 1.4 seconds), with a mean

difference of 0.5 (95% CI [-0.9, 1.9]) and a small effect size (Hedges' g = 0.25, 95% CI [-0.18, 0.79]).

The nine participants who completed the one-month post-intervention neuropsychological assessment had the same average time to complete the Trail Making Test A at T2 (Mean = 6.9 ± 1.1 seconds) as at baseline (Mean = 6.9 ± 1.5 seconds), with a mean difference of 0.0 (95% CI [-1.3, 0.9]) and no measurable effect (Hedges' g = 0.00, 95% CI [-0.43, 0.38]). The nine control participants took slightly longer on the Trail Making Test A at T2 (Mean = 8.0 ± 1.5 seconds) compared to their baseline (Mean = 7.3 ± 1.2 seconds), with a mean difference of 0.7 (95% CI [-0.6, 1.8]) and a small effect size (Hedges' g = 0.44, 95% CI [-0.11, 1.15]) (Figure 3.20).

No significant between-group differences in Trail Making Test A scores were observed at T0, T1, or T2 (Table 3.7).

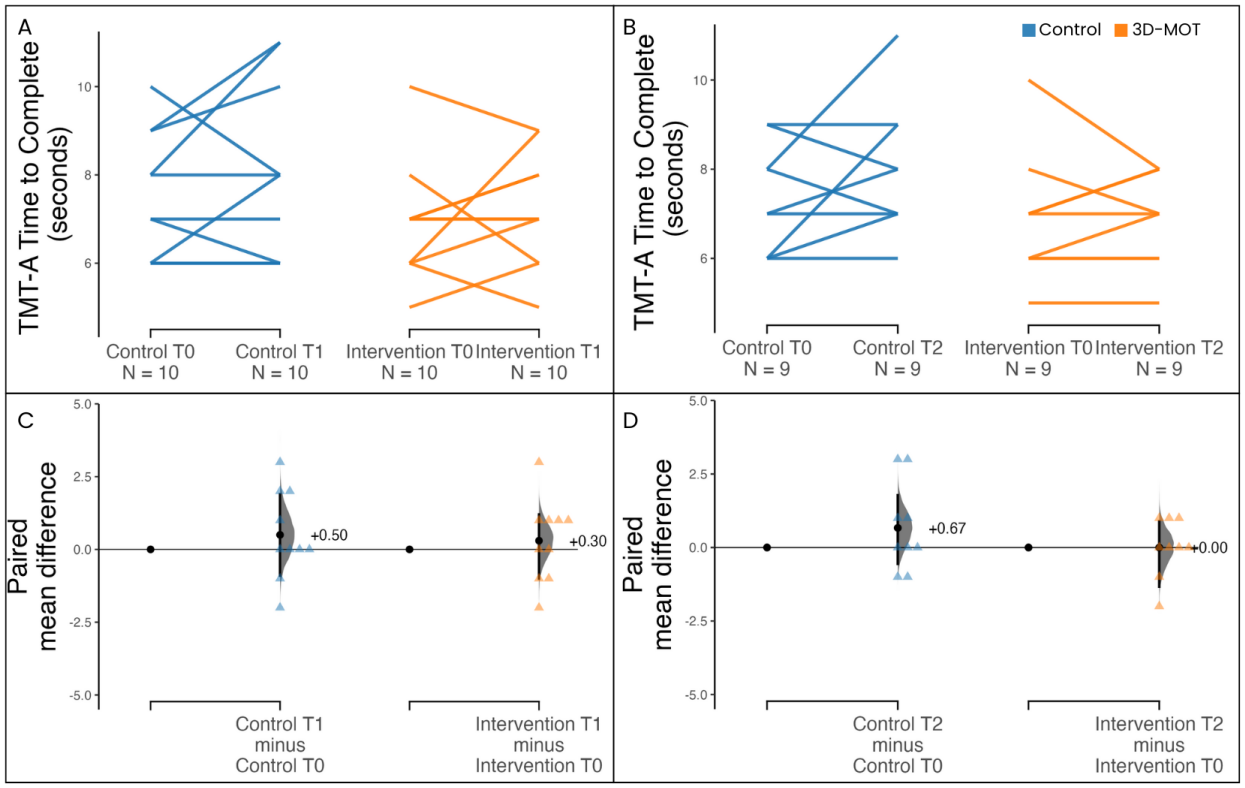

Figure 3.20 Performance on the TMT-A following 3D-MOT
(A, B) TMT-A completion times in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and the nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). (C, D) Paired mean differences of TMT-A scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

On the Trail Making Test B, intervention participants took slightly longer to complete the task at T1 (Mean = 62.7 ± 52.6 seconds) compared to baseline (Mean = 49.7 ± 30.3 seconds), with a mean difference of 13.0 (95% CI [-15.8, 58.5]) and a small effect size (Hedges' *g* = 0.24, 95% CI [-0.20, 1.05]). Control participants had no meaningful change on the Trail Making Test B at T1 (Mean = 54.9 ± 39.8 seconds) compared to baseline (Mean = 48.9 ± 27.6 seconds), with a mean difference of -6.0 (95% CI [-18.0, 42.1]) and a negligible effect size (Hedges' *g* = 0.15, 95% CI [-0.51, 0.58]).

The nine participants who completed the one-month post-intervention neuropsychological assessment took slightly less time to complete the Trail Making Test B at T2 (Mean = 38.1 ± 12.9 seconds) compared to baseline (Mean = 53.3 ± 29.7 seconds), with a mean difference of -15.2 (95% CI [-40.3, 0.9]) and a small effect size (Hedges' *g* = -0.40, 95% CI [-1.04, -0.11]). The nine control participants took slightly less time to complete the Trail Making Test B at T2 (Mean = 40.8 ± 28.7 seconds) compared to baseline (Mean = 50.0 ± 29.0 seconds), with a mean difference of -9.2 (95% CI [-31.6, 19.8]) and a small effect size (Hedges' *g* = -0.29, 95% CI [-0.92, 0.08]) (Figure 3.21).

No significant between-group differences in Trail Making Test B scores were observed at T0, T1, or T2 (Table 3.7).

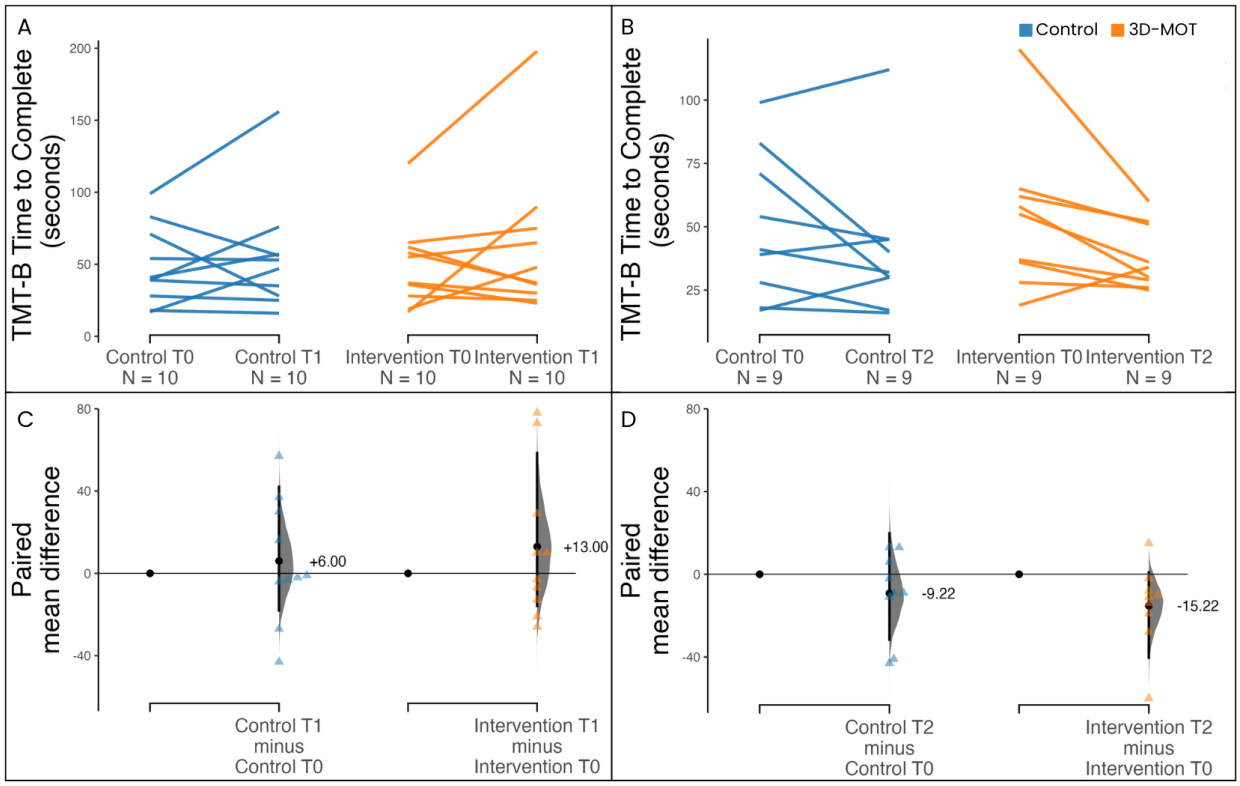

Figure 3.21 Performance on the TMT-B following 3D-MOT
(A, B) TMT-B completion times in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and the nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). (C, D) Paired mean differences in TMT-B scores in the control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

3.3.6 Verbal Fluency Tests: Executive Function and Semantic Memory

On the Verbal Fluency Animals Test, participants in the intervention group had a slight reduction in their performance at T1 (Mean = 20.3 ± 4.0) compared to baseline (Mean = 18.8 ± 5.2), with a mean difference of -1.5 (95% CI [-5.2, 2.4]) and a small effect size (Hedges' g = -0.28, 95% CI [-0.96, 0.14]). The control group had no meaningful difference on this test at T1 (Mean = 18.0 ± 5.2) compared to baseline (Mean = 17.1 ± 5.4), with a mean difference of 0.9 (95% CI [-2.8, 6.1]) and a negligible effect size (Hedges' g = 0.15, 95% CI [-0.34, 0.64]).

The nine participants who completed the one-month post-intervention neuropsychological assessment performed similarly on the Verbal Fluency Animals Test at T2 (Mean = 20.2 ± 5.9) compared to their baseline (Mean = 20.9 ± 3.7), with a mean difference of -0.7 (95% CI [-4.9, 3.4]) and a negligible effect size (Hedges' g = -0.11, 95% CI [-0.67, 0.37]). The control participants had

no meaningful difference on Verbal Fluency Animals at T2 (Mean = 16.6 ± 4.3) compared to their baseline (Mean = 17.3 ± 5.7), with a mean difference of -0.8 (95% CI [-4.7, 4.1]) and a negligible effect size (Hedges' *g* = -0.14, 95% CI [-1.12, 0.53]) (Figure 3.22).

No significant between-group differences in Verbal Fluency Animals Test scores were observed at T0, T1, or T2 (Table 3.7).

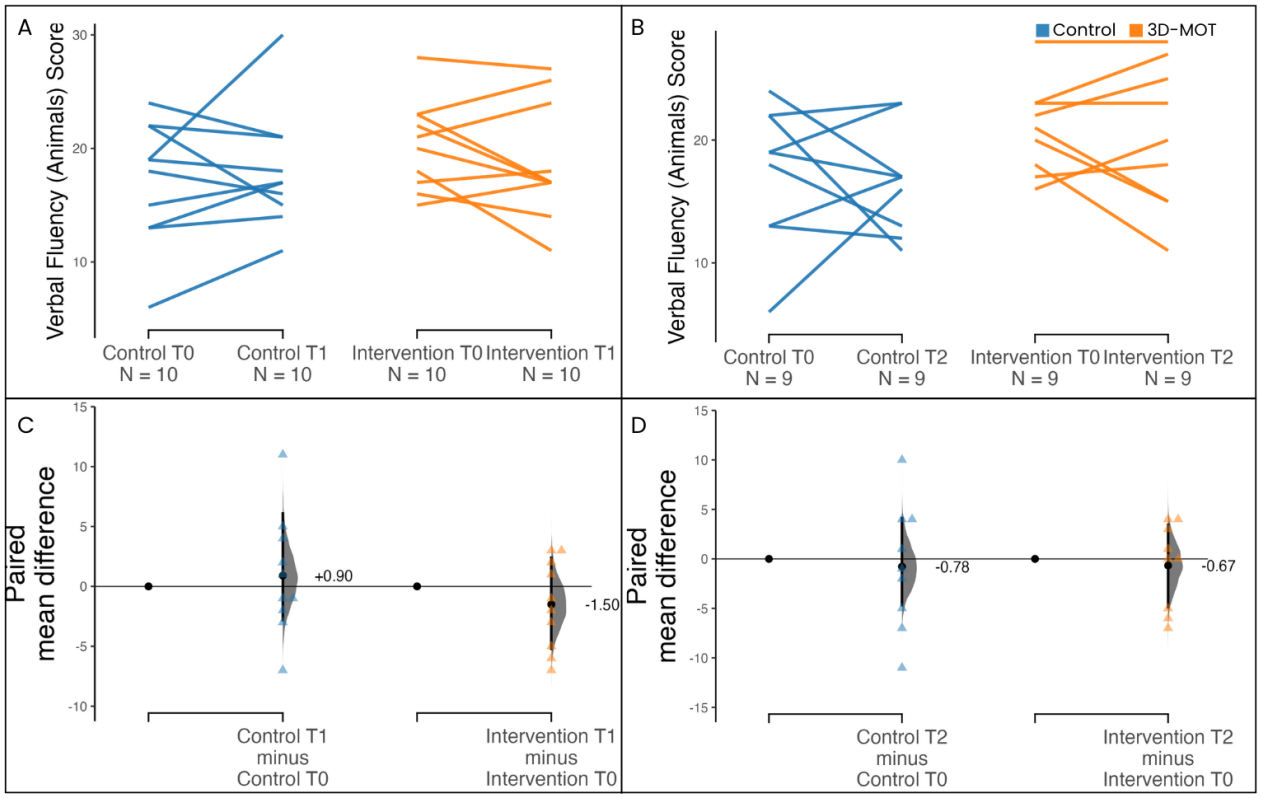

Figure 3.22 Performance on Verbal Fluency Animals Test following 3D-MOT
(A, B) Verbal Fluency Animals Test scores in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and the nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). Scores reflect the number of words generated in the animal category. (C, D) Paired mean differences of Verbal Fluency Animals scores in control group and 3D-MOT intervention group at T1 versus baseline (Panel C) and T2 versus baseline (Panel D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

On the Verbal Fluency FAS Test, participants in the intervention group improved their performance at T1 (Mean = 45.4 ± 14.0) compared to baseline (Mean = 38.5 ± 8.4), with a mean difference of 6.9 (95% CI [-3.0, 15.8]) and a medium effect size (Hedges' *g* = 0.50, 95% CI [-0.10, 1.10]). The control group had no meaningful change on this test at T1 (Mean = 45.2 ± 7.9)

compared to baseline (Mean = 43.9 ± 13.6), with a mean difference of 1.3 (95% CI [-9.1, 9.7]) and a negligible effect size (Hedges' g = 0.07, 95% CI [-0.22, 0.39]).

The nine participants who completed the one-month post-intervention neuropsychological assessment demonstrated improvements on the Verbal Fluency FAS Test at T2 (Mean = 45.2 ± 11.9) compared to their baseline (Mean = 37.3 ± 8.0), with a mean difference of 7.9 (95% CI [-1.7, 16.1]) and a medium effect size (Hedges' g = 0.61, 95% CI [0.16, 1.32]). The nine control participants did not show meaningful change on the Verbal Fluency FAS Test at T2 (Mean = 45.3 ± 13.5) compared to baseline (Mean = 44.6 ± 14.3), with a mean difference of 0.8 (95% CI [-11.7, 13.2]) and a negligible effect size (Hedges' g = 0.05, 95% CI [-0.40, 0.68]) (Figure 3.23). A summary of results from the neuropsychological assessments is presented in Table 3.6.

No significant between-group differences in Verbal Fluency FAS Test scores were observed at T0, T1, or T2 (Table 3.7).

