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The Effect of Spinal Cord Stimulation and Video Games Training on Body-machine Interface Control

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WASHINGTON UNIVERSITY IN ST. LOUIS

McKelvey School of Engineering
Department of Biomedical Engineering

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The Effect of Spinal Cord Stimulation and Video Games Training on Body-machine Interface Control

by
Jie Fei

A thesis presented to
the McKelvey School of Engineering
of Washington University in
partial fulfillment of the
requirements for the degree
of Master of Science

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Jie Fei

Washington University in St. Louis

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Dedicated to my favorite parents, Shunli Ji, and Youbin Fei,

my loving partner, Zhiqing Pu, a 23’ MPH candidate at WashU,

my fantastic advisor, Dr. Ismael Seáñez,

and mentors who have provided me with invaluable guidance and support.

ABSTRACT OF THE THESIS

The Effect of Spinal Cord Stimulation and Video Games Training on Body-machine Interface Control

by

Jie Fei

Master of Science in Biomedical Engineering

Washington University in St. Louis, 2023

Professor Ismael Seáñez, Chair

Damage to the spinal cord causes long-lasting loss of motor and sensory function, and currently, there is no 'cure' for paralysis. However, even people with severe spinal cord injuries (SCI) have some residual mobility. Studies have shown that transcutaneous electrical spinal cord stimulation (tSCS) combined with functional training targeting residual mobility can further improve the motor function of individuals with SCI. In this study, we present a technical framework that aims to enhance rehabilitation outcomes by targeting residual mobility through a motor training-based approach. Our technical framework centers around a non-invasive body-machine interface (BoMI) that relies on the use of several inertial measurement units (IMUs) to capture the residual mobility of the participant's body and translate it into the ability to control a two-dimensional (2D) cursor on a computer screen. Participants can manipulate this 2D computer cursor by using their residual body movements to complete a series of self-developed tasks for functional motor training, such as center-out reaching tasks and 2D video games. Additionally, tSCS electrodes were placed at designated spinal segments during the motor training and attempted to produce neuromodulatory effects that facilitate leg and trunk movement and performance of BoMI control.

Subsequently, our work aimed to investigate the effect of using non-invasive tSCS and immersive 2D video games on participants' performance of motor control and learning rate through the above training framework. Participants' performance was recorded and quantified using four assessment metrics based on different center-out reaching tasks. Therefore, a multi-day experiment recruiting both unimpaired control participants and people with SCI was conducted to investigate the effect of training with tSCS and 2D video games on the performance of center-out reaching tasks.

Our findings revealed that the BoMI performance of the unimpaired control group improved after training with center-out reaching tasks, and the final performance and learning rate were unrelated to the application of tSCS. However, the effect of tSCS on individuals with SCI varied from person to person. Specifically, we found that tSCS had a clear facilitation effect on the BoMI performance, resulting in a better final performance and a significant learning rate for SCI participant BMS002 but not for SCI participant BMS001. Moreover, our results showed that training with reaching tasks and video games resulted in similar final BoMI performance within the unimpaired control group, but training with reaching tasks generated a better learning rate. Regarding participants with SCI, training with video games led to a significant learning rate in BMS001 and a non-significant learning rate in BMS002. In addition, we observed that there was no significant difference between the final performance after training with reaching task and video games in both unimpaired control and SCI participants.

In conclusion, our results suggest that functional training with tSCS could be an effective approach to enhancing motor function and learning rate for individuals with SCI. Also, video games could be considered as a promising training strategy, equivalent to traditional center-out reaching tasks.

Chapter 1: Introduction

1.1 Spinal Cord Injury

1.1.1 Introduction

Spinal cord injury (SCI) is characterized by damage to the spinal cord, resulting in the permanent loss of motor function, sensory function, or both(1). The spinal cord serves as a bundle of nerve tissue, which extends from the brain and runs down through the vertebral column. It plays a vital role in transmitting signals between the brain and the rest of the body(2,3). Any damage to the spinal cord can lead to temporary or permanent changes in strength, sensation, and other functions below the site of injury(1). The severity of SCI is determined by the location and extent of damage, which is classified as either complete or incomplete(4). Typically, the higher the injury level is, the greater the loss of motor control and sensation below the level of the injury. Complete SCI is characterized by a total loss of sensation and voluntary movement below the site of injury, while incomplete means there is some degree of sensory or motor function below the level of the injury. The development of SCI is commonly associated with a range of complications, including but not limited to weakness, altered reflexes, respiratory disorders, spasms, bowel and bladder dysfunction, cortical atrophy, and autonomic dysreflexia(1). These complications can manifest differently depending on the location and extent of the injury(1,5).

1.1.2 Contributing Factors to the Significant SCI Population

SCI can be categorized into two types based on their etiology: traumatic and non-traumatic(1,6). Traumatic SCI (tSCI) is the result of an external physical impact, including motor vehicle accidents (37.6%), falls (31.5%), and acts of violence (15.4%, such as gun wounds), are the primary causes of tSCI in the country(7). Other contributing factors include sports injuries, recreational accidents, as well as medical and surgical complications. On the other hand, non-traumatic SCI occurs when a disease process, such as a tumor, infection, or degenerative disc disease, causes the primary injury, either acutely or chronically(6).

Most spinal cord injuries are trauma-based, and they are debilitating conditions that affect thousands of individuals in the US every year. According to recent estimates, the population of individuals living with tSCI in the country in 2022 was around 302,000 people(8). The latest statistics show that the annual incidence of tSCI in the United States is approximately 54 cases per one million people, which equates to roughly 18,000 new tSCI cases every year(9). Since 2015, there has been an increase in the average age of patients diagnosed with tSCI, rising from 29 years to 43 years. Also, there is a gender disparity in the incidence of new cases of tSCI, with males accounting for about 79% of all reported new cases(7) in the United States.

1.1.3 Serious Harm Caused by Motor Impairments Resulting from SCI

SCI can have profound and life-altering consequences, with the development of motor impairments being one of the most common and impactful complications. Motor impairments resulting from SCI can significantly impair patients' mobility, independence, and ability to perform daily activities(1,10). These disorders can manifest in various forms, such as paralysis, spasticity, tremors, and dystonia(11–13). The degree of mobility loss experienced by people with SCI is also dependent on the location and extent of the injury(14). Patients may experience prolonged bedridden status or require the use of various assistive devices, such as wheelchairs, crutches, or braces, to aid in their mobility. The specific mobility challenges faced by SCI patients can vary significantly, with some individuals able to walk with assistance, while others are entirely dependent on mobility aids.

tSCI can have a lasting effect on patients' physical, mental, financial, and social well-being(15). After receiving initial emergency care, patients with tSCI require a range of interventions, including drug therapies, surgery, physical therapy, other treatment, and rehabilitation strategies, to promote functional recovery and optimize outcomes. The complex and prolonged nature of tSCI treatment can pose a significant burden to patients' physical and mental health and the loss of income due to the inability to work, coupled with the high cost of medical care and assistive devices, can further exacerbate the financial burden on the whole family(16,17). Research has demonstrated that the healthcare costs and living expenses associated with SCI can be staggering, particularly for those with the most severe injuries. Individuals with high tetraplegia (C1-C4), for instance, can incur first-year costs of up to \$121,806. Furthermore, those who sustain SCI at the age of 25 can expect lifetime costs of up to \$5,404,774(7). In conclusion, tSCI is a significant public health concern that requires ongoing attention in research, treatments, and clinical outcomes. The development of innovative treatments and rehabilitation approaches is critical to address the multifaceted impacts of tSCI on individuals' lives, including the impairments that can significantly affect their mobility, independence, and quality of life(18).

1.1.4 Neural Plasticity and Residual Mobility are Key Factors for SCI Rehabilitation

A complete cure for SCI is not currently available. However, some degree of residual mobility may be retained even in cases of complete SCI(19–21). For instance, patients with cervical SCI may retain shoulder, elbow, or wrist movements, while those with thoracic or lumbar SCI may retain partial leg movement or control over the bowel and bladder. Rehabilitation training involves repetitive movements that are designed to utilize and enhance residual mobility(22). Additionally, some assistive technologies are capable of converting these residual motor capabilities into analog signals that can be used to control assistive equipment to facilitate motor training(23). For instance, the utilization of residual mobility through early and intensive physical therapy is known to result in remarkable improvements in motor function following SCI. Besides, the lost mobility of people with SCI can be restored to some extent through early rehabilitation interventions that target the remaining neural pathways in the spinal cord and the brain(10). These interventions, such as physical therapy, occupational therapy, and assistive technologies, aim to promote the growth of new connections and strengthen existing ones. This process is called neural plasticity, which refers to the brain and nervous system's ability to adapt and reorganize in response to injury or new experiences(23,24).

Specifically, previous studies have suggested that the restoration of post-exercise motor function in individuals with SCI is associated with the connectivity and activation of the motor cortex(25–28). This highlights the potential role of the brain in facilitating recovery of motor function following SCI and emphasizes the importance of interventions that target neural plasticity in the rehabilitation process(29–32). Therefore, early, and intensive interventions are essential for maximizing the potential for restoration of lost mobility. Through targeted rehabilitation interventions, individuals with SCI can improve their residual mobility, the degree of movement that is retained after injury. This can lead to functional improvements, such as increased independence in daily activities, improved quality of life, and decreased healthcare costs.

1.2 Transcutaneous Spinal Cord Stimulation

1.2.1 Introduction

Transcutaneous spinal cord stimulation (tSCS) is a neuromodulation technique that involves the non-invasive application of electrical current to the skin surface overlying the spinal cord(33). The setup of tSCS involves the placement of surface electrodes over the skin at specific locations on the back and abdomen(34). The exact electrode placement and stimulation parameters may vary depending on the individual's specific needs and characteristics. The surface electrodes are connected to a portable stimulator, which generates the electrical currents used to stimulate the spinal cord. The stimulator may be programmed to deliver different stimulation frequencies, pulse widths, and amplitudes to optimize the therapeutic effects of the stimulation. During tSCS, the electrical currents are delivered to the spinal cord through the surface electrodes, which stimulate the proprioceptive fibers within the dorsal roots and modulate the activity of the spinal cord circuitry(35,36). The stimulation parameters are adjusted to modulate spinal excitability and promote neural plasticity, which can lead to improvements in motor function, sensory function, and pain management.

1.2.2 The Potential Mechanisms of tSCS to Improve Motor Function

tSCS has been shown to have a positive and evident effect on motor function in individuals with SCI(11,29,34,37). However, the exact mechanisms underlying this therapeutic effect are still being investigated(38,39). One proposed mechanism is that tSCS modulated the excitability of spinal neurons, leading to changes in their firing patterns and ultimately, improvements in motor function(40,41). This modulation of spinal excitability is thought to be due to changes in the balance between inhibitory and excitatory neural signals in the spinal cord. The tSCS enhances the functional state of spared spinal sensory-motor networks below the lesion. The activation of these spared networks can lead to residual descending pathways transmitting activity, which enables and amplifies voluntary motor control(42). This process is thought to involve the modulation of spinal excitability, which can enhance the responsiveness of these sensory-motor networks to sensory input and descending motor commands. By enhancing this responsiveness, tSCS can improve the ability of these networks to generate motor outputs and facilitate voluntary motor control.