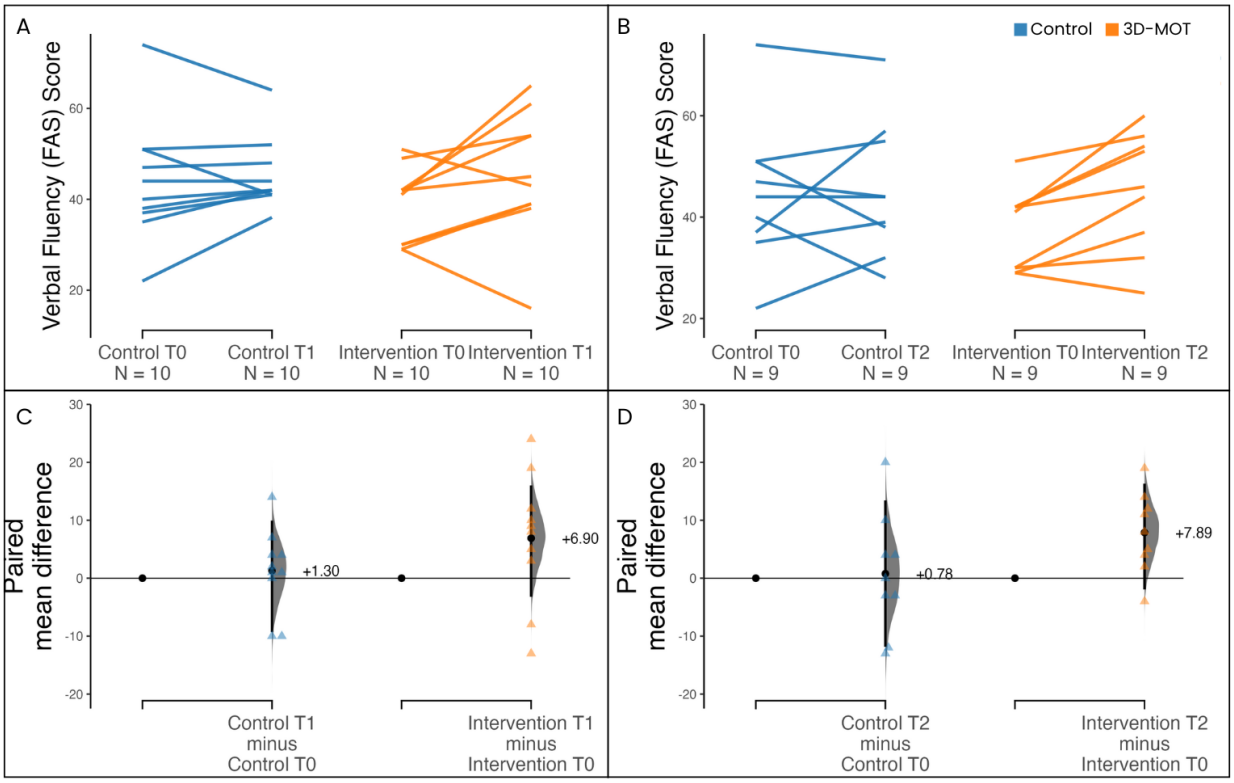

Figure 3.23 Performance on the Verbal Fluency FAS Test following 3D-MOT
(A, B) Verbal Fluency FAS Test scores in 10 control and 10 3D-MOT intervention participants with msTBI, assessed at baseline (T0) and follow-up (T1) (Panel A), and the nine control and nine 3D-MOT intervention participants assessed at the one-month follow-up (T2) (Panel B). Scores reflect the total number of words generated in the FAS categories. (C, D) Paired mean differences of Verbal Fluency FAS scores in control group and 3D-MOT intervention group at T1 versus baseline (C) and T2 versus baseline (D), with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

Table 3.6 Summary of results for the neuropsychological assessments in msTBI survivors.

Assessment	Group	Comparison	Mean difference	95% CI	Hedges' g
Digit Span Total score	3D-MOT intervention	T0 vs T1	1.7	[-1.0, 4.5]	0.46
		T0 vs T2	1.9	[-1.0, 5.0]	**0.50**
	Control	T0 vs T1	-0.6	[-4.3, 2.9]	-0.12
		T0 vs T2	0.3	[-4.1, 4.2]	0.06
Digit Span Forward score	3D-MOT intervention	T0 vs T1	1.2	[0.0, 2.5]	**0.72**
		T0 vs T2	0.9	[-0.2, 2.1]	**0.58**
	Control	T0 vs T1	-0.5	[-2.5, 1.5]	-0.19
		T0 vs T2	-1.0	[-3.0, 0.9]	-0.41
Digit Span Backward score	3D-MOT intervention	T0 vs T1	0.0	[-2.0, 1.4]	0.00
		T0 vs T2	0.2	[-1.2, 1.9]	0.11
	Control	T0 vs T1	0.5	[-1.7, 2.0]	0.21
		T0 vs T2	1.3	[-1.3, 3.0]	**0.50**
Digit Span Sequencing score	3D-MOT intervention	T0 vs T1	0.5	[-0.5, 1.4]	0.42
		T0 vs T2	0.8	[-0.9, 2.2]	0.36
	Control	T0 vs T1	-0.6	[-2.2, 0.7]	-0.32
		T0 vs T2	0.0	[-1.6, 1.3]	0.00
Mini Mental State Examination score	3D-MOT intervention	T0 vs T1	0.0	[-1.3, 1.2]	0.00
		T0 vs T2	0.1	[-1.6, 1.4]	0.06
	Control	T0 vs T1	-0.7	[-2.9, 1.1]	-0.25
		T0 vs T2	-0.2	[-2.0, 1.4]	-0.10
Symbol Digit Modalities Test correct responses	3D-MOT intervention	T0 vs T1	1.7	[-8.4, 11.0]	0.13
		T0 vs T2	0.8	[-9.3, 10.1]	0.06
	Control	T0 vs T1	4.25	[-6.8, 14.8]	0.31
		T0 vs T2	6.9	[-3.2, 16.4]	**0.53**
Trail Making Test A seconds to complete	3D-MOT intervention	T0 vs T1	0.3	[-1.0, 1.2]	0.20
		T0 vs T2	0.0	[-1.3, 0.9]	0.00
	Control	T0 vs T1	0.5	[-0.9, 1.9]	0.25
		T0 vs T2	0.7	[-0.6, 1.8]	0.44
Trail Making Test B seconds to complete	3D-MOT intervention	T0 vs T1	13.0	[-15.8, 58.5]	0.24
		T0 vs T2	-15.2	[-40.3, 0.9]	-0.40
	Control	T0 vs T1	-6.0	[18.0, 42.1]	0.15
		T0 vs T2	-9.2	[-31.6, 19.8]	-0.29
Verbal fluency (animals) score	3D-MOT intervention	T0 vs T1	-1.5	[-5.2, 2.4]	-0.28
		T0 vs T2	-0.7	[-4.9, 3.4]	-0.11
	Control	T0 vs T1	0.9	[-2.8, 6.1]	0.15
		T0 vs T2	-0.8	[-4.7, 4.1]	-0.14
Verbal fluency (FAS) score	3D-MOT intervention	T0 vs T1	6.9	[-3.0, 15.8]	**0.50**
		T0 vs T2	7.9	[-1.7, 16.1]	**0.61**
	Control	T0 vs T1	1.3	[-9.1, 9.7]	0.07
		T0 vs T2	0.8	[-11.7, 13.2]	0.05

Note. Medium and large effect sizes ($|g| \geq 0.5$) are bolded.

Table 3.7 Between-group comparisons of neuropsychological assessment scores.

Assessment	T0 comparison p-value	T1 comparison p-value	T2 comparison p-value
Digit Span Total	0.171	0.859	0.312
Digit Span Forward	**0.022**	0.597	0.318
Digit Span Backward	0.777	0.805	0.176
Digit Span Sequencing	0.370	0.546	1.000
Mini Mental State Examination	0.358	0.127	0.398
Symbol Digit Modalities Test	0.133	0.629	0.658
Trail Making Test A	0.278	0.245	0.088
Trail Making Test B	0.951	0.821	0.860
Verbal fluency (Animals)	0.149	0.735	0.153
Verbal fluency (FAS)	0.300	0.850	0.985

Note. P-values are calculated from independent samples t-tests or Mann-Whitney U tests, depending on data normality. P-values < 0.05 are bolded.

3.4 Effects of 3D-MOT on a Biomarker of Aging in msTBI Survivors

Participants had no meaningful change in estimated telomere length at T1 (Mean = 7972 ± 1154 bp) compared to baseline (Mean = 8070 ± 1815 bp), with a mean difference of -98.6 bp (95% CI [-1475, 1065]) and negligible effect size (Hedges' g = -0.05, 95% CI [-0.53, 0.28]). The control group had no meaningful change in estimated telomere length at T1 (Mean = 7810 ± 1728 bp) compared to baseline (Mean = 7695 ± 2110), with a mean difference of 115.4 bp (95% CI [-1377, 1797]) and negligible effect size (Hedges' g = 0.05, 95% CI [-0.56, 1.01]).

One-month post-intervention, participants had no meaningful change in estimated telomere length at T2 (Mean = 8487 ± 2317 bp) compared to baseline, with a mean difference of -416.4 bp (95% CI [-1267, 2167]) and negligible effect size (Hedges' g = 0.17, 95% CI [-0.17, 0.41]). The control group had a minor increase in estimated telomere length at T2 (Mean = 8132 ± 1524 bp) compared to baseline, with a mean difference of 436.7 bp (95% CI [-992.5, 2097.6]) and small effect size (Hedges' g = 0.21, 95% CI [-0.46, 0.92]) (Figure 3.24).

No significant between-group differences in estimated telomere length were observed at T0, T1, or T2 (Table 3.8).

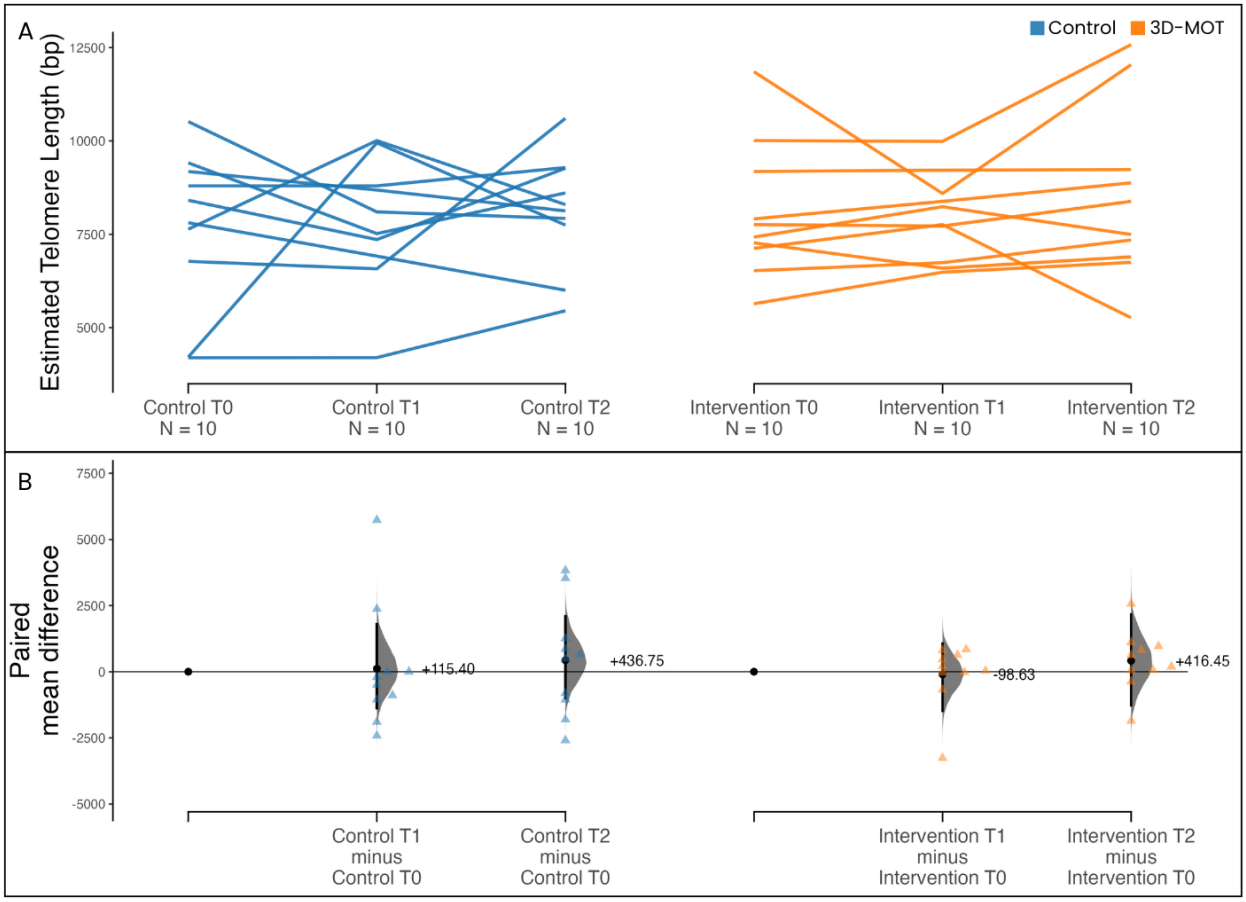

Figure 3.24 Estimated telomere length following 3D-MOT
(A) Estimated telomere length (base pairs) in msTBI survivors from the 10 control participants and 10 3D-MOT intervention participants assessed at baseline (T0), follow-up (T1), and one-month follow-up (T2). (B) Paired mean differences of estimated telomere length in the control group and 3D-MOT intervention group, with bias-corrected and accelerated 95% confidence intervals estimated from 5000 bootstrap resamples.

Table 3.8 Between-group comparisons of estimated telomere length.

Assessment	T0 comparison p-value	T1 comparison p-value	T2 comparison p-value
Estimated Telomere Length	0.675	0.809	0.691

Note. P-values are calculated from independent samples t-tests or Mann-Whitney U tests, depending on data normality.

3.5 Participant Perspectives on 3D-MOT

Of the 17 TBI survivors initially assigned to the intervention group, 10 chose to participate in the semi-structured interview. Of these participants, seven completed the intervention, and three were participants who dropped out for reasons related to the intervention (participants P05, P06,

and P10). The remaining intervention participants either chose not to complete the semi-structured interview or did not reply to communication offering the interview. Participants answered six questions regarding their thoughts on the NeuroTracker 3D-MOT intervention (Tables 3.9-3.14). The majority of participants reported having a positive experience with 3D-MOT, and all participants reported that they would recommend the tool to other brain injury survivors.

Table 3.9 Participant responses to "How was your experience with the NeuroTracker intervention?"

Participant	Response
P01	"I think it's fabulous."
P02	"I like the program and was surprised it didn't bore me."
P03	"Experience was good, one little issue with tech but only one hiccup in the 30 sessions. For someone in my stage who has a hard time on computers it was straightforward from you and them – that was very appreciated."
P04	"It was fun."
P05	"I did like being included and I'm glad I did it. It's my own sense of self negation telling me I should have done better."
P06	"Was not able to do it. Felt immediately nauseous. I really wanted to be part of the study but was not able to do it. I think I should not have tried to do it online from home but come to VBIS."
P07	"5 of 5 for enjoyment, even though it was a difficult journey. All along I knew that it would foster healing. That gave me motivation."
P08	"I liked it. It did test my limits, and I feel I made improvements. I was surprised how taxing I found it at first. This decreased as the study progressed."
P09	"I liked the NeuroTracker of how its set up and explained well for people with or without brain injury. I feel that I was getting better at it. I hope it can help people with brain injuries."

Table 3.10 Participant responses to "What did you like about the NeuroTracker intervention?"

Participant	Response
P01	"It's easy to learn, its challenging to do, but it's actually quite short, and it doesn't take too much time out of your day and shows results."
P02	"I was excited by the improvement."
P03	"It was very well laid out getting access and logging in. I see some benefits not sure exactly what. Curious to see if it does continue to show improvements. The software was user-friendly, not complicated. 3 sessions in a day were straight forward. Everything laid out was amazing. Telephone and email reminders were great to help and get me involved."
P04	"Fun experience and interesting. I would like to know the results of the study."
P05	"It wasn't difficult to use. It was fairly simple. I began to find a state of mind to be in while I was doing work that I haven't felt before. I noticed changes in how I felt after doing it."
P06	"I liked it that the screen was not too colorful. Green color was calming. The screen was not filled with too much."
P07	"I liked the constant feedback. This kept me interested. Also, I liked the ease of turning on the program when I was the lone operator."
P08	"I like how it responded in getting harder or easier to reflect my scores. I found the leaps in either direction too big at times. It would go from ok to very hard to ok to easy."
P09	"I liked that it is available and offered to people in places throughout the community and other countries."

Table 3.11 Participant responses to "What did you not like about the NeuroTracker intervention?"