Another proposed mechanism is that tSCS activates neural pathways in the spinal cord, leading to the release of neurotransmitters that can enhance motor function in an animal model(43). Specifically, tSCS has been shown to activate the release of serotonin, a neurotransmitter that has been linked to improvements in motor function. Serotonin has been shown to modulate the activity of motor neurons in the spinal cord, enhancing their excitability and promoting the generation of motor output. Additionally, tSCS has been shown to promote neural plasticity by promoting the growth of new synapses and enhancing the strength of existing synapses in the spinal cord(44). This can lead to the formation of new neural connections and circuits, which may facilitate the recovery of motor function. The promotion of neural plasticity is thought to be a key mechanism underlying the long-term benefits of tSCS, as it allows for sustained improvements in motor function even after the stimulation has been discontinued(30,45).

1.2.3 The Advantage and Disadvantages of tSCS

The tSCS is a promising technique for improving motor function in individuals with SCI. With some advantages, tSCS has been extensively researched and gradually popularized in clinical practice(46). At the same time, we also need to consider the disadvantages for improvement and compensation in future research and development. One significant advantage of tSCS is its non-invasiveness, which makes it a more attractive alternative to invasive spinal cord stimulation techniques. Unlike other forms of spinal cord stimulation, tSCS does not require surgery or implantation of devices, which reduces the risk of complications associated with invasive interventions. Additionally, the non-invasive nature of tSCS allows for more flexibility in the stimulation parameters and placement of electrodes, which may be adjusted more easily to optimize therapeutic effects and minimize adverse effects. In addition, tSCS is a relatively cost-effective neuromodulatory technique compared to other forms of neuromodulation such as epidural spinal cord stimulation. This is primarily due to the non-invasive nature of tSCS, which eliminates the need for expensive surgical procedures and implantation of devices. Furthermore, the simplicity of the tSCS setup and the ability to use portable stimulators may further reduce the cost and increase the accessibility of this technique. Finally, tSCS is relatively easy to use and can be administered by trained healthcare professionals or even by the patients themselves.

However, while there is some evidence to support the effectiveness of tSCS, more research is needed to fully understand its mechanisms of action and therapeutic potential. A disadvantage of tSCS is that its effects can vary from person to person, and not all individuals may benefit from this neuromodulation technique(33,46). The response to tSCS may depend on various factors, such as the severity and type of spinal cord injuries, the timing of the intervention, and individual differences in neural plasticity and responsiveness to electrical stimulation(47). Another potential disadvantage of tSCS is the risk of adverse effects, although these are generally considered rare and relatively minor. Skin irritation or discomfort at the site of stimulation can occur, particularly if the electrodes are not placed properly or if the stimulation intensity is too high(48). In very rare cases for people with SCI, tSCS may also cause autonomic dysreflexia(49), which is a potentially life-threatening condition characterized by an exaggerated sympathetic nervous response to a noxious stimulus below the level of the spinal cord injury. Autonomic dysreflexia can cause symptoms such as high blood pressure, headache, sweating, and bradycardia, and requires immediate medical attention to prevent serious complications(50). Therefore, while tSCS is generally considered safe, the potential risk and adverse effects should be carefully evaluated and monitored in real-time.

Despite promising results, the effectiveness of tSCS for motor function recovery is still being explored(30), and further research is needed to better understand its mechanisms of action and optimal treatment parameters. Nevertheless, tSCS holds great potential as a therapeutic option for individuals with SCI who seek to improve their motor function and overall quality of life.

1.3 The Available Assistive Technologies and Rehabilitation Tools for SCI Population

A wide range of assistive devices has been developed and commercialized to improve the independence, mobility, and quality of life of individuals with SCI. These devices are designed to compensate for or enhance the motor ability of individuals with SCI, considering their injury conditions, residual mobility, and usage scenarios. Here we classify the existing assistive devices into two categories according to the mechanism of action. The first category includes technologies that provide a direct effect on the patient, and the second category is the technology that converts the patient's residual mobility to control other assistive devices.

The first type of assistive technologies for individuals with SCI includes wheelchairs, assistive robots, orthotics, etc. Wheelchairs are essential for individuals with SCI to maintain mobility and independence. Manual and power wheelchairs are available and may be customized to meet the specific needs of the individual. Assistive robots can take on a variety of roles, from helping with daily activities such as getting dressed and preparing meals, to providing mobility assistance through exoskeletons or robotic wheelchairs(51). Telepresence robots can also be used to enable individuals with SCI to participate in social activities and work remotely. Orthotic devices are assistive technologies that are designed to help individuals with SCI maintain joint stability, prevent contractures, and improve mobility(52). Overall, these types of assistive devices are designed to expand the mobility of individuals actively and directly with SCI by compensating for or enhancing their motor abilities, thereby removing certain restrictions on movement. These devices can improve the independence, mobility, and quality of life of individuals with SCI.

In cases of severe SCI, such as complete SCI, more sophisticated assistive devices are often required to compensate for lost function. The second type of assistive device utilizes advanced technology to convert some of the still-existing physiological functions of the patient into the ability to control other devices, thereby enhancing the patient’s ability to perform different tasks(53). For example, tongue sensors work by detecting changes in tongue position and movements, which are then translated into commands for the external device(54). In addition to tongue sensors, other assistive techniques such as eye-tracking devices(55), voice recognition systems, and motion sensors (IMUs) (23,56,57) have been developed for individuals with SCI who have limited or no motor function. These devices utilize different characteristics of body motion and voice to control external tools and devices, enabling individuals with SCI to operate different devices and improve their daily living. Eye-tracking devices use the movement of the eyes to control external devices, such as computers or wheelchairs, through a wireless connection. Voice recognition systems allow individuals to control external devices using their voice, without the need for physical movement. These devices can be customized to the individual user's specific needs and abilities, allowing them to perform a wide range of tasks.

Furthermore, electrophysiological signals such as EEG (electroencephalography) (58,59) or EMG (electromyography) (60,61) can be recorded by invasive or non-invasive methods and be decoded using advanced algorithms and machine learning techniques to extract meaningful information about the user’s intended movement, which can then be used to control the external device, such as computers, wheelchairs, and robotic arms. These technologies can greatly enhance the ability of individuals with SCI to use different assistive devices, helping them to overcome barriers to mobility, communication, and other daily activities(62).

As technology continues to evolve, we can expect to see more and more advanced and effective assistive devices developed for individuals with SCI. These devices should be designed to meet the specific needs and challenges of individuals with SCI and should be stable, precise, easy to use, and cost-effective to be widely accessible.

1.4 Video Games as a Promising Rehabilitation Strategy for SCI

Video games have emerged as a promising functional training strategy for individuals with SCI, providing a fun and engaging approach to improving motor function and cognitive abilities(63–65). Traditionally, rehabilitation for SCI has focused on physical therapy, occupational therapy, and other traditional therapies. However, the use of video games as a rehabilitation tool has gained popularity in recent years(66). Video games can be designed to target specific motor skills and cognitive functions and can be customized to meet the specific needs and challenges of individuals with SCI to promote physical activity, improve range of motion, and rebuild muscle strength(67,68). For example, video games can be designed to improve upper and lower limb function, balance, coordination, and other motor skills that may be impaired due to SCI. Another advantage of video games is that they provide immediate feedback and can be easily adjusted to challenge the individual at an appropriate level(69). This can help to maintain motivation and engagement, which is important for successful rehabilitation outcomes.

While training with video games has several potential advantages for individuals with SCI, there are also some disadvantages to consider. One potential disadvantage is that not all individuals may be able to participate in video game training. For example, individuals with severe cognitive deficits or visual impairments may not be able to effectively engage with video games. Another potential disadvantage is that video game training may not translate directly to real-world functional improvements. While video games can target specific motor and cognitive skills, the transfer of these skills to real-world activities may be limited(66). Therefore, it is important to supplement video game training with other rehabilitation strategies to ensure that individuals with SCI can effectively apply their skills in daily life.

Overall, video games have shown promising results as a rehabilitation strategy for individuals with SCI, and they offer several advantages over traditional rehabilitation methods, as technology continues to evolve, video games will become more sophisticated and customized, allowing for more targeted and effective rehabilitation interventions(70,71). In addition to promoting physical activity, range of motion, and muscle strength, video games also offer a unique opportunity to engage individuals with SCI in fun and motivating activities. This can be particularly important for individuals who may be struggling with the psychological and emotional impacts of their injury. Further research is needed to fully understand the effectiveness of video games as a rehabilitation tool, as well as the underlying neural mechanisms that drive the improvements seen with video game training.

In conclusion, this thesis presents a novel body-machine interface (BoMI) along with tSCS and immersive video games as a new motor training strategy to enhance rehabilitation outcomes such as motor function and learning rate for individuals with SCI. A multi-day experiment was designed for both the unimpaired control group and individuals with SCI to investigate the effects of tSCS and video game training on BoMI control performance. Through this thesis, we aim to deepen our understanding of the impact of different training strategies on the motor function of the population with SCI and develop and modify more effective rehabilitation tools based on these conclusions to ultimately improve their quality of daily life.

Chapter 2: Overall Methods

2.1 Participants Recruitment

In recruiting both unimpaired control participants and individuals with SCI for this multi-day study, adherence to the inclusion and exclusion criteria as stipulated in the consent form was ensured. This study was subjected to review and approval by the Institutional Review Board of Washington University in St. Louis, in compliance with ethical guidelines. Prior to participating, all participants were required to fully comprehend the experimental protocols and provide their consent. A total of 18 individuals were recruited as the unimpaired control group for this study, out of which two withdrew early from the study due to discomfort from the spinal cord stimulation. Additionally, two other unimpaired control participants were excluded based on the identification of outliers through the interquartile range method based on four different performance metrics during the reaching training session. Furthermore, two additional participants with SCI were recruited and participated in the study (Figure 2.1).

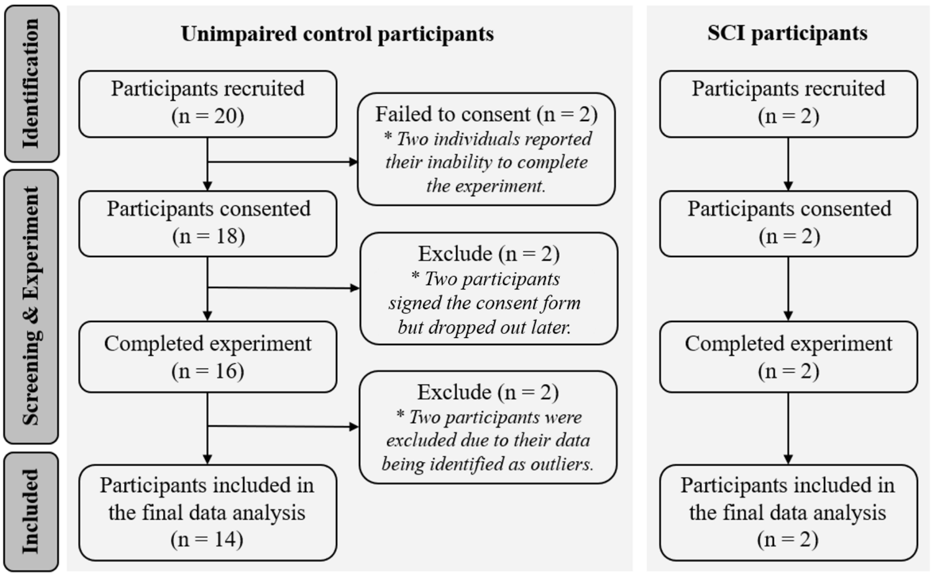


Figure 2.1 Flow chart of participants' identification and inclusion.