Participant	Response
P01	"Accessibly issue. Older people and people who are remote aren't necessarily up to date on tech."
P02	"I had a difficult time with some of the instructions like how far away to have the device from your face and the progress number."
P03	"If something comes up I didn't feel like I could put NeuroTracker on pause – I felt locked in. If something came up I would like to more easily put it on pause."
P04	"I had to remember to do it."
P05	"I found that doing the same test over and over again became stressful. It's not that I was bored, I began to. I found that I was dreading doing the tests. I became irritated by the monotony of it. It was an irritation, and the more I thought about sitting down and logging in, I became more irritated. I need novelty. If there was a selection of 3-4 types of tests, I could have chosen what I wanted to do. I found no sense of achievement in doing the same test over and over again. I get bored with monotony very quickly. I would get better, than worse because I was getting bored with the task. I built up resentment. I was frustrated with myself, because I had committed myself to this, and I felt that I failed."
P06	"I could not wear 3D glasses because I immediately felt like throwing up and also when I tried to do that from home it did not work, and my friend could not figure it out either."
P07	"Only the evidence that my brain injury was Significant. Without the tasks that this program assigns I would not have been able to identify some of my challenges and degree of injury."
P08	"Smaller increments of change between tests I think is needed. If I knew how it was scored, I think I would understand."
P09	"I can say there is not anything that I did and do not like about the NeuroTracker."
P10	"I got headaches every time I tried and found it to be overall stressful. It was not so much the tool itself, but the motion of the balls and trying to track them. I noticed myself getting stressed trying to track things, I would drop in and out of focus."

Table 3.12 Participant responses to "Do you believe NeuroTracker provided you with any benefits?"

Participant	Response
P01	"Significant benefits, I walked in from my last assessment and told [the researcher] I've got my brain back."
P02	"I am absolutely aware that NeuroTracker has helped me. Cognitive improvement, amazingly, was noticeable both during and following experiment. I was and continue to be very grateful for this program which has renewed my hope for coping with TBI syndrome."
P03	"It is hard to say – I noticed the first two weeks were very difficult, I felt like there was a lot of strain involved tracking it and it felt very much like a task. It was mentally strenuous in a way. Week 3 and week 4 got easier, that was good. I noticed the process of it becoming easier to do and there was no crazy outside of the box things, but it has maybe helped a little bit in some ways I can't really tell what – a little bit more attention to it and wasn't as much of a mental task as I did it."
P04	"Hard to say, probably some benefits. Probably improved my driving skills incrementally and made me more aware of tracking things. Yeah, so probably some benefit."
P05	"I felt that I got benefits from doing it. It was almost like learning meditation. A form of meditation, controlling my breathing, concentrating my thinking, focusing on the task. It was training me to think more clearly and more patiently. That's what it did to help me get to that state of mind."
P06	"No."
P07	"Yes. Along with being able to identify and measure my progress, the program encouraged me to see possibilities to heal as I used it."
P08	"Yes. It helped with eye tracking as well as focus and memory. I would find myself being angry if it misinterpreted my verbal answers and it was obvious I overreacted to this trigger… so NeuroTracker also gave me practice in my emotional control."
P09	"Yes with starting it and doing it weekly I have seen an improvement for when I started it and stopped it and restarted it, having a more clear vision with understanding things."

Table 3.13 Participant responses to "Would you recommend NeuroTracker to other brain injury survivors?"

Participant	Response
P01	"I do, I constantly do. I tell everyone I know it's available through VBIS! I spread the good word."
P02	"Yes 100%, I would recommend NeuroTracker to other survivors. It is an effective tool that works if you work it."
P03	"Yeah I think so – it is hard being limited to only doing it two times per week. Would be interested in seeing if there is a more vigorous period doing it more often. I found it to be very useful building mental repour and tracking. Interested in a few times more a week and see the potential in it. I would for sure recommend it to people so long as they can handle it. If they take it at their own pace and all that, I do see there is some potential there for sure and would 100% recommend it for other people."
P04	"Sure, they're injured. Go for it."
P05	"I would. With a suggestion that it may help people like me to have more support doing it. When people like me hit the wall, they can be talked through it, they need to be talked through into a positive mindset. Ok, you have got to this point, this is what are things you can to think positively about the outcome. If someone was able to drop by and come in and see and watch me do it. More personal support with it."
P06	"Everyone's brain injury is different, so why not try it. Everyone should try it. I heard from people that 3D glasses did not bother them."
P07	"Absolutely I would build a program for children which has interesting characters and colours to keep their interests."
P08	"Yes. I think I would warn people of how fatiguing it was at first and how this improved. I felt I was being active in trying to improve myself instead of being passive and waiting for improvements. The feeling of being active instead of being passive feels like I have some control and hope."
P09	"Yes absolutely, I already have and will continue to recommend it to other brain injury survivors as well others that do not have brain injury."

Table 3.14 Participant responses to "Is there anything you would change about the NeuroTracker intervention?"

Participant	Response
P01	"Just wish it was more accessible, pricewise and technology wise."
P02	"For brain injury, a prompt to put on 3D glasses. When NeuroTracker tells you which ones you got right and wrong, maybe having them flash green to signify which ones you got correct. Having all the balls flash white is confusing and is easy to miss when it moves so fast."
P03	"No, I don't think so. Our minds love looking for patterns when I first sat down. The first time is fast then it doesn't recognize our pattern recognition. I inherently did like that it threw you curve balls going faster testing mental capabilities. Nothing much I would change – more or less straight forward."
P04	"Maybe more frequent, every other day."
P05	"I would like to have a variety of formats and colours would be nice. The colour was a bit ugly."
P06	"Do not use 3D glasses or at least have a choice for no 3D glasses. Have better instructions on what to exactly do. It would have been great if I could have done the exercises without wearing the 3D glasses and have someone beside me to help because I felt helpless about the directions what to do. Maybe easier exercises in the beginning with better explanation what to do."
P07	"I would recommend it to all sufferers of brain injury. For children, I think that it might be boring. Expand the accessibility to include youngsters."
P08	"Maybe more in-depth tutorial how to use or explanation how it scores and changes the speed. I feel to get better, you have to push the limits and I think NeuroTracker made me feel the right level of comfortableness to achieve progress without discouragements."
P09	"One thing I noticed is sometimes the balls stop directly behind other balls, then you cannot see the number of the ball, also hard to figure out which one it lit up with the white ring around it."

Chapter 4: Discussion

4.1 Summary of Main Findings

The goal of this study was to explore whether a 5-week 3D-MOT intervention could positively influence perceived well-being, cognitive performance, and a biological marker of aging in msTBI survivors. Potentially meaningful improvements, suggested by medium to large effect sizes, were observed on certain measures of daily life challenges, TBI symptom severity, perceived stress, short-term verbal memory and retrieval, long-term verbal memory and retrieval, attention, and executive function following 3D-MOT. Many of these changes were persistent one-month after discontinuing 3D-MOT (T2), suggesting the potential for sustained benefits of this intervention. However, these findings should be interpreted with caution due to the small sample size, lack of active control group, and few significant between-group differences. There was no observed change in telomere length, a biological marker of aging, after intervention. Participant perspectives highlight the perceived benefits and acceptability of this 3D-MOT intervention, while also raising considerations about its suitability for individuals experiencing more severe challenges after msTBI.

4.2 Effects of 3D-MOT on Self-Reported Outcomes in msTBI Survivors

Self-reported outcomes were included in this study to support a patient-oriented approach and explore whether msTBI survivors notice changes in their daily functioning following 3D-MOT intervention. It was hypothesized that reductions in daily life challenges, TBI symptoms, and perceived stress with large effects would be observed. The results from this study mostly support this hypothesis. Medium and large effect sizes were found after 3D-MOT in almost all self-report measures evaluated (Table 3.2). The primary outcome measure of this study was total daily life challenges, as measured through the MPAI-4. Following 3D-MOT, reductions in total daily life challenges were observed with large effect sizes at both T1 and T2. In contrast, the control group demonstrated smaller reductions in total daily life challenges, associated with small and negligible effect sizes at T1 and T2, respectively (Figure 3.2).

Breaking down the MPAI-4 into its subscales, medium to large effect sizes were observed for ability, adjustment, and participation challenges at both T1 and T2, highlighting persistent improvements in these domains even one month after cognitive training. In contrast, only small

and negligible effect sizes were observed in the control group across these domains and time points. The largest effect size among the MPAI-4 subscales post-intervention was observed for reductions in ability challenges, suggesting participants perceived improvements in basic sensory functioning and cognitive abilities (Figure 3.3). This aligns with what would be expected from a 3D-MOT intervention, which theoretically engages multiple domains assessed on the ability subscale (e.g., vision, attention/concentration, memory, visuospatial skills). The medium effect sizes observed in relation to reductions in adjustment challenges at both follow up time points suggests participants may be perceiving improvements in emotional well-being (Figure 3.4). The improvements observed on both of these subscales align with research stating subjective measures of cognition, like those in the MPAI-4 ability subscale, strongly relate to emotional well-being (139).

The effect sizes for reductions in participation challenges following intervention were the smallest out of the three subscales, but still met the threshold to be considered medium effects (Figure 3.5). This finding could broadly be interpreted as perceived improvements in cognitive functioning translating to an increased capacity for msTBI survivors to engage in community and daily life activities. Prior research supports this relationship, as it has been found that MPAI-4 ability and adjustment scores predict social participation in TBI survivors (140). Overall, the MPAI-4 is commonly used in the literature to assess functional outcomes at chronic time points for TBI survivors, supporting the idea that 3D-MOT use may lead to clinically meaningful improvements in the daily lives of msTBI survivors (141,142).

Following 3D-MOT, medium effect sizes were observed for reductions in SCAT-5 TBI symptom severity at both T1 and T2. In contrast, smaller reductions in symptom severity were observed in the control group, with negligible and small effect sizes at T1 and T2, respectively (Figure 3.6). This study's findings are consistent with previous literature suggesting certain types of cognitive training can improve symptom severity in individuals with TBI (73,143). Furthermore, reductions in symptom severity compliment the observed improvements in ability challenges following 3D-MOT, as both assessments evaluate similar domains (e.g., memory, concentration, vision, balance). Despite reductions in symptom severity, there was no meaningful change in total number of TBI symptoms reported following 3D-MOT, as observed through small and negligible effect sizes at T1 and T2, respectively (Figure 3.7). These findings together suggest that five-weeks of 3D-MOT may reduce symptom severity, but the intervention's duration or

overall efficacy may not be sufficient to fully eliminate TBI symptoms. To our knowledge, this study is unique in that it provides support for the role of the 3D-MOT task in symptom severity reduction for msTBI survivors at a chronic time point. The mechanism behind symptom severity reduction after 3D-MOT is unknown, however it could be hypothesized to be attributed to 3D-MOT inducing neuroplasticity and strengthening neural connections related to processes such as cognitive load and sensory processing. Strengthened abilities to handle such processes could result in improvements in an individual's ability to handle overstimulation in real-world environments, decreasing perceived TBI symptom severity. This speculation is supported by a previous study in chronic TBI which found cognitive training aimed at improving cognitive load induced neuroplasticity in this population, as measured through resting-state functional connectivity (144). Further research is needed to better understand biological mechanisms underlying symptom improvement following 3D-MOT.

Participants also demonstrated reductions in perceived stress following 3D-MOT, with medium effect sizes at both T1 and T2. In contrast, the control group had smaller reductions in perceived stress with negligible and small effect sizes at T1 and T2, respectively (Figure 3.8). Reductions in perceived stress after intervention may be related to improvements in TBI symptom severity, as previous research has shown significant associations between perceived stress and TBI symptoms (145,146). However, any causality or directionality in the relationship between perceived stress and symptom severity after 3D-MOT is unknown. Furthermore, the 3D-MOT task requires repeated engagement of working memory and attention, which are executive functions associated with the dorsolateral prefrontal cortex (147,148). Studies have also implicated this brain region in emotional-processing and cognitive reappraisal, suggesting neuroplasticity in this region may be linked to improvements in perceived stress and adjustment challenges (147,149,150). While these mechanisms are speculative, future studies could incorporate neuroimaging techniques and quantify cortisol levels in participants to better understand biological processes that may be influencing perceived stress following 3D-MOT (151,152).

It should be noted that there were no significant between-group differences at any time point for the self-reported outcome measures in this study. However, the within-group improvements seen on several domains of patient-oriented outcome measures and their persistence one month after intervention, supports the idea that 3D-MOT may improve functional outcomes for msTBI survivors in a clinically meaningful way.

4.3 Effects of 3D-MOT on Cognition in msTBI Survivors

Neuropsychological assessments were used to explore whether cognitive performance in msTBI survivors could be improved after five-weeks of 3D-MOT. The hypothesis of large effect size improvements in cognitive performance after 3D-MOT was minimally supported by the results, as most improvements observed were associated with medium effect sizes. Intervention participants did not improve on all neuropsychological assessments used in this study but demonstrated improvements with medium to large effect sizes on certain measures of short-term verbal memory and retrieval, long-term memory and retrieval, attention, and executive function (Tables 3.3 and 3.4). Notably, any improvements in the control group on these same measures were only associated with small or negligible effect sizes. These findings provide insight towards the types of cognitive domains that may be improved in msTBI survivors following 3D-MOT. Understanding the specific domains that can be improved by 3D-MOT is beneficial for implementing this tool in clinical settings as it allows patients and clinicians to decide if the potential benefits are relevant to their needs.

Immediately following intervention, the slight participant improvements on the CVLT-II measures of short-term free or cued recall and long-term free or cued recall were likely not clinically meaningful, as they were associated with small to negligible effect sizes. However, by one-month post-intervention, participant improvements on all four of these measures were associated with medium or large effects sizes (Figures 3.10-3.13). Between group analyses found a significant difference in CVLT-II short-delay free recall scores at this T2 time point (Table 3.5). It could be suspected that improvements one-month post-intervention were due to practice effects, however, the control group did not show meaningful improvements on these measures, as suggested by the associated small and negligible effect sizes. The finding of improved verbal memory following 3D-MOT is consistent with prior research studying the use of this tool in a military population (52). Furthermore, these delayed improvements are consistent with literature that has found benefits of cognitive training to emerge at a later follow up, rather than immediately following intervention (153–155). One study in older adults with cognitive impairment found a language-based cognitive training program resulted in improved verbal learning, but these effects were only present six months after completion of the intervention (156). These delayed benefits of cognitive training have been referred to as the "sleeper effect" within literature, however the exact

mechanisms underlying this phenomenon remain unknown. Researchers have suggested that neuroplastic changes may take time before they are translated to observable behaviours (156–158). Teixeira-Santos et al. (2022) also observed this effect in older adults and suggested it could be related to neurodegeneration, which may explain why this effect is being seen in this msTBI population (158).

No meaningful improvements were seen in verbal learning after 3D-MOT, as suggested through the negligible change in CVLT-II Trials 1-5 score (Figure 3.9). Interestingly, there was a minor improvement in verbal learning performance with a small effect size one-month post-intervention compared to baseline. This finding was supported by a significant between-group difference at this T2 time point (Table 3.5). This trend may further support the idea of this "sleeper effect" following 3D-MOT in msTBI survivors. While these results could indicate delayed cognitive improvement, caution should be noted during interpretation, as sample sizes were one participant smaller per group at T2 neuropsychological assessments compared to T1.

Participants demonstrated improvements in the Total Digit Span score one-month post-intervention with a medium effect size (Figure 3.14). Evaluating the Digit Span subtests to better contextualize this finding, found participants had improvements associated with medium effect sizes on the Digit Span Forward test at both T1 and T2 (Figure 3.15). This test is the simplest of the three Digit Span subtests, reflecting auditory attention and short-term memory. In contrast, no meaningful improvements were seen on the Digit Span Backward or Sequencing tests after 3D-MOT, which are more complex and primarily reflect working memory and cognitive flexibility (Figures 3.16 and 3.17). These findings are consistent with previous studies that have found older adults to improve on the Digit Span Forward, but not the Digit Span Backward following other forms of cognitive training (159,160). These improvements on the Digit Span Forward subtest may be influenced by the demands that 3D-MOT places on attention for a sustained period (161). Lack of improvements in the Backward and Sequencing components of the Digit Span Task may be related to the 3D-MOT task not targeting the specific verbal-working memory and cognitive flexibility skills required (110,111). Control participants had no meaningful differences on the Digit Span Forward or Sequencing tasks, but interestingly demonstrated an improvement on the Digit Span Backward task with a medium effect size at the one-month follow up. This improvement could be related to individual variability attributed to small sample size or uncontrolled engagement in cognitively demanding activities outside of the study (162).

Furthermore, between-group analyses revealed that the control group performed significantly better than the intervention group on the Digit Span Forward at baseline, which should be considered when interpreting these findings.

Participants did not demonstrate improvements in global cognition after 3D-MOT, as measured by the MMSE (Figure 3.18). This could be related to 3D-MOT not targeting the broad domains assessed in the MMSE, but rather engaging specific cognitive processes. Furthermore, with the MMSE being a general screening tool for global cognition, it may lack the sensitivity to detect the domain specific changes that would be expected from a 3D-MOT intervention (e.g., attention and visuospatial processing) (114,161). The lack of improvements in global cognition could also be attributed to study participants being in the chronic time point of msTBI recovery. Literature suggests that most cognitive recovery after TBI occurs in the more acute time points, making notable global cognitive improvements less likely in this study's population (88).