Consequently, data processing and analysis in this study were carried out on a final sample of 14 control participants and 2 participants with SCI. The results of the analysis are presented in the subsequent chapters for various research questions. The demographics of 14 unimpaired control participants are presented in Table 2.1, and the demographic characteristics of 2 participants with SCI are presented in Table 2.2.

Table 2.1 The demographics of unimpaired control participants.

Variable	Unimpaired control participants (N=14)
Age *(years)*	
Mean *(SD)*	24.79 (2.19)
Gender	
Male *(n, %)*	7 (50)
Female *(n, %)*	7 (50)
Height *(m)*	
Mean *(SD)*	1.71 (0.07)
Weight *(kg)*	
Mean *(SD)*	67.26 (16.09)
Race	
White *(n, %)*	4 (28.57)
Asian *(n, %)*	10 (71.43)
Ethnicity	
Hispanic or Latino or Spanish Origin *(n, %)*	0 (0)
Not Hispanic or Latino or Spanish Origin *(n, %)*	14 (100)

Table 2.2 Characteristics of participants with SCI.

Subject ID	Age	Gender	Level of Injury	Complete or Incomplete	AIS (self-reported)	Time after Injury
BMS001	38	Male	T4-T6	Incomplete	C	14 years
BMS002	24	Male	C6-C7	Incomplete	C	5 years

2.2 Overview of the Experimental Setup

Generally, this study utilized transcutaneous spinal cord stimulation (tSCS) as a non-invasive neuromodulation approach for rehabilitation and motor training. The participants’ movements were captured using several wireless motion sensors, i.e., inertial measurement units (IMUs), to create a map between body movements and a 2D cursor on the screen based on a novel and non-invasive body-machine interface (BoMI)(23,56,57). This allowed participants to engage in a range of tasks, including center-out reaching and various 2D video games utilizing their leg and trunk movements. Additionally, real-time movement kinematics were recorded using a 3D motion capture system, while muscle activity data were captured using a wireless electromyography system (EMG), during the performance of the center-out reaching task or different video games. Participants sat at a 0° in a stable position on a chair (Figure 2.2). One stimulation electrode was affixed to the participant's back, and two electrodes were symmetrically placed on the abdomen as return electrodes. Four IMU sensors were placed bilaterally on the body to capture motion data, and 12 wireless EMG sensors were attached to designated muscles to record muscle activity during movement. The kinematics of the participant's movements were measured using the video-based motion capture system.

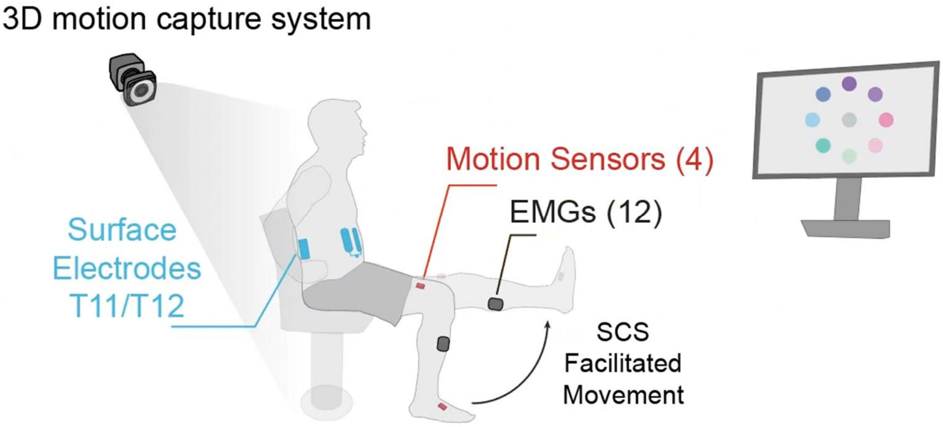


Figure 2.2 Experimental setup of hardware.

2.3 Transcutaneous Spinal Cord Stimulation

2.3.1 Placement of Stimulation Electrodes

Figure 2.3 illustrates the placement of stimulation electrodes. The tSCS was applied using a 5 x 9 cm rectangular PALS neurostimulation electrode (Axelgaard Manufacturing Co., Ltd., USA) as a stimulation electrode, which was positioned centrally over the interspinous ligament of the targeted vertebral segment (T11/T12). Manual palpation was employed using anatomical landmarks to locate the vertebral segments. Firstly, the iliac crest of the pelvis was identified, and the center of the connection on the left and right sides was marked with a sterile regular tip surgical utility marker (Medline Industries Co., Ltd., USA) as the L4 spinous process. Next, the spinous processes are counted upwards from L4, and the interspinous ligaments were identified from L3/L4 to T11/T12. Photos of the target vertebral segment obtained through manual palpation were taken and archived for future reference on the subsequent experiment days. Two interconnected 7.5 x 10 cm rectangular PALS neurostimulation electrodes (Axelgaard Manufacturing Co., Ltd., USA) were positioned bilaterally on the abdomen, extending from the navel, and were used as return electrodes. Prior to the placement of all electrodes, cotton swabs (Q-tips®) were immersed in abrasive cream (NuPrep®, Weaver and Co. USA) and applied to the target area in a swirling motion to eliminate impurities from the skin surface. Subsequently, alcohol prep pads (Medline Industries Co., Ltd., USA) were used to clean the target area again. Furthermore, conductive spray (Signa® Spray, Parker Laboratories, Inc., USA) was applied to improve the conductivity between the electrode and the skin. Once all the electrodes were positioned, they were secured using transparent film dressing (Tegaderm^{TM}, 3M Co., Ltd., USA). The placement of stimulation electrodes was identical for both unimpaired participants and those with SCI.

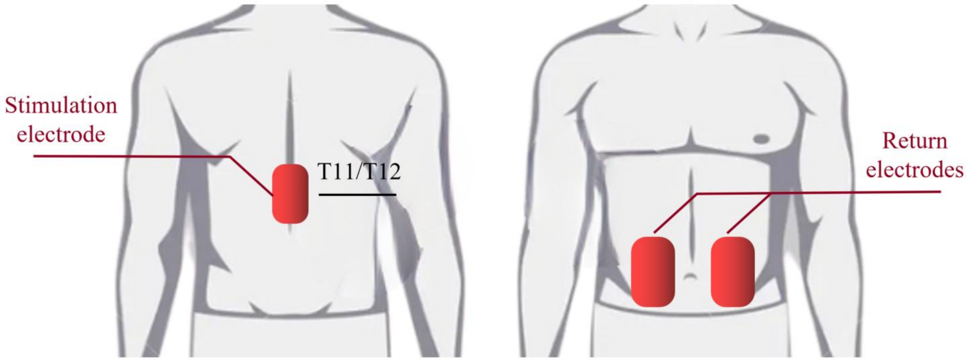


Figure 2.3 The placement of stimulation electrodes for all participants.

2.3.2 Placement of Wireless Electromyography Sensors

Muscle activity during cursor control movement was recorded using a 16-channel wireless EMG system (Trigno® Avanti, Delsys Inc., USA) with a sampling frequency of 2,000 Hz. Twelve lower limb muscles, including rectus femoris, vastus lateralis, semitendinosus, tibialis anterior, medial gastrocnemius, and soleus, were monitored bilaterally according to SENIAM EMG sensor placement guidelines. If necessary, the skin over the target muscles was shaved. Prior to the placement of all EMG sensors, cotton swabs (Q-tips®) were immersed in abrasive cream (NuPrep®, Weaver and Co. USA) and applied to the target muscle area in a swirling motion to eliminate impurities from the skin surface. Subsequently, alcohol prep pads (Medline Industries Co., Ltd., USA) were also used to clean the target muscle area again. To align stimulation pulses offline, an additional wireless sensor (Trigno® Analog Input Adapter, Delsys Inc., USA) was connected via a BNC cable to the biphasic stimulator's sync output. Stimulation pulse amplitude and triggering were controlled using a data acquisition board (NI USB 6009, National Instruments, USA). The EMG signals were displayed on a Python V3.10-based interface developed by our lab members, and the EMG data were filtered using a 2nd order Butterworth band-pass filter between 10-1,000 Hz.

2.3.3 Paired Pulse tSCS and Recruitment Curves

In this study, the paired pulse tSCS and recruitment curve measurements were used to evaluate the efficacy of tSCS in inducing muscle responses in the lower limb and to assess the general accuracy of stimulation electrode placement(72). Concurrently, the position of the stimulation electrodes was manually adjusted based on the feedback from the lower limb to attain optimal muscle responses. The paired pulse tSCS was administered using an isolated constant current stimulator (DS8R, Digitimer Ltd., UK) with a pair of biphasic pulses utilizing a train generator (DG2A, Digitimer Ltd., UK). These biphasic pulses were set to have a duration of 1 ms and an inter-stimulus interval of 33.3 ms. Pulses of increasing stimulation amplitude were administered to determine the motor threshold and saturation amplitude of each participant. The motor threshold was defined as the stimulus amplitude at which the muscle first responds with a peak-to-peak amplitude (> 20μV). Similarly, motor saturation was defined as the stimulus amplitude at which all muscles respond or the maximum stimulus amplitude that the participant can tolerate, whichever was lower. The recruitment curve recordings involved increasing the stimulation intensity from 5 mA below the motor threshold to the saturation amplitudes or the largest stimulation amplitudes that participants can tolerate, with 8 steps between amplitudes, resulting in a total of 10 stimulation amplitudes. Each amplitude was tested four times using double-pulse stimulation.

2.3.4 Continuous tSCS for Motor Training

In contrast to the tSCS used in the previous assessment (i.e., paired pulse tSCS and recruitment curves), the subsequent motor training sessions utilized continuous 30 Hz tSCS with a pulse duration of 1ms, a recovery phase ratio of 100%, and an interphase interval of 1μs, to attempt to facilitate the leg movements. The stimulus amplitude gradually increased from 0 mA until it reached the maximum amplitude that the participants could tolerate through titration. Furthermore, sham stimulation was utilized in the experiment to control potential placebo effects. The sham stimulation was generated by connecting the positive and negative poles of the stimulator to two stimulation electrodes on the abdomen and applying a constant 5mA continuous tSCS at 30 Hz.