No meaningful improvements were seen in attention and processing speed after 3D-MOT as measured through the SDMT (Figure 3.19). This finding may seem counterintuitive, as attention and processing speed are among the main domains thought to be engaged in 3D-MOT training (46). In alignment with these findings, a recent study found that processing-speed specific cognitive training, with the same duration of 10 sessions over five-weeks, did not significantly improve SDMT performance in msTBI survivors (163). These findings are further supported by no meaningful improvements measured on the TMT-A after 3D-MOT, another well-established measure of processing speed (Figure 3.20) (116). Since processing speed deficits are some of the most prevalent and persisting challenges faced by TBI survivors, it is possible that longer training durations or multi-modal methods of rehabilitation are needed to see improvements (164). Together, these findings highlight potential limitations in the transfer of skills trained through 3D-MOT to other processing speed tasks in msTBI survivors. It should be noted that control participants demonstrated improvements on the SDMT with a medium effect size at the one-month follow-up. This finding could also be explained by cognitive engagement outside of the study and individual variability amongst the small sample size.

Evaluating executive functioning, this study found no improvements in performance on the TMT-B after 3D-MOT (Figure 3.21). However, improvements were seen in performance on the Verbal Fluency FAS test with a medium effect size at both follow-up time points post-intervention (Figure 3.23). These differences may be due to the TMT-B and Verbal Fluency FAS evaluating

distinct components of executive function. The TMT-B primarily assesses cognitive flexibility and set-shifting, which may not be strongly engaged during 3D-MOT sessions (165). In contrast, the Verbal Fluency FAS test evaluates phonemic fluency, which has been associated with activation in the dorsolateral prefrontal cortex (166). Improvements on a task linked to the dorsolateral prefrontal cortex, also implicated in emotional regulation and cognitive reappraisal, may further support the observed improvements in emotional adjustment and perceived stress, as reflected in the MPAI-4 adjustment subscale and Perceived Stress Scale.

Participants demonstrated no improvements in semantic fluency after 3D-MOT, as measured by the Verbal Fluency Animals test (Figure 3.22). This discrepancy in results on the two Verbal Fluency tests may be explained by the different cognitive processes underlying each test. The Verbal Fluency Animals test relies more heavily on accessing knowledge through semantic memory, and therefore is suggested to be related to temporal lobe structures (166,167). As 3D-MOT has been suggested to train distributed attention, complex motion integration, and visual working memory, functions that are associated with the dorsolateral prefrontal cortex, these Verbal Fluency test findings appear consistent with 3D-MOT's proposed mechanism of action (46).

Interestingly, these findings align with results from a systematic review and meta-analysis of cognitive training for TBI survivors at least 12 months post-injury. Hallock et al. (2016) evaluated 14 studies and found significant improvements in verbal memory, executive function, and functional outcomes for TBI survivors at this time point. This current study contributes to the growing literature on cognitive training, suggesting that 3D-MOT may be a promising CCT intervention for cognitive and functional improvements in msTBI survivors at chronic time points.

4.4 No Change in a Biomarker of Aging after 3D-MOT in msTBI Survivors

This study did not find meaningful change in telomere length after 3D-MOT at either follow-up time point. Several possible explanations may account for the lack of observed change. The duration of the 3D-MOT intervention may be too short to elicit changes in telomere length. This study's intervention was only five-weeks in duration, whereas studies that found increases in telomere length involved participants in interventions for several months to years (69,168). It is possible that a cognitive training intervention on its own is not sufficient to elicit changes in telomere length, and rather is effective when combined with exercise and other beneficial lifestyle changes, which has been previously suggested (69). Furthermore, cognitive training may help

maintain telomere length over time, rather than increase it, which has been suggested from studies of mindfulness and education interventions (169,170). This study was unable to assess if telomere maintenance occurred, as research suggests closer to a year may be needed to see detectable shortening of telomere length (171).

Overall, these results do not support the hypothesis that a five-week 3D-MOT intervention improves biological aging, as measured by telomere length, in msTBI survivors. Future research could evaluate telomere length after a longer-term cognitive training intervention to better understand if a longer-duration of 3D-MOT is needed to elicit longer telomere length, or if 3D-MOT can result in telomere maintenance. Despite no changes on the biological level, this study still found meaningful reductions in perceived stress, TBI symptoms, emotional adjustment, and cognitive performance after 3D-MOT. To better understand how cognitive training may influence biological aging after TBI, levels of inflammatory markers could also be evaluated before and after interventions.

4.5 Participant Perspectives on 3D-MOT

The majority of participants reported having a positive experience with the 3D-MOT intervention. However, it should be noted that three participants did drop out due to intervention-related reasons. One participant found that using 3D-MOT lead to a lot of stress, mainly associated with doing the same task repetitively. This participant wished that they had the support of someone guiding them through the intervention from their home. This individual also suggested changing the stimuli and colours of the 3D-MOT task to keep it more engaging. Another participant could not complete the task as the 3D glasses immediately made them feel nauseous, however they appreciated the simplicity of the task's design and how it was not too colourful. This individual also had challenges with the instructions for the task at home, and wish they did the intervention with in-person support at VBIS. The other individual to drop-out of the intervention found that they ended up with headaches each time they tried 3D-MOT related to the motion of the targets, leading to stress and the inability to focus on the task. These findings suggest that 3D-MOT is appropriate for the majority of, but not all msTBI survivors as the tool may exacerbate symptoms in certain individuals and cause perceived stress. Furthermore, this input suggests that some survivors require more in-person support while doing the training, and that the remote nature of

this intervention with weekly check-ins from team members may not sufficiently meet the needs of all msTBI survivors.

The participants that completed the intervention reported enjoying seeing improvement on the 3D-MOT task as they progressed, the adaptive nature of the task, how the task does not take too much time, and how the software was straightforward to use. Almost all participants believed they received benefits from doing the 3D-MOT intervention. Reported benefits included cognitive improvements, including focus and memory, feeling optimistic about healing after TBI, practicing emotional control, and vision improvements. However, participants highlighted drawbacks to the intervention, including how it may not be accessible for older adults who experience challenges with technology use, how some instructions were confusing, and having to remember to complete the training days.

As for what participants would change in the 3D-MOT experience, multiple individuals highlighted how they would be interested in using the tool more than twice per week to see if the benefits increased. One individual suggested that a prompt reminding users to put on the 3D glasses would be beneficial for brain injury survivors. Another individual suggested that a more in-depth tutorial and explanation of what the NeuroTracker scores represent would be useful.

Despite some individuals not being able to complete the 3D-MOT intervention, all participants stated they would recommend 3D-MOT to other brain injury survivors. Multiple participants stated they are already recommending this tool to other survivors. Other participants emphasized how every brain injury is unique and to ensure that survivors are well-aware of how the tool can be mentally strenuous and to try it at their own pace. Overall, participant feedback emphasizes how 3D-MOT can be a beneficial tool for msTBI survivors, however due to the diverse nature of these injuries, it is important to take an individualized approach to enrolling survivors in such interventions and ensure they are adequately supported.

4.6 Limitations

While the present study has promising findings surrounding patient-oriented outcomes in msTBI survivors after 3D-MOT use, several limitations must be acknowledged. First, this study was mainly interested in exploring if cognitive training with 3D-MOT is a feasible way to improve patient-oriented outcomes in msTBI survivors, rather than isolating the specific effects of 3D-MOT compared to other cognitive training modalities, and therefore only implemented a passive

control group. This study's control group accounted for the social aspect of weekly participant check-ins and asked participants to ensure they were receiving at least one-hour of screen-time per week, however there was no inclusion of a scheduled cognitively engaging task for the control group. This passive control design was chosen to minimize participant burden for msTBI survivors and allow for more clear isolation of practice effects on the neuropsychological assessments. However, due to this design, the study cannot adequately control for placebo effects or demand characteristics, which should be acknowledged as limitations when interpreting these findings and drawing conclusions about the efficacy of 3D-MOT (172).

Randomization of participants was not entirely successful, as the simple randomization method resulted in unequal allocation of participants to the control and intervention groups. Additionally, participants in the 3D-MOT intervention group reported engaging in significantly more social activities per week than the control group, which could have influenced the findings of this study.

Furthermore, another challenge with the study design was the lack of blinding of research team members when scoring the self-report questionnaires, which could have introduced bias into the results. Blinding during these questionnaires was not feasible due to the sensitive nature of TBI and the importance of building trust with survivors. It was important to numerous participants that they worked with the same research team member throughout the study for consistency and comfort, and our team ensured to respect these participant wishes.

It should be acknowledged that this sample of msTBI survivors is inherently biased, in that it included survivors who the capacity to reach out to engage in a research study. While this study aimed to incorporate individuals with varying levels of functioning after msTBI by recruiting through the diverse community at VBIS, many msTBI survivors have severe physical, cognitive, and functional deficits that could limit their ability to seek out and volunteer in research studies. Furthermore, there were seven participants who dropped out of the intervention group for varying reasons, leading to analyses being biased towards those who could complete the intervention. At an attempt to incorporate perspectives from those who dropped out, this study included semi-structured interview data from the three participants who did not complete the study due to intervention-related reasons. However, the remaining four participants did not respond to communications regarding completing the semi-structured interview.

The small sample size of this study limits the generalizability of these results. The sample size was justified due to the challenges that can occur when recruiting and maintaining participation of survivors living with lasting symptoms of msTBI. However, the small sample size could have caused individual variations to impact the results, especially since cognitive abilities are known to fluctuate in msTBI survivors on a regular basis (55). Lastly, it is known that outcomes of TBI can vary based on sex and gender, however, this study's small sample size limited the ability to meaningfully analyse these differences (173,174).

4.7 Future Directions

This study supports further investigation of 3D-MOT as a therapeutic tool for improving functional and cognitive outcomes in TBI survivors. Regarding study design, future studies should incorporate larger sample sizes to increase generalizability and minimize the impact of individual variability on results. As well, an active control group should be implemented in future studies to isolate the effects of 3D-MOT and control for potential placebo effects. The length of intervention could be increased to determine if a greater dose of 3D-MOT can lead to larger effects. Longer-term follow-up time points (e.g., greater than 6 months) would be useful in determining if benefits of 3D-MOT persist upon completion of the intervention, or if continuous use is required to maintain benefits. Furthermore, longer intervention duration and follow-up time points would be valuable for more appropriately assessing the effect of this tool on biological markers of aging, such as telomeres.

The next step of this study will be to analyze levels of inflammation and neuroplasticity through serum samples collected in these participants. Serum biomarker analyses were not completed in time, and therefore could not be included as part of this thesis. Understanding if neuroplasticity markers (e.g., brain-derived neurotrophic factor) and inflammatory markers change after intervention will provide further insight into potential biological mechanisms that could be related to the functional and cognitive improvements seen after 3D-MOT in msTBI survivors.

To further a patient-oriented approach and ensure that this research works toward real-world change, implementation studies of 3D-MOT should be conducted. It would be important to conduct such studies in rural and underserved populations to understand if the remotely accessible nature of 3D-MOT meets the needs of msTBI survivors in these communities.

4.8 Conclusions

Cognitive training with 3D-MOT has potential to improve daily life challenges, TBI symptom severity, perceived stress, short-term verbal memory and retrieval, long-term verbal memory and retrieval, attention, and executive function, in msTBI survivors. Improvements in a variety of these domains were maintained at a one-month follow-up, suggesting potential lasting benefits of this intervention. While these within-group improvements after intervention are promising, these findings should be interpreted with caution due to limitations of this study, including the small sample size and lack of active control group. This tool was appropriate for the majority of participants, however, it should be acknowledged that it may not be suitable for all msTBI survivors, as some individuals had to drop out due to increased symptoms and intervention-related stress. Further research into the biological changes occurring in relation to 3D-MOT is required to better understand the underlying reasons for the cognitive and functional improvements seen. Overall, 3D-MOT has potential as an accessible, therapeutic option to aid in recovery from msTBI at chronic time points and should be implemented in a patient-oriented manner.

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Appendices

Appendix A – Ethics Approval Certificate

University of Victoria

Office of Research Services | Human Research Ethics Board
Michael Williams Building Rm B202 PO Box 1700 STN CSC Victoria BC V8W 2Y2 Canada
T 250-472-4545 | F 250-721-8960 | uvic.ca/research | ethics@uvic.ca

Certificate of Approval - Annual Renewal

PRINCIPAL INVESTIGATOR:	**Brian Christie** (Supervisor)	**ETHICS PROTOCOL NUMBER:** Full board review	**23-0350**
PRINCIPAL APPLICANT:	**Jamie Morrison** **Master's student**	ORIGINAL APPROVAL DATE:	09-Nov-2023
UVIC DEPARTMENT:	**Medical Sciences DMSC**	APPROVED ON:	25-Oct-2024
		APPROVAL EXPIRY DATE:	08-Nov-2025

PROJECT TITLE: **Investigating the effects of three-dimensional multiple-object tracking on markers of oxidative stress and cognition in brain injury survivors**

RESEARCH TEAM MEMBERS:
Taylor Snowden-Richardson - Trained in Phlebotomy, University of Victoria
Dr. Jodie Gawryluk - Neuropsychologist, University of Victoria
Ian Encina Guerrero - Undergraduate Research Assistant, University of Victoria
Colleen Lacey - Neuropsychology Student, University of Victoria
Danielle Peros - Undergraduate Research Assistant, University of Victoria
Dr. Sandy Shultz - Fluid Biomarker Analyst, University of Victoria
Katie Sternig - Undergraduate Research Assistant, University of Victoria
Emma Skaug - Trained in Phlebotomy, University of Victoria

DECLARED PROJECT FUNDING:
Mitacs Accelerate Fellowship, University of Victoria

DOCUMENTS INCLUDED IN THIS APPROVAL:
tcps2-eptc2-certificate.pdf - 03-Aug-2023
VBIS Consent for Research Project.pdf - 28-Aug-2023
Biosafety_Concussion_Lab_December08_2021_FINAL.docx - 28-Aug-2023
Verification_of_Registration Christie.pdf - 31-Aug-2023
NeuroTrackerx_guide.pptx - 31-Aug-2023
AppendixC_SCAT6.docx - 09-Sep-2023
AppendixD_MPAI4.pdf - 09-Sep-2023
AppendixF_References.pdf - 09-Sep-2023
AppendixH_Ongoing_Consent.docx - 09-Sep-2023
JamieMorrison_PhlebotomyCertificate.pdf - 13-Oct-2023
TaylorSnowden_PhlebotomyCertificate.pdf - 13-Oct-2023
AppendixE_Cognitive_Assessments_V2.pdf - 14-Oct-2023
AppendixI_GOSE.pdf - 07-Nov-2023
AppendixA_RecruitmentPoster_V3.pdf - 07-Nov-2023
AppendixB_IntakeForm_V2.docx - 17-Jan-2024
AppendixJ_Perceived_Stress_Scale.pdf - 17-Jan-2024
AppendixK_Semi-StructuredInterview.pdf - 12-Jun-2024
EmmaSkaug_PhlebotomyCertificate.pdf - 12-Jun-2024
AppendixG_ConsentForm_V3.docx - 03-Jul-2024
AppendixL_SampleEmail.pdf - 03-Jul-2024
AppendixM_EmailFollowUp.docx - 03-Jul-2024
AppendixN_PhoneScript.docx - 03-Jul-2024
AppendixO_ReachBCPost.pdf - 03-Jul-2024

Conditions of approval

This Certificate of Approval is valid for the above term provided there is no change in the protocol.

Amendments
To make changes to the approved research procedure in your study, please submit "Amendments" or "Annual renewal with amendments" form. You must receive research ethics approval before proceeding with your amended protocol.

Renewals

Your ethics approval must be current for the period during which you are recruiting participants or collecting data. To renew your protocol, please submit a “Request for Renewal” form before the expiry date on your certificate. You will be sent an emailed reminder prompting you to renew your protocol about six weeks before your expiry date.

Project Closures

When you have completed all data collection activities and will have no further contact with participants, please notify the Human Research Ethics Board by submitting a “Notice of Project Completion” form.

Certification

This certifies that the UVic Human Research Ethics Board has examined this research protocol and concluded that, in all respects, the proposed research meets the appropriate standards of ethics as outlined by the University of Victoria's policies for research involving human participants.

Appendix B – Participant Consent Form

Participant Consent Form

Investigating the effects of three-dimensional multiple-object tracking on markers of oxidative stress and cognition in brain injury survivors

Christie Laboratory
University of Victoria & Victoria Brain Injury Society

Investigator: Dr. Brian Christie (brain64@uvic.ca)
Co-Investigator: Jamie Morrison (jamiemorrison@uvic.ca)

Table of Contents

Participant Selection

You have been invited to participate in a study conducted by the Christie Laboratory at the University of Victoria. You are invited to participate in this study because you are:

- ➢ Over the age of 19 years old with a history of acquired brain injury (BI)
- ➢ Over the age of 19 years old without a history of acquired brain injury (BI0)

Your participation is voluntary, and you are under no obligation to participate in this study. There is no reason to believe participants will experience a brain injury during the study. Should you experience a brain injury, training can continue; however, the tests used in our research laboratory are not intended to take the place of a proper evaluation by your doctor.

Jamie Morrison is a master's student in the Neuroscience Graduate Program at the University of Victoria. This research project is being conducted as part of Jamie's master's thesis and is supervised by Dr. Brian Christie. You may contact Jamie by email jamiemorrison@uvic.ca for any questions.

Dr. Christie, Ph.D. is a faculty member in the Division of Medical Sciences at the University of Victoria. You may contact him by phone at (250) 472-4244 or email brain64@uvic.ca should you have further questions.

CogniSens Inc., the developer of NeuroTracker, is not funding this research.

Voluntary Participation

Your participation in this research must be entirely voluntary. If you participate, you may withdraw at any time without any consequences or any explanation. If you withdraw from the study, data will be used only if you give permission.

Purpose and Objectives

The purpose of this research is two-fold. First, to explore if individuals with a history of acquired brain injury show an increased amount of markers of oxidative stress and brain injury, including decreased cognitive performance and increased levels of oxidative stress-related fluid biomarkers, compared to individuals with no prior history of acquired brain injury. Second, to investigate a cognitive training intervention with three-dimensional multiple-object tracking (3D-MOT) aimed at decreasing these oxidative stress-related markers. Brain injury is a leading cause of life-long disability worldwide and can cause increased oxidative stress in individuals. Oxidative stress is problematic as it has been linked to cognitive decline and neurodegenerative diseases. Accessible and effective therapeutic interventions for symptom management and recovery in brain injury survivors are lacking. 3D-MOT is a promising therapeutic tool for improved cognition that can be administered at home with a low-cost. It is important to

investigate the transferability of 3D-MOT to real-life settings, and therefore we hypothesize that improvements in cognitive function from 3D-MOT may be attributed to decreases in oxidative stress. In collaboration with the Victoria Brain Injury Society (VBIS), our goal is to conduct a randomized controlled trial with an online, at-home 3D-MOT intervention.

Research has demonstrated that 3D-MOT using NeuroTracker can improve sports performance in elite athletes and aid in recovery post-concussion. For example, higher scores on the NeuroTracker are related to better performance in professional athletes. NHL, NFL, and pro soccer players have been found to have better visual perceptual skills when compared to adult amateur athletes and non-athletes. After several sessions on NeuroTracker, differences in learning curves can also be seen between individuals. We are interested in examining whether history of brain injury is a factor in individual differences of NeuroTracker scores and learning curves in adults. We are also interested in learning more about how the current cognitive functioning of adults, as measured by an assortment of neuropsychological assessments, are affected by a history of brain injury.

Recent research has shown potential for cognitive training to improve oxidative stress in adults with mild cognitive impairment. Our goal is to investigate the relationship a 3D-MOT intervention has on cognitive functioning and biological oxidative stress-related markers in individuals with a history of acquired brain injury.

There is no reason to believe that participants will experience brain injury during the study period. In the unlikely case an individual experiences a brain injury during the study period, they will be sent to their primary care physician/nurse practitioner/walk-in clinic for advice/clearance/prescriptions.

Importance of this Research

It is estimated that every three minutes someone in Canada receives a traumatic brain injury. Symptoms of brain injuries can manifest physically, cognitively, and socially. Often these symptoms compound, resulting in intersecting challenges such as homelessness, addiction, and mental health problem. Survivor resources are lacking, especially since many existing therapies and interventions are inaccessible due to the cost associated with them. The multifactorial impact that brain injury has on an individual's life is one reason why it is of utmost importance to have accessible, research-based interventions for survivors during the recovery journey.

In addition, due to cellular injury and subsequent neuroinflammatory responses, brain injury results in a heightened rate of oxygen consumption, putting the survivor at increased risk of oxidative stress. Oxidative stress has been linked to cognitive decline and other neurodegenerative diseases. Therefore, examining ways to reduce oxidative stress can be especially beneficial for the population of brain injury survivors.

Overall, the lack of knowledge about the changes in cognitive function and the clinical validity/relevance of the long-term effects of brain injuries is still being explored. This study aims to explore further the long-term cognitive and biological effects of brain injuries in adults.

What is Involved?

All those who meet the criteria and consent to participate in this study will be enrolled in this study. This is a partially randomized study based on concussion history (i.e. participants in Group 1 have a history of concussion, participants in Group 2 have no history of concussion).

As part of **Group 1**, you will be asked to complete:

- a cognitive assessment and blood/saliva sampling at baseline (T0),
- a randomly assigned intervention (cognitive training or activity as usual for 5 weeks) (T1)
- a second cognitive assessment and blood/saliva sampling following the intervention (T2)
- a follow up cognitive assessment blood/saliva assessment after one month (T3)
- a final semi-structured interview to gain participant feedback on the research process

As a part of **Group 2***, you will be asked to complete:

- a cognitive assessment and blood/saliva sampling at baseline (T0)
- a second cognitive assessment and blood/saliva sampling

following five weeks of activity as normal (T2)
- a follow up cognitive assessment blood/saliva assessment after one month (T3)

**You will be able to participate in the intervention following study participation if desired*

Study Population

The sample will consist of cognitively healthy adults

Group 1 (BI)	
Inclusion Criteria	1. Age 19 and over; **2. Have a history of acquired brain injury (minimum of 6 months since the most recent injury)** 3. Willing to provide physician, health practitioner, or walk-in clinic information in case of incidental findings
Exclusion Criteria	1. Presence of medical diagnosis of a Major Neurocognitive Disorder (e.g. Alzheimer's disease, frontotemporal lobe dementia, Lewy Body dementia, vascular dementia); 2. Presence of sensory deficits (e.g. colour blindness, monocular/binocular blindness, macular degeneration);

	3. Participation in NeuroTracker training within the past year 4. Presence of severe aphasia or cognitive deficits that would impede participation in the intervention
Group 2 (BI0)	
Inclusion Criteria	1. Age 19 and over; **2. No history of brain injury** 3. Willing to provide physician, health practitioner, or walk-in clinic information in case of incidental findings
Exclusion Criteria	1. Presence of medical diagnosis of a Major Neurocognitive Disorder (e.g. Alzheimer's disease, frontotemporal lobe dementia, Lewy Body dementia, vascular dementia); 2. Participation in NeuroTracker training within the past year

The Protocol

Step 1: Assessment pre-treatment (T0)

Cognitive Assessments

We will use a Neuropsychological Battery of tests (NBT) to investigate specific cognitive areas such as memory and executive functions (60 min). All these assessments will be conducted by a licenced neuropsychology resident and occur over ZOOM. This session can be done from home or in a private room at the University of Victoria Concussion Lab.

- STROOP TEST: This test is considered to measure selective attention, cognitive flexibility, and processing speed and is used to evaluate executive functions. To complete STROOP TEST (2 practice tests, one scored test), we will use a computerized version of the assessment tool, providing a baseline of your attention abilities. The test is non-invasive, and you can stop at any point if you wish.

- DIGIT SPAN BACKWARD TEST: A digit-span backward task is used to measure verbal working memory's capacity. Verbal working memory is involved in many everyday tasks, such as remembering a friend's telephone number while entering it into a phone and understanding long and complex sentences.

- TRAIL MAKING TEST: The Trail Making Test is a neuropsychological test of visual attention and task switching, which can provide information about visual search speed, scanning, speed of processing, mental flexibility, and executive functioning.

- VERBAL FLUENCY TESTS are a kind of psychological test in which participants have to say as many words as possible from a category in a given time (usually 60 seconds). This category can be semantic, like animals or fruits, or phonemic, such as words that begin with a particular letter.

- A LIST OF WORD AS AUDITORY VERBAL LEARNING TEST: The California Verbal Learning Test – Second Edition (CVLT-II) evaluates a wide diversity of functions such as immediate recall, short delay-free and cued recall, long delay-free and cued recall, long delay recognition.

- SYMBOL DIGIT MODALITIES TEST: The Symbol Digit Modalities Test (SDMT) evaluates executive functions and involves a simple substitution task using a reference key to pair specific numbers with given geometric figures in a given amount of time (usually 90 seconds).

- CORSI BLOCKS TEST: The Corsi block-tapping test assesses visuospatial short-term and working memory. It involves mimicking a researcher as they tap a sequence of up to nine identical spatially separated blocks. The sequence starts simple, usually using two blocks, and becomes more complex until the subject has lowered performance.

Biological fluid collection

With your consent, a certified Island Health phlebotomist or medical technician will insert a needle into your arm vein, and blood will be collected into several small tubes, for a total of no more than 60mL or 12 teaspoons. Blood will be collected in the Medical Sciences Building (MSB 105) on the University of Victoria Campus. Blood sampling is a standard, slightly invasive procedure and should not take more than 10 minutes for most people.

A trained individual will instruct you to drool saliva into a collection tube passively. This is a non-invasive procedure, can be self-administered and takes less than 15 minutes for most people. The goal of this procedure is to collect between 2-5mL of saliva. Saliva samples will be collected in the Medical Sciences Building (MSB 105).

You are under no obligation to participate in the blood and saliva sampling. You may participate in none, one or both of the fluid collections and still be eligible for the rest of the study. The samples you provide will be de-identified, meaning that no identifiable information will be directly on the samples. Samples will be stored in a locked freezer in MSB and then transported to Vancouver Island University for analysis by our collaborators. Samples will be stored at Vancouver Island University for one year following the first analysis, and then disposed of according to biosafety protocols.

Step 2: Training (T1), 5-weeks

Intervention: Cognitive Training with NeuroTrackerX

NeuroTrackerX is an at-home cognitive training tool that uses three-dimensional multiple object tracking at increasing difficulties to develop the high-level brain functions critical to recovery & cognitive health. Brain function is constantly challenged by increasing the difficulty with each correct response and decreasing the difficulty when mistakes are made. Each session (7 mins) delivers a series of mini-tests where the participant needs to remember key targets, then tracks them moving among distractors for several seconds and then identifies them. Simple to do, but always challenging, NeuroTracker adaptively optimizes difficulty to each patient's level, maximizing cognitive stimulation every step of the way. Participants will use the remote NeuroTracker X software, which allows participants to do cognitive training from home. Our lab will loan out any equipment needed for participation (e.g. computer, 24" monitor, 3D glasses, and cables). Participants will receive introductions to the software virtually and a manual for assistance. Along with this, participants will have access to a research hotline from 8:30 am-8:30 pm Monday-Saturday in the case of needing assistance. Participants will engage in two 30-minute NeuroTrackerX sessions per week. A research assistant will check in with you once per week via your preferred communication method (phone, email, ZOOM) to check on your progress and answer any questions.

Control: Activity as Normal

Participants in the control group will be asked to continue their daily activities as usual during the five-week intervention period. Given the potential for beneficial effects of the intervention, participants in this group will have access to NeuroTrackerX training after the study is completed.

Step 3: Assessment Post-treatment (T2)

At the end of the intervention, the participants will be evaluated with the same neurocognitive battery of tests and blood/saliva collection used at baseline T0 to identify any cognitive and biological changes resulting from the interventions.

Step 4: Longitudinal Assessment (T3)

One-month post-intervention completion, the participants will be evaluated with the same neurocognitive battery of tests and blood/saliva collection used at baseline T0 and one-week follow-up to identify any sustained cognitive and biological changes resulting from the interventions.

Implications

Inconvenience

Participation in this study should cause minor inconvenience. Steps 1, 3 and 4 may require you to visit the University of Victoria. Parking and costs for public transportation for these sessions will be reimbursed by the study team. Due to the remote nature of this research, you will be able to conduct your sessions at any

time that works for you. We will have research assistants available from 8:30 am - 8:30 pm Monday through Saturday to answer questions and assist if needed. This research project requires that participants complete two sessions per week for five weeks. We recommend evenly dispersing the training sessions throughout the week. A recommended training plan will be provided.

Risks

Blood sampling may result in mild discomfort and bruising. Swelling or clotting of the blood vessel or inflammation at the venipuncture site may occur. Some people report feeling faint when having blood drawn and may sometimes faint. Infection is rare but can be easily treated.

Participation in NeuroTrackerX does not pose any health risks. As documented in the literature, the use of Neurotracker is safe and widely used in young, adult and elderly populations (M. Medeiros et al., 2016; https://neurotracker.net/cognitive/references). Various studies have highlighted the non-invasiveness of this technique. None of the studies published to date have reported significant side effects or adverse reactions produced by Neurotracker. However, we observed in the pilot study that after completing computerized versions of the Neurotracker, some of the participants experienced a few transient effects, such as mental fatigue and eye redness. Participants have the option to take a 5-minute break at the end of each run during the Neurotracker sessions to reduce these risks. In the case of fatigue, we recommend participants sit and relax and enjoy cool water and

a snack.

Other methods used to prevent risk include providing specific instructions regarding the closest parking lot to the building in which the study will occur will be provided before participation to reduce the walking distance for the participants. Participants will be reminded that they are under no obligation to continue NeuroTrackerX training or the study as a whole.

Incidental Findings

Incidental findings are defined as observations of potential clinical significance unexpectedly discovered that are unrelated to the purpose of study. In rare cases, a researcher may see something in the cognitive assessment scores that suggests the presence of a medical condition. If a medical question arises in your case, the researcher will contact your primary care physician using the contact information you provide below if you give your permission. For this reason, we ask you to provide us with the name of your family physician/nurse practitioner/walk-in clinic in the unlikely event that it will be needed. If you are not willing to provide the name of your physician/nurse practitioner/walk-in clinic, we **will not** be able to include you in this study. Please remember that **any tests we administer are strictly for research purposes** and should not be considered a diagnosis for or against any physiological or psychiatric status/disorder; only a doctor can determine if this is the case. In the rare case that abnormalities are observed, you will be able to continue your participation in this study. An individual's results from the standardized neuropsychological

assessments and fluid collection analyses will **not** be made available to participants because these data are not for diagnostics; however, the final study results (**no individual information**) will be made available to all participants.

Benefits

Aging difficulties such as memory, attention, and processing speed act as obstacles to effective processing of complex visual information and can be exasperated in people with histories of brain injury. Studies on executive functions have found statistically significant difficulties in visual-perceptual processing in the observed elderly population (i.e. the need for more processing abilities such as reaction time, speed processing, inhibition of non-appropriate responses and decision making). Furthermore, studies demonstrate that executive functions play an essential role in both memory and instrumental activities of daily living. Maintenance of these functions through cognitive training may lead to increased independence and quality of life in the aging population and improved performance in memory tasks.

Our previous research also suggests that a NeuroTrackerX intervention is effective at symptom reduction and improving quality of life for brain injury survivors (Snowden et al., 2023). NeuroTrackerX has a monetary value of $35 per month. This cost will be covered by the research team for all participants engaged in the cognitive training intervention.

Anonymity

To protect your anonymity, a number will be assigned to you so that names will not be used. All attempts will be made to ensure your data remains anonymous. No links or codes will be provided to CogniSens Athletics Inc., allowing participants to be re-identified.

Confidentiality

Your confidentiality and the confidentiality of the data will be protected by storing all data in a password-protected computer program (i.e., NeuroTrackerX system) and excel file. All paperwork will be stored in a locked filing cabinet at the University of Victoria Concussion Lab. De-identified NeuroTracker data will also be shared with and stored by CogniSens Inc. CogniSens Inc. may use this de-identified data for future analyses. You will also be provided with a randomly generated number, such that your data is not stored with your personal information electronically. Notwithstanding the confidential requirements of the preceding paragraph, both UVic and CogniSens Athletics Inc. acknowledge that CogniSens Athletics Inc. shall be entitled to disclose the existence and nature of this collaboration for internal and commercial purposes as well as retain and use any and all information, data or results emanating from the collaboration, provided that CogniSens Athletics Inc. shall not in any way, directly identify or associate such results with the participants in the study.

Data

Dissemination of Results

It is anticipated that the results of this study will be shared with others in the following ways:

1. Directly to participants via PowerPoint Presentation at the end of the study;
2. With recruitment partners including the Institute on Aging and Lifelong Health, Victoria Brain Injury Society, and Nanaimo Brain Injury Society;
3. Published articles;
4. Theses and/or dissertations;
5. Presentations at scholarly meetings; and
6. Company promotions (CogniSens Inc., CBI).

Additional use of Data

Danielle Peros is an undergraduate honours student in the department of Exercise Science, Physical & Health Education at the University of Victoria. Danielle will be working under the supervision of Dr. Brian Christie and Jamie Morrison to use data collected from this study to complete her honours degree.

Disposal of Data

Data from this study will be stored in locked filing cabinets and password-protected computer files for ten years, after which all hard copies of the data collected relating to the study will be shredded. De-identified electronic data will be stored indefinitely in a password-protected database by CogniSens Athletics Inc. (but will remain de-identified). The principal investigator will

delete all electronic files after ten years.