2.4 3D Motion Capture System

In this study, a 3D markerless motion capture system (Miqus-Hybrid, Qualisys, Sweden) with 10 HD cameras was used to capture trunk and bilateral upper and lower limb kinematics at a sampling rate of 100 Hz. All recording operations were carried out in Qualisys Track Manager (QTM), which is the supporting software for the motion capture system from Qualisys. Before starting a new recording, a new project needs to be created with a specific folder path, the gait PAF module was used, and the corresponding setting file for markerless recording should be selected. Participant information, including the subject ID, name, height, and weight, must be entered before creating a full markerless recording session. Calibration is a prerequisite and critical step that must be performed before each recording to ensure the accuracy of the motion tracking data. During the calibration, a T-pole with reflective markers was swung in the desired capture volume to establish the relationship between the camera locations and the marker positions. Once the calibration was completed successfully, the 3D motion markerless recordings can be performed, with parameters such as capture period set accordingly.

2.5 Body-machine Interface

2.5.1 Technology Framework

The BoMI platform utilized in this study was an adaptation of the previous research work by our research group and was further optimized and updated to align with the current research objectives (23,56,57,73–75). The primary concept of BoMI involved controlling a two-dimensional cursor on a computer screen using leg movements. Figure 2.4 depicts the placement of the IMU sensors on the participant's body and the data streaming pipeline. To measure the lower limb movements, four IMUs (3-Space^{TM} Wireless 2.4GHz DSSS, Yost Lab, Inc., USA) were placed bilaterally on participants' thighs and knees. However, for participants with SCI, the IMU's placement would differ and two of four IMUs would be placed on the upper torso to increase the available residual mobility and ensure a smooth trial run. The input signals of roll and pitch angles were obtained from each IMU sensor in Euler formalism. However, the yaw angle was discarded because it was susceptible to interference from magnetic resources. To enable real-time data transmission from the IMU sensors to the computer workstation, an adapter (3-Space^{TM} Wireless Dongle, Yost Lab, Inc., USA) was connected to the computer workstation via a USB cable. A software application was developed using MATLAB R2020a (MathWorks, Inc., USA) and Simulink (MathWorks, Inc., USA) to enable the real-time collection of motion data from the four IMU sensors at a rate of 50 samples/second.

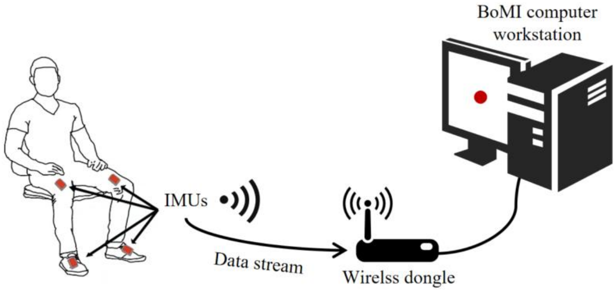


Figure 2.4 The placement of IMU sensors and the pipeline of IMU data streaming.

2.5.2 Calibration

Calibration is a critical step in the process of establishing a mapping between body motion and two-dimensional cursor control. It follows the successful pairing of the IMU sensors with the computer workstation. The figure presented below (Figure 2.5) illustrates the complete BoMI calibration workflow. Participants were instructed to maintain a comfortable and upright zero position and then perform a continuous dancing-like movement to explore their range of motion using lower limbs for 45 seconds. This process generated an eight-dimensional vector of motion data (each IMU sensor has two data streams), which was subsequently transformed into two-dimensional control signals using a principal component analysis (PCA) that selected the first two PCA components as the control of the cursor's X and Y coordinates. This transformation generated a map between the leg movements and cursor control. Participants were then asked to learn how to control the horizontal and vertical, veal the combined movements of the cursor through body movements, followed by 45° oblique movements, and finally, master the ability to reach the four sides and four corners of the screen with skillful control. It is important to note that unimpaired participants will perform the calibration process without tSCS, while participants with SCI used tSCS during the calibration.

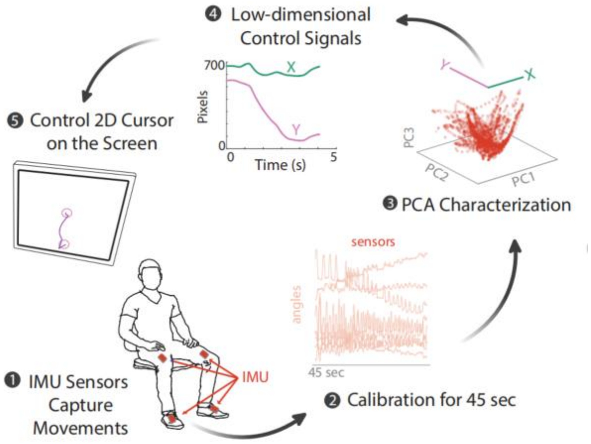


Figure 2.5 The workflow and mechanism of BoMI calibration.

2.5.3 Familiarization and Customization

Upon completion of the PCA, a preliminary map between leg movements and cursor control was established, allowing participants to control the 2D cursor using motions similar to those used in the previous calibration process. Next, a familiarization and customization step was implemented to further acclimate participants to the control of the 2D cursor. This process involves adjusting the control parameters (gains and angle of rotation) of the cursor based on the control performance after calibration and PCA. Customization can help participants gain a better control performance by modifying the control parameters in BoMI. For example, if the participant's lateral movement is insufficient to control the cursor to the far left or right of the screen, the larger gain value (>1) can be set to expand the control range of the cursor. If the participant's lateral movement caused the cursor to move obliquely, which is not sufficiently intuitive for control, the angle of rotation value can be modified to rotate the entire map to get a more vertical or horizontal control. After the final customization and familiarization, participants could complete specific tasks, including two types of center-out reaching tasks and five video games, by controlling the 2D cursor in real-time on the screen.