Future Use of Data

PLEASE SELECT 1 OF THE STATEMENTS BELOW:

1) I consent to the use of my data in future UVic research: _____ (Participant to provide initials)

OR

2) I **do not** consent to the use of my data in future UVic research: _____ (Participant to provide initials)

OR

3) I consent to be contacted in the event my data is requested for future UVic research: _____ (Participant to provide initials)

Consent and Statements

Ongoing Consent

To ensure that you continue to consent to participate in this research, we will schedule all appointments well in advance and provide you with a summary of dates and times. You will provide initials at T0, T2 & T3 to indicate ongoing consent.

Participant Data Statement

I understanding that my individual [data and test results] will not be shared with me. _____ (Participant initials)

I understand that in this study [the data/test results] are collected for research purposes and not for diagnostic purposes. _____ (Participant initials)

Healthcare Contact Statement

If there is an incidental finding (abnormality) on the neuropsychological assessments, I wish for my physician, health practitioner, or walk-in clinic (_____) to be informed. I give the research team permission to disclose information to the physician, health practitioner, or walk-in clinic I have named for medical follow-up. (If you do not have a family physician, please list another medical practitioner, such as a nurse practitioner or walk-in medical clinic.)

Withdrawal Statement

To only be completed in the event of a withdrawal

I (_____) (Participant name) wish to withdraw from the present study. I give the research team consent to use my data up until my withdrawal.

Yes No (please circle)

Use of Laboratory Materials Statement

I (_____) (Participant name) agree to care for the borrowed laboratory equipment (*e.g.* computer, computer monitor, 3D glasses, computer cables) and return all the equipment to the laboratory after the cessation of the current

research study.

Contacts

Individuals that may be contacted regarding this study include:

Jamie Morrison:
Email: jamiemorrison@uvic.ca

Dr. Brian Christie:
Email: brain64@uvic.ca
Phone: (250) 472-4244 or (250) 634-4471

In addition, you may verify the ethical approval of this study or raise any concerns you might have by contacting the Human Research Ethics Office at the University of Victoria (250-472-4545 or ethics@uvic.ca).

Your signature below indicates that you understand the above conditions of participation in this study, that you have had the opportunity to have your questions answered by the researchers, and that you give your consent for your child to participate in this research project.

_____ _____

Name of Participant *Date of Intake*

_____

Signature of Participant

Appendix C – Participant Recruitment Poster

CHRISTIE LAB

VBIS
Victoria Brain Injury Society

VOLUNTEERS NEEDED FOR BRAIN INJURY RESEARCH

The Christie Lab & Victoria Brain Injury Society are partnering to research:

- The effects of traumatic brain injury on biological and cognitive functioning.
- A cognitive training intervention to improve outcomes of traumatic brain injury.

We are recruiting participants who are:

- Aged **19** years or older
- With a history of **moderate to severe traumatic brain injury**

This study will include:

- A cognitive assessment, blood & saliva collection
- Participation in a **5-week cognitive training intervention with NeuroTracker**

Note: blood & saliva collection not mandatory for participation

If you are interested in learning more

Please contact us at jamiemorrison@uvic.ca
Subject line: **Brain Injury Study**

Appendix D – Semi-Structured Interview Questions

Post Study Semi-Structured Interview

Questions for all

How was your experience in this research study?	
What did you like about the study process/design/experience?	
What did you not like about the study process/design/experience?	
Do you have any suggestions for improving brain-injury research studies in the future?	
What do you think are important topics that need to be researched for brain injury survivors?	
What needs to be improved for long-term outcomes/recovery for brain injury survivors?	
Anything other comments?	

Questions for intervention group

How was your experience with the NeuroTracker intervention?	
What did you like about the NeuroTracker intervention?	
What did you not like about the NeuroTracker intervention?	
Do you believe NeuroTracker provided you with any benefits?	
Would you recommend NeuroTracker to other brain injury survivors?	
Is there anything you would change about the NeuroTracker intervention?	

Appendix E – NeuroTrackerX Participant Instructions

Visual and written NeuroTrackerX instructions shared with participants are shown in the below images. Participants were also provided with a link to a video outlining how to use NeuroTrackerX (https://youtu.be/gu95p4e22oc?si=YXK8lbW257m3Qhf_).

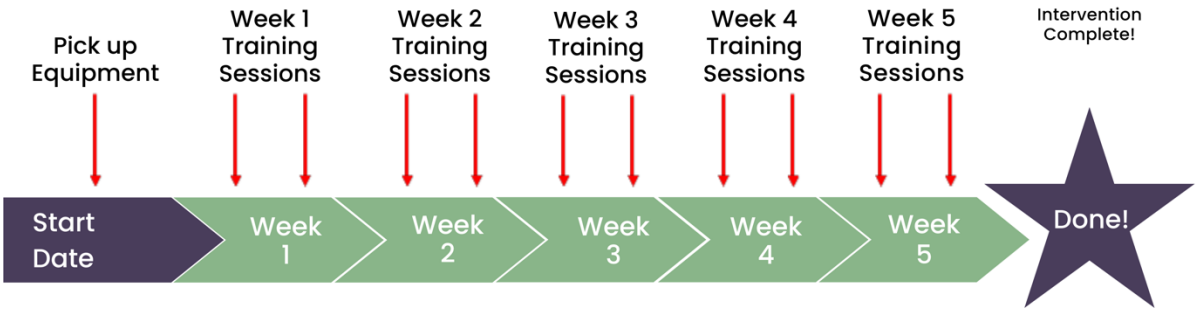
VBIS
Victoria Brain Injury Society

Using NeuroTracker

Visual and Written Instructions

Contact jamiemorrison@uvic.ca with questions

Intervention Timeline & Overview



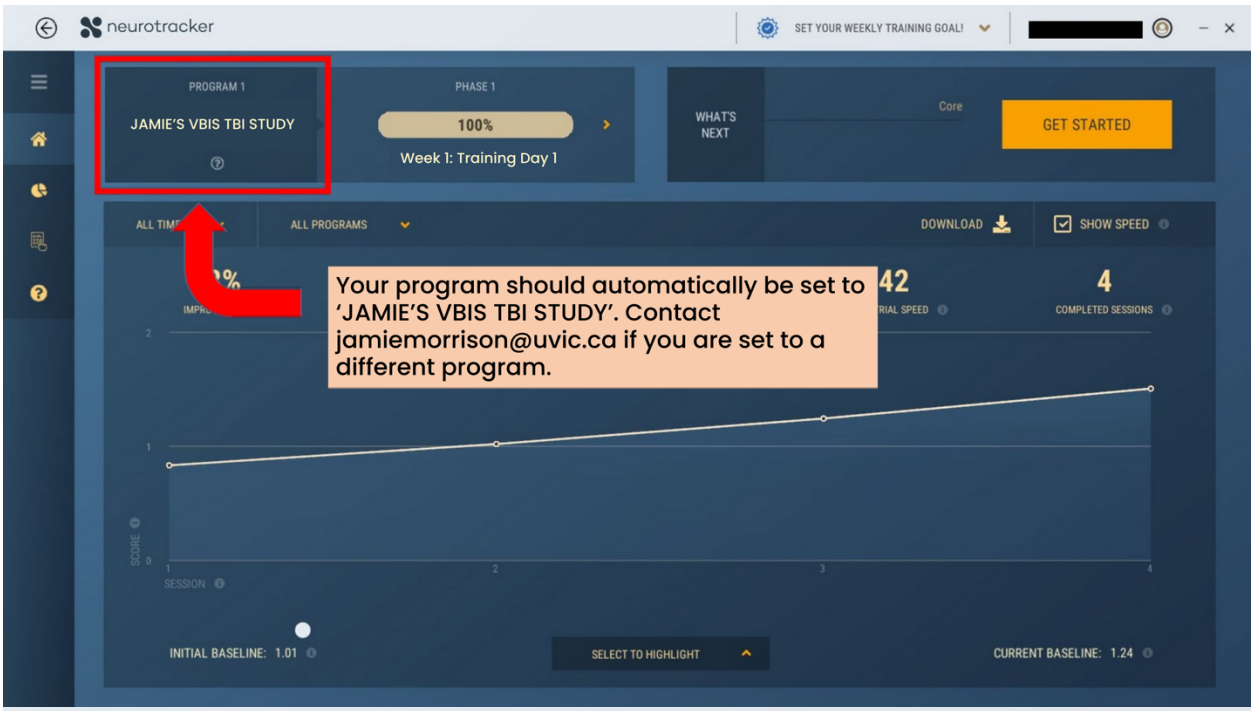
- The NeuroTracker intervention involves ~1 hour of screen time per week with NeuroTracker
- This document details instructions for the NeuroTracker training
- Your NeuroTracker training involves 10 training days over 5 weeks (2 training days per week)
- Each training day is made up of 3 training sessions (~6-8 minutes each session, ~20-25 minutes total per day)

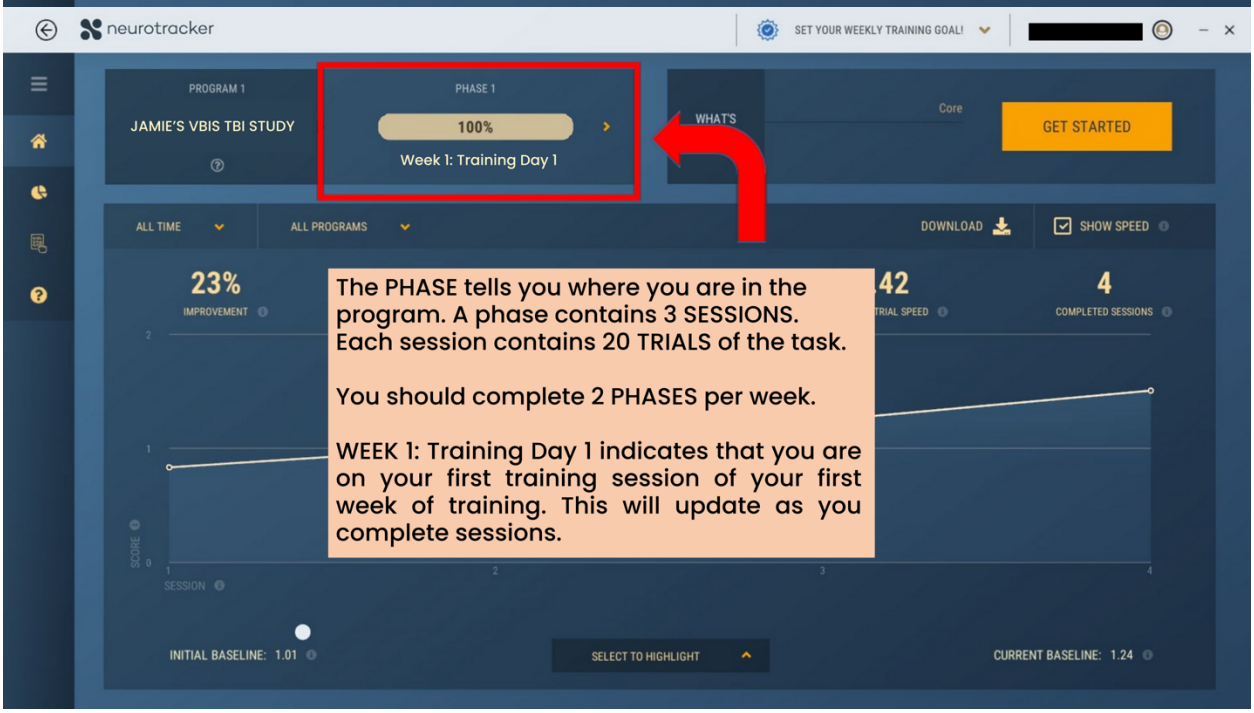
Weekly Example

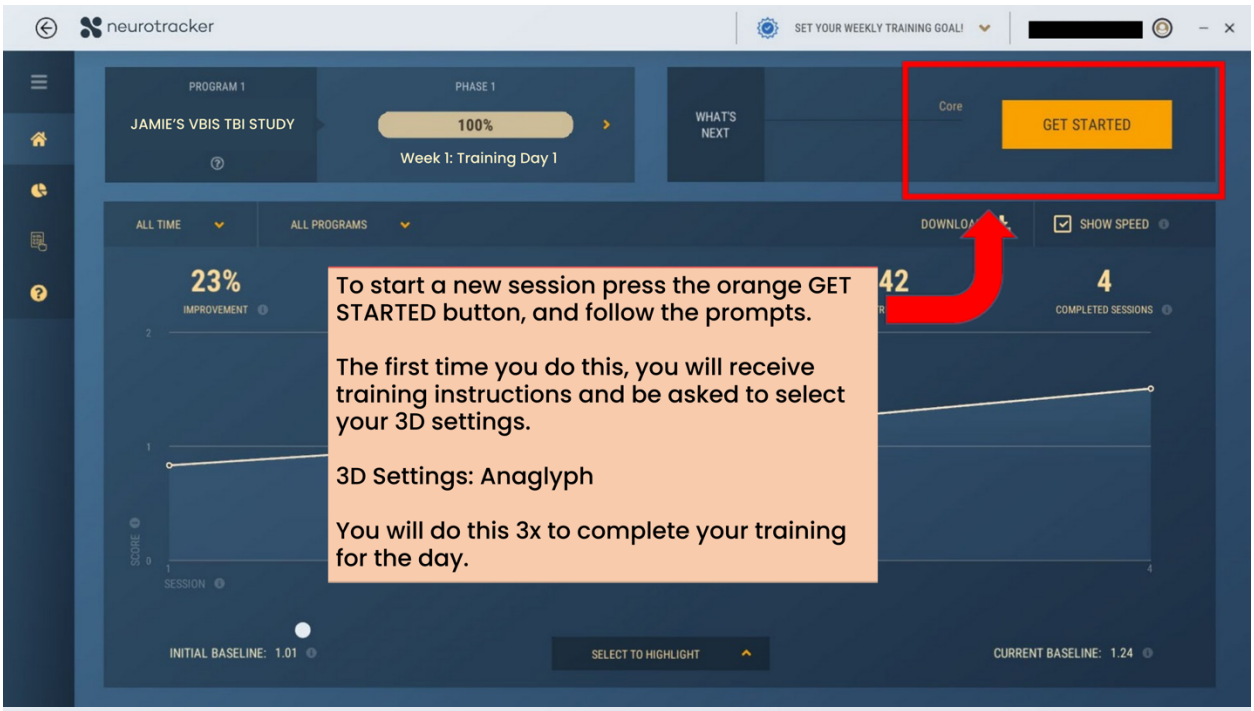
This is just an example. We recommend at least one rest day in between NeuroTracker days. This intervention is flexible, and you can modify it to work in your schedule.

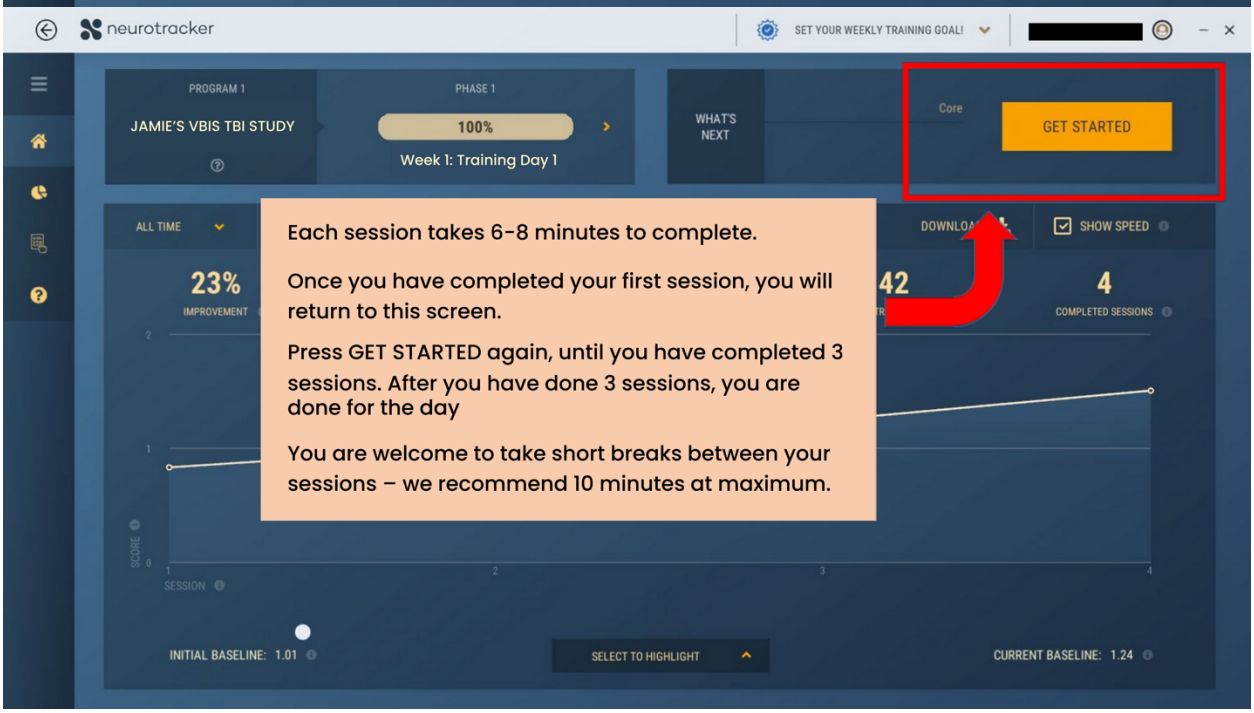
Navigating NeuroTrackerX


neurotracker
When you open NeuroTrackerX you will see this screen.
1.Enter your user ID that has been provided to you
2.Enter the password that has been provided to you
3.Press the orange LOGIN button
Enter your email or user ID
Enter your password
LOGIN
REMEMBER ME
RESET PASSWORD
NEED HELP?
neurotracker
SET YOUR WEEKLY TRAINING GOAL!
PROGRAM 1
JAMIE'S VBIS TBI STUDY
PHASE 1
100%
Week 1: Training Day 1
WHAT'S NEXT
Core
GET STARTED
ALL TIME
ALL PROGRAMS
DOWNLOAD
SHOW SPEED
23%
IMPROVEMENT
1.50
LAST SESSION SCORE
1.50
BEST SCORE
1.42
HIGHEST TRIAL SPEED
4
COMPLETED SESSIONS
This is an example of your HOME screen.
SCORE
SESSION
INITIAL BASELINE: 1.01
SELECT TO HIGHLIGHT
CURRENT BASELINE: 1.24


neurotracker
SET YOUR WEEKLY TRAINING GOAL!
PROGRAM 1
JAMIE'S VBIS TBI STUDY
PHASE 1
100%
Week 1: Training Day 1
WHAT'S NEXT
Core
GET STARTED
ALL PROGRAMS
DOWNLOAD
SHOW SPEED
Your program should automatically be set to 'JAMIE'S VBIS TBI STUDY'. Contact jamiemorrison@uvic.ca if you are set to a different program.
COMPLETED SESSIONS
SCORE
SESSION
INITIAL BASELINE: 1.01
SELECT TO HIGHLIGHT
CURRENT BASELINE: 1.24


neurotracker
SET YOUR WEEKLY TRAINING GOAL!
PROGRAM 1
JAMIE'S VBIS TBI STUDY
PHASE 1
100%
Week 1: Training Day 1
WHAT'S
Core
GET STARTED
ALL TIME
ALL PROGRAMS
DOWNLOAD
SHOW SPEED
23%
IMPROVEMENT
The PHASE tells you where you are in the program. A phase contains 3 SESSIONS. Each session contains 20 TRIALS of the task.
You should complete 2 PHASES per week.
WEEK 1: Training Day 1 indicates that you are on your first training session of your first week of training. This will update as you complete sessions.
COMPLETED SESSIONS
SCORE
SESSION
INITIAL BASELINE: 1.01
SELECT TO HIGHLIGHT
CURRENT BASELINE: 1.24


neurotracker
SET YOUR WEEKLY TRAINING GOAL!
PROGRAM 1
JAMIE'S VBIS TBI STUDY
PHASE 1
100%
Week 1: Training Day 1
WHAT'S NEXT
Core
GET STARTED
ALL TIME
ALL PROGRAMS
SHOW SPEED
23%
IMPROVEMENT
42
4
COMPLETED SESSIONS
SCORE
SESSION
INITIAL BASELINE: 1.01
SELECT TO HIGHLIGHT
CURRENT BASELINE: 1.24
To start a new session press the orange GET STARTED button, and follow the prompts.
The first time you do this, you will receive training instructions and be asked to select your 3D settings.
3D Settings: Anaglyph
You will do this 3x to complete your training for the day.


neurotracker
SET YOUR WEEKLY TRAINING GOAL!
PROGRAM 1
JAMIE'S VBIS TBI STUDY
PHASE 1
100%
Week 1: Training Day 1
WHAT'S NEXT
Core
GET STARTED
ALL TIME
SHOW SPEED
23%
IMPROVEMENT
42
4
COMPLETED SESSIONS
SCORE
SESSION
INITIAL BASELINE: 1.01
SELECT TO HIGHLIGHT
CURRENT BASELINE: 1.24
Each session takes 6-8 minutes to complete.
Once you have completed your first session, you will return to this screen.
Press GET STARTED again, until you have completed 3 sessions. After you have done 3 sessions, you are done for the day
You are welcome to take short breaks between your sessions – we recommend 10 minutes at maximum.


This is where you will see your scores on NeuroTracker.
After you have completed 2 PHASES (3 sessions each) you will be able to see percent improvements, scores and a graph of your performance over time.
See later slides for definitions of each phrase used in this section
WEEKLY TRAINING GOAL!
Core
GET STARTED
ALL TIME
ALL PROGRAMS
DOWNLOAD
SHOW SPEED
23%
IMPROVEMENT
1.50
LAST SESSION SCORE
1.50
BEST SCORE
1.42
HIGHEST TRIAL SPEED
4
COMPLETED SESSIONS
SCORE
SESSION
INITIAL BASELINE: 1.01
SELECT TO HIGHLIGHT
CURRENT BASELINE: 1.24
neurotracker
SET YOUR WEEKLY TRAINING GOAL!
Press the PIE CHART on the left side of the screen for a more in-depth look at your training results. We will go over this together at the end of the program.
SHOWING LAST SESSION (SESSION # 4)
CORE
4 TARGETS
8 SECONDS
DEC 31, 2020 12:03 PM PST
HIGH IMPROVEMENT
High session score relative to previous baseline
A SURE THING
Low number of misses at slower speeds
FLAWLESS STREAK
Several perfect trials in a row
A full achievements section will be coming in the future
SCORE
1.5
CONSISTENCY SCORE
47%
FASTEST TRIAL SCORE SUCCESS
1.42
LOWEST TRIAL SCORE MISS
0.57
TRIAL SUCCESS BREAKDOWN
THRESHOLD SPEED
LOWER SPEED
HIGHER SPEED
PERFECT TRIALS
NEAR MISSES
SIGNIFICANT MISSES
RESPONSE TIME PER TRIAL
PERFECT TRIALS
NEAR MISSES
SIGNIFICANT MISSES

Written Instructions for using NeuroTrackerXthe first time

1. Open NeuroTrackerX and enter your UserID and Password. Both of these will have been emailed to you.

2.A pop-up window will appear with the Terms and Conditions of Use. You must agree to these terms to continue using the program.

3. A pop-up window will appear to explain the training dashboard, program progression and changing profile settings. Click 'NEXT' to move through the explanations.

4.Select 'GET STARTED' in the upper right corner of the screen to begin your first session!

5. Enter your 3D settings (ANAGLYPH)

6.Follow the instructions in the 'HOW TO TRAIN' pop-up, and follow the prompts to begin your session

7.After each session you will see your score, and be able to enter any comments. Feel free to include anything you noticed during your session (I was tired, distracted by my pet, there was construction outside etc.)

8.Congratulations on completing your first session!

9.You need to complete 3 sessions in one sitting. Press 'GET STARTED' again to complete your second session

10.and again to complete your third session. Once you have finished your 3 sessions, you are done for the day! Be sure to do this 2 times per week (for a total of 6 sessions over 2 days). If you have questions about this please contact the researcher.

TIPS for Using NeuroTrackerX

SETTING-UP

•If you have a computer monitor, see attached document for set up help.

•Your computer monitor should be at a height such that your eyes are level with the middle of the screen. If you are sitting too high or too low, the 3D may be distorted.

•You should sit at a distance equal to the diagonal of your screen size.
•The 3D may be distorted if you sit too close or too far.
•Example: If you are using a 24" monitor, sit aprox. 24" away

•You should sit in a quiet area, free from distractions while engaging in NeuroTrackertraining
•Turn off music, silence your phone, turn off the TV
•It is OK to have coffee/tea and snacks with you during the sessions

•We do NOT recommend putting the 3D glasses on prior to your screen being in 3D. This can cause dizziness and headaches. You are welcome to wear the 3D glasses overtop of your regular glasses.

TIPS for Using NeuroTrackerX

During the Sessions:

•To select targets, you can use the number pad on your keyboard, or you can use your mouse to select the targets

•To deselect a target, either type its assigned number again, or click on the target again

•Once you have selected 4 targets, you will not be able to change your answer

•To PAUSE: press the ESC key. Note: the session will only pause once the balls are no longer moving

•To QUIT: press the ESC key and press quit. If you did not finish your session, do not save it. You will have to re-do this session.

•Stare at the centre dot in the middle of the screen, and do your best to use your peripheral vision to follow the targets. This will likely be very challenging at first!

•If it starts out too fast, just do your best and do not fret. Soon the program will learn the perfect speed for you!

•Have fun! You are not expected to get everything right. The system works to challenge you, so you should expect to have a range of successes and failures.

TIPS for Using NeuroTrackerX

Analyzing your results:

•Following completion of all your training sessions, together we will go over your progress throughout the sessions

•On your dashboard (main screen), you will begin to see your scores as you complete sessions

•Your SCORE from each session gives you an idea of your "Speed Threshold". A Speed Threshold is the speed at which you can successfully track the targets about 50% of the time. A higher score means that you can track the targets at a faster rate. The goal of this program is to see how high you can get your score.

•Initial Baseline: This is the average score of your first three sessions

•Current Baseline: This is the average score of your most recent three sessions (This will only appear once you have done at least 4 sessions)

•% Improvement: This compares your current baseline to your initial baseline. Sometimes it will be positive (you scored higher), and sometimes it will be negative (you scored lower).

•Best Score: This is your highest session score

•Highest Trial Speed: This is your highest trial speed that you have successfully tracked the targets

TIPS for Using NeuroTrackerX

Creating a Training Schedule:
•For this program, we ask that you complete 10 phases over 5 weeks. Each phase consists of 3 sessions. Each session consists of 20 trials. This means you should be completing 2 phases per week for 5 weeks.

•We recommend doing your phases 2-3 days apart, and try to do them at fairly similar times, in the same environment. You choose the days and times for your training.

•We will be able to track your progress through the program period, if you fall off track we will check in with you and send you friendly reminders :-)

Good Example	Bad Example
•Jane schedules her weekly NeuroTracker training for Monday's and Thursdays •Jane tries to start her Phases between 10-11am each time •Jane takes quick 5 minute breaks between each session to rest •Jane always does her training in a quiet room with few distractions	•John does all his weekly phases back-to-back on the same day •John does his training at random times. Sometimes 7am, and sometimes 11pm •John takes very long, 1 hour breaks between sessions •John leaves the TV and music on, and also tries to cook dinner while doing his sessions

TIPS for Using NeuroTrackerX

Helpful Videos:
•To better understand the task, watch a demo of NeuroTrackerbefore you get started on your training.

https://www.youtube.com/watch?v=HAnvc_II0X0&t=46s

•Completing your first NeuroTrackerXSession

https://www.youtube.com/watch?v=LVGrehYXGQ0

•Introducing your user dashboard

https://www.youtube.com/watch?v=ZVLJVZUF3OM

Appendix F – qPCR Amplification and Melting Curves

Amplification and melting curve graphs with NTC wells labelled are provided for the four qPCR runs. One well from a control participant's T2 sample in the telomere assay showed late amplification and a melting curve resembling that of the NTC and was therefore excluded from analysis (Figures F5 and F6). For this participant at T2, estimated telomere length was calculated using the remaining valid sample well, rather than the average of two.

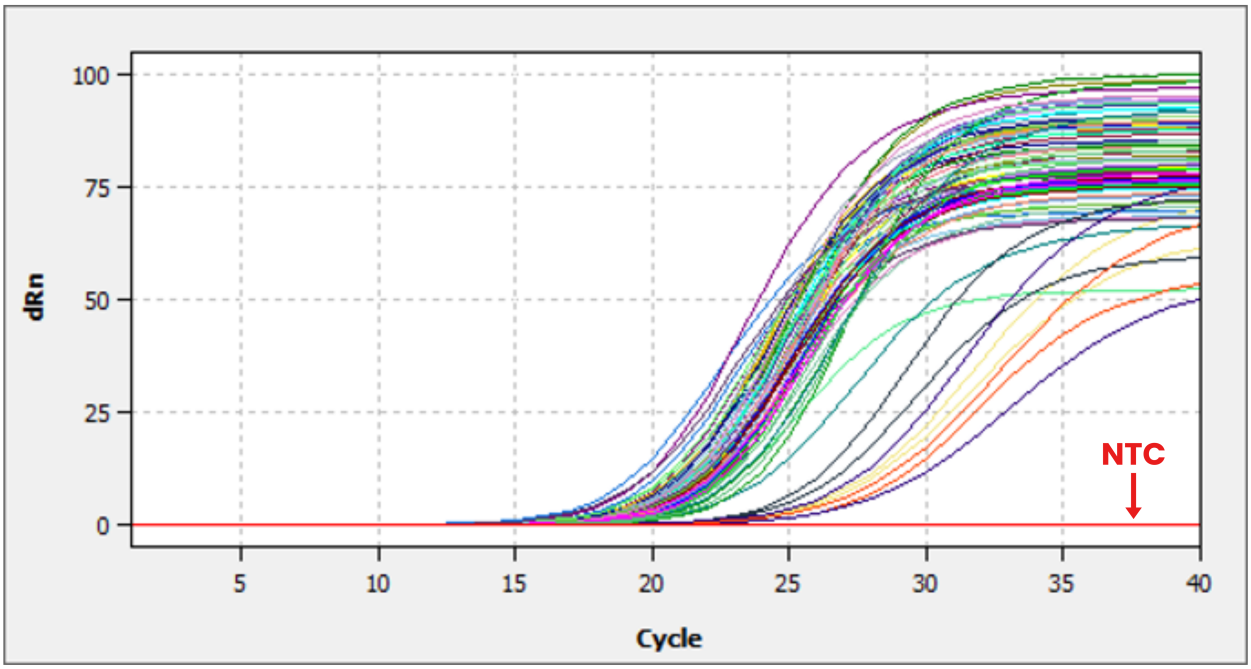


Figure F1. Amplification curve for Plate 1 of the telomere qPCR assay with the NTC labelled for reference.

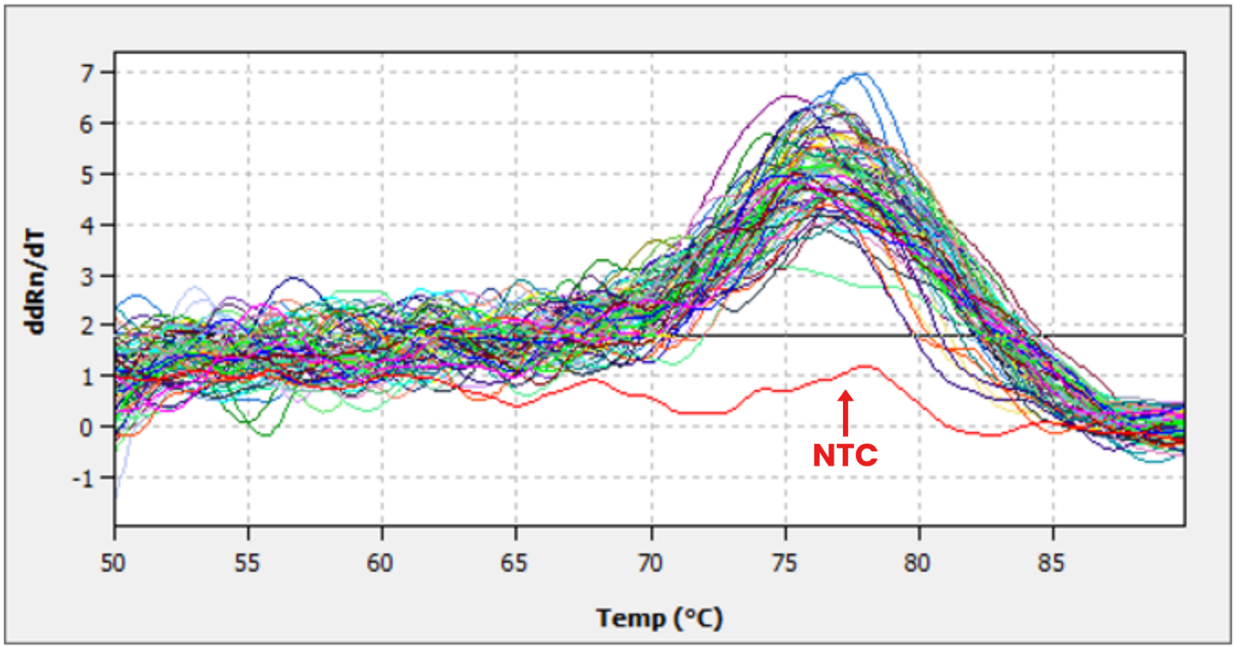


Figure F2. Melting curve for Plate 1 of the telomere qPCR assay with the NTC labelled for reference.

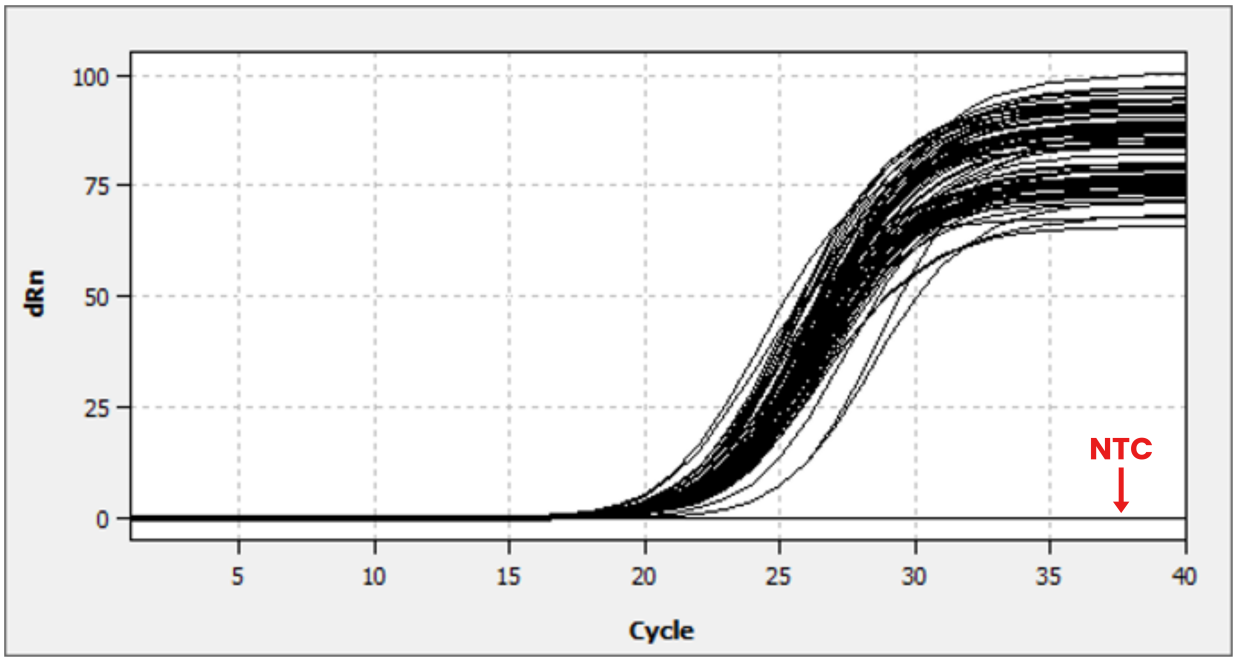


Figure F3. Amplification curve for Plate 1 of the 36B4 qPCR assay with the NTC labelled for reference.

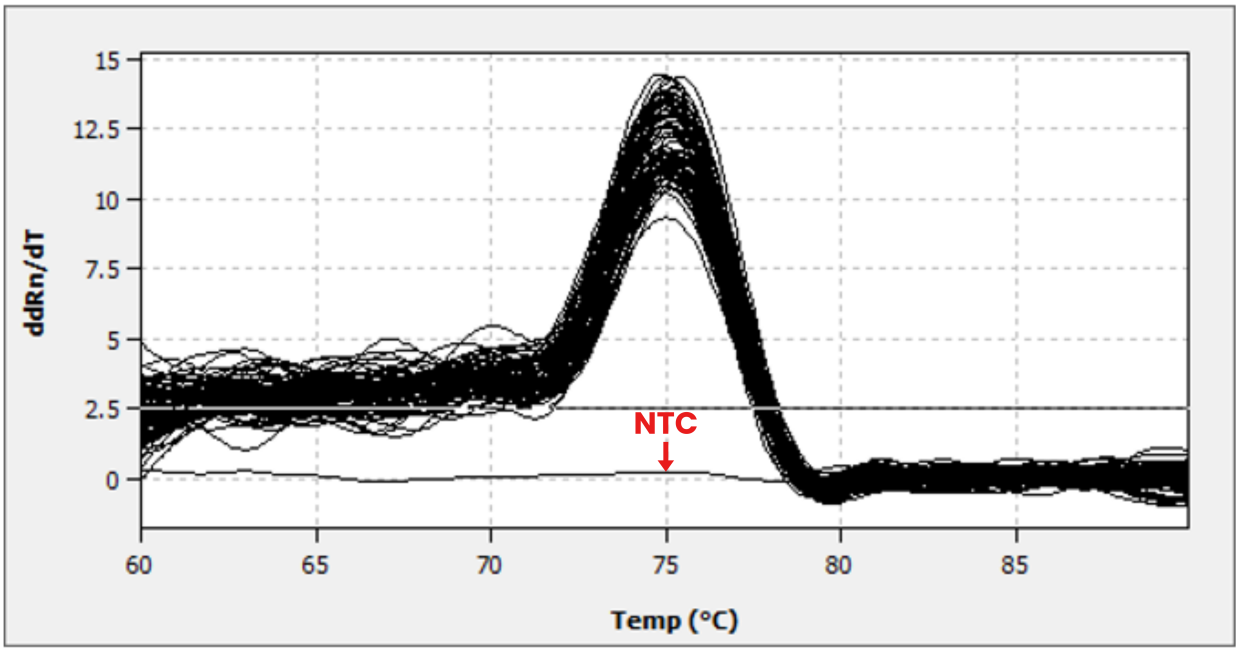


Figure F4. Melting curve for Plate 1 of the 36B4 qPCR assay with the NTC labelled for reference.

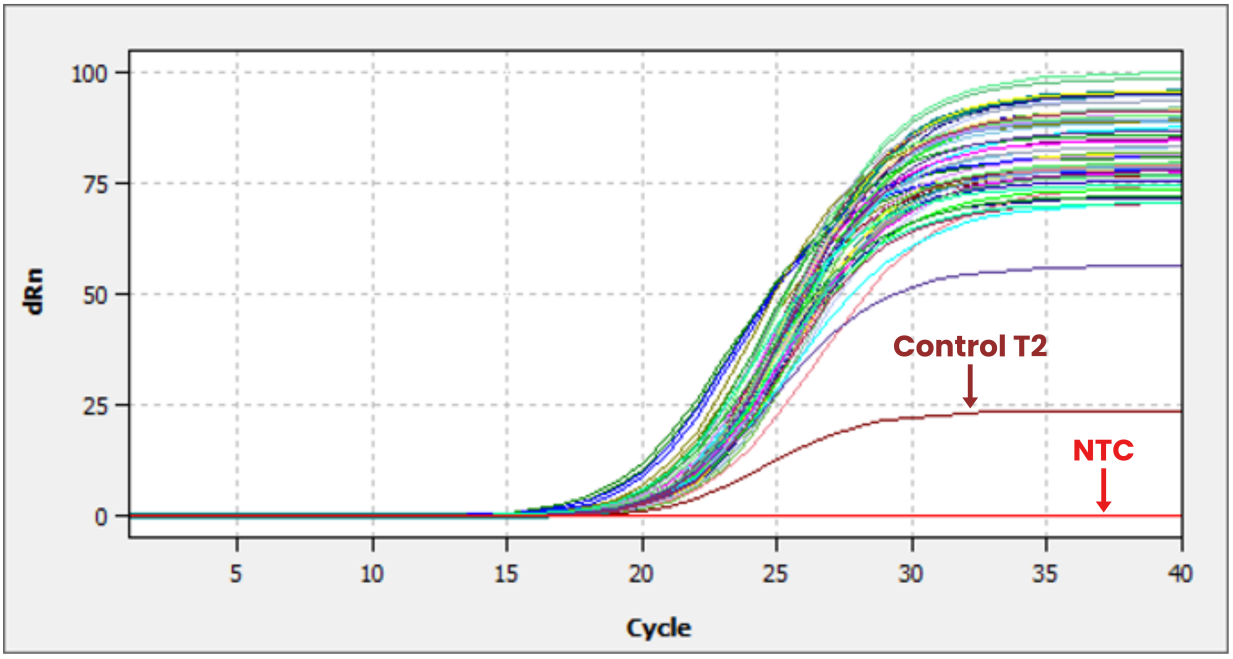


Figure F5. Amplification curve for Plate 2 of the telomere qPCR assay. The excluded control T2 sample and the NTC are labelled for reference.

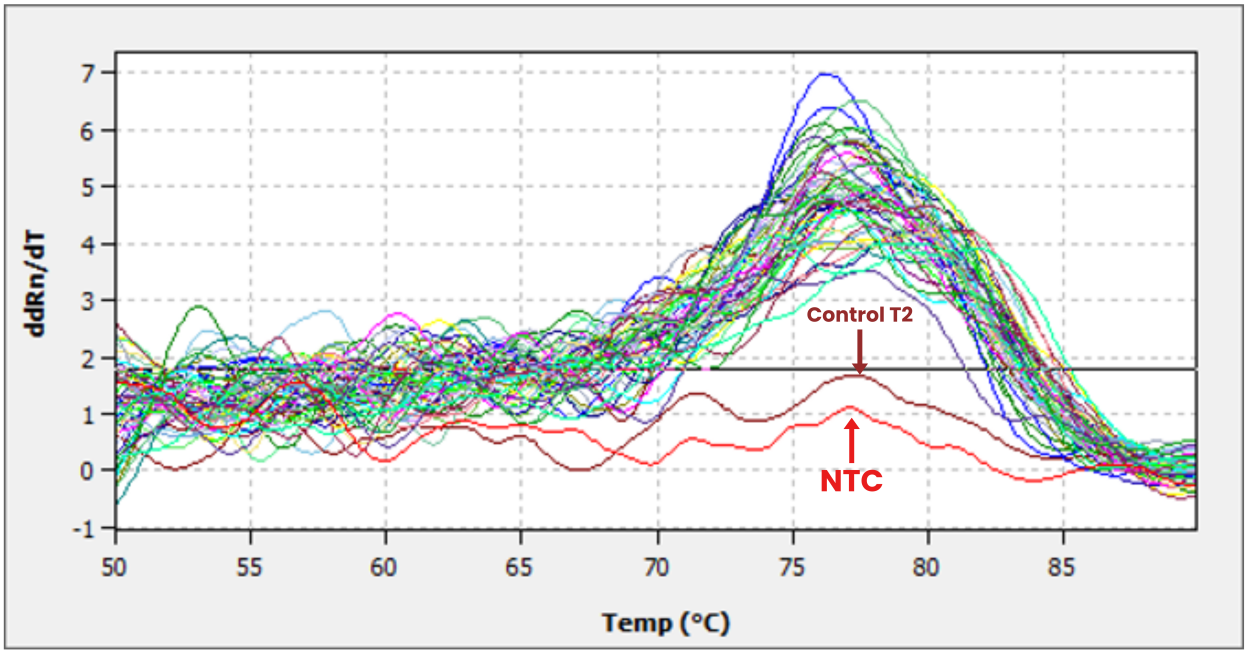


Figure F6. Melting curve for Plate 2 of the telomere qPCR assay. The excluded control T2 sample and the NTC are labelled for reference.

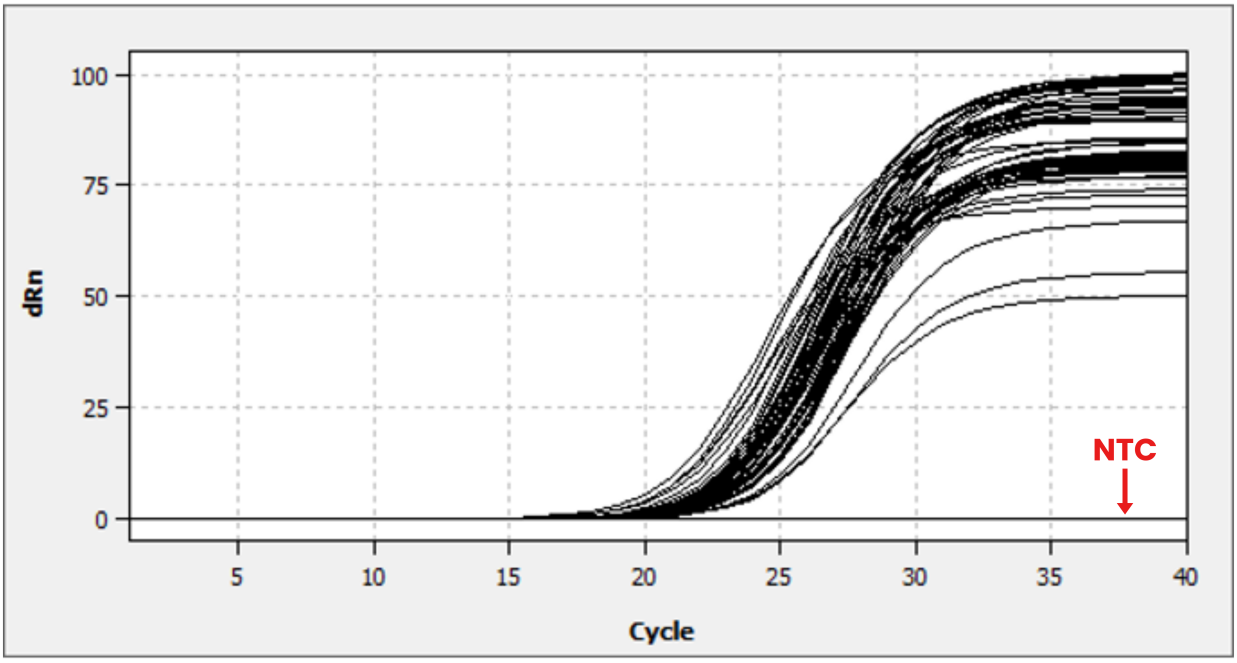


Figure F7. Amplification curve for Plate 2 of the 36B4 qPCR assay with the NTC labelled for reference.

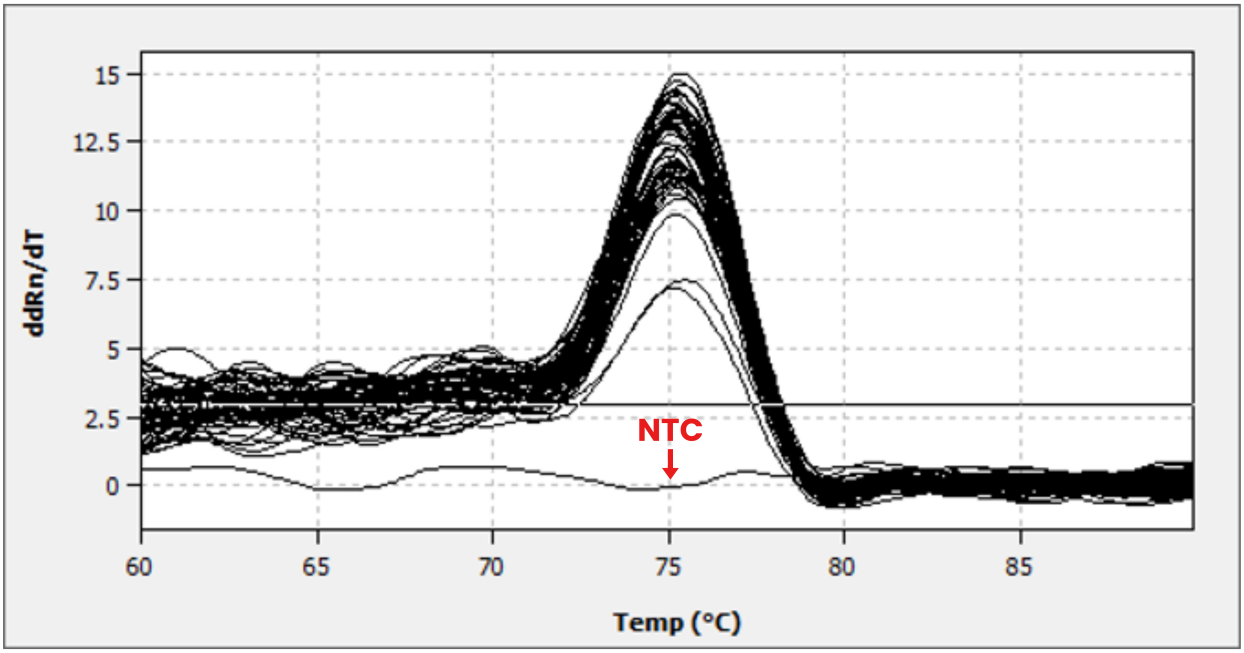


Figure F8. Melting curve for Plate 2 of the 36B4 qPCR assay with the NTC labelled for reference.