2.5.4 Center-out Reaching Tasks

In this study, two types of center-out reaching tasks were developed using MATLAB to evaluate cursor control performance, including center-out reaching task for training (i.e., reaching training and) and center-out reaching task for generalization (i.e., generalization). The first task was the center-out reaching task for training, where participants were required to control the movement of a red cursor from the center circle to one of eight peripheral target circles that were evenly and radially distributed around the center circle. Figure 2.6 illustrates the circle distribution and workflow of the center-out reaching task for training. Each target circle needed to be reached in three trials, resulting in a complete block consisting of 24 reaching trials. The order of the target circles appearing in each reaching trial was randomized. To begin a reaching trial, the participants needed to move the cursor to the center circle and maintain it within the circle for one second. After one second, the center circle would disappear, and one of the eight target circles would appear. Participants had two seconds to move the cursor from the center of the screen to the target circle and keep the cursor within the circle for one second, indicating a successful trial. Then, the target circle would disappear, and the center circle would reappear, prompting the participant to move the cursor into the center circle to start the next reaching trial.

Figure 2.6 The circle distribution and workflow of center-out reaching task for training.

The second task is center-out reaching tasks for generalization and had a slightly different circle distribution and workflow compared to the reaching training task. Figure 2.7 illustrates the circle distribution and workflow of the center-out reaching task for generalization. The number of target circles was smaller (three circles in total), with a smaller diameter and a shorter distance from the center circle. The overall deflection angle was also reduced to 45°. The center-out reaching task for generalization consisted of three target circles, with each target circle requiring four reaching trials, resulting in a total of 12 trials per block. The position of the target circles appearing in each reaching trial was also randomized. Among the four reaching trials of each target circle, two reaching trials had the same requirements and workflow as the center-out reaching task for training, and the cursor remained visible throughout the trial, referred to as "visible trials". The other two reaching trials for the same circle had the cursor disappear two seconds after the appearance of each target circle and reappear two seconds later, referred to as "invisible trials". During the invisible trials, participants had to rely on their understanding of the BoMI and task experience to reach the target circle with the cursor. The 2 visible trials and 2 invisible trials for each target circle appeared randomly.

Generalization blocks were performed to test the formation of an internal model between body and cursor movements. If participants were simply memorizing 8 movements to complete the reaching training task or relying on the visual feedback of the 2D computer cursor to complete the task, then the generalization trials would be highly challenging. If, instead, participants were forming a body-cursor internal model, they would be able to move the cursor in the correct direction, and with the correct amplitude, even in the absence of visual feedback, and when the target directions had been scaled and rotated.

Figure 2.7 The circle distribution and workflow of center-out reaching task for generalization.

In the experiment involving a participant with SCI (BMS002), it was observed that the participant had difficulty controlling the 2D cursor at a stable point. To facilitate his temporary performance, the duration required for the cursor to remain in the center circle and target circle was reduced from 1 second to 0.5 seconds manually. The purpose was to increase the participant's ability to complete each reaching trial and ensure the smooth running of the experiment.

2.5.5 2D Video Games

In this study, a set of five 2D video games was integrated with the BoMI to evaluate and train the participants' 2D cursor control performance in terms of reaction time, direction control ability, stability, and endurance. The games, including maze game, pong game, slicing game, link game, and snake game, were either developed or modified by Unity (2020.3.26f1, Unity Technologies, USA) and Visual Studio (2017, Microsoft Corporation, USA) with C# programming language. The games require the participants to control the cursor's movement on the screen by moving their bodies to trigger various in-game mechanisms. All materials used in the games, such as pictures, fonts, special effects, and music, were taken from open resources, and no commercial purpose was intended during the use process.

The following section provides an overview of the workflow and detailed rules for each of the five video games. (1) Maze game (Figure 2.8, top left): There are 12 levels in the maze game, where the participants are required to navigate a red cursor along a white path until it reaches a yellow star. If the cursor touches the gray danger zone, the level is considered a failure, and participants have to restart the game from the current level. The total time taken to complete all 12 levels was recorded and used as the performance metric for this game task.

(2) Pong game (Figure 2.8, top right): In this game, each play has 60 seconds, and the participants need to control the movement of a paddle to hit a blue ball as many times as possible within 60 seconds. The number of successful hits on the upper edge of the paddle in each play was recorded as the score.

(3) Slicing game (Figure 2.8, middle left): The participants need to move the cursor to cut the colored spheres that are randomly ejected upwards. In each play, the score was recorded as the total number of balls cut within 90 seconds, with one point awarded for each small sphere cut and a multiplier for consecutive hits.

(4) Link game (Figure 2.8, middle right): The participants need to connect two similar fruits in a 4 by 4 fruit matrix by clicking on each fruit. When two identical fruits are connected, they will simultaneously disappear from the screen. The game is won when all fruits on the screen are paired and removed. The time taken to connect all similar fruits is recorded as the final performance. The line connecting two identical fruits must be horizontal or vertical, cannot pass through any other fruit, and cannot bend more than twice. The experimenter will tap the left button of the mouse to simulate the participant's clicking action.

(5) Snake game (Figure 2.8, bottom): The participants need to move the cursor to the different arrow keys around the center of the screen to control the snake's movement direction. The goal is to eat as much food as possible to increase the score, with one food item recorded as one point. Each time the snake eats, its body length increases by a section. The final performance of this game was determined based on the score achieved before the end of the game. If the head of the snake touches any part of its body, the game is over. In addition, there are no boundaries in the game, and when the snake reaches the left boundary, it will appear on the right edge and continue to move to the left.

In the training session utilizing video games on gaming stim day, the participants were required to play these five video games in a specific and prescribed sequence and duration. For instance, the Pong game was designated for training and the duration was set at 7 minutes, with each play in the Pong game lasting one minute, the participants were instructed to play 5 to 6 rounds of Pong game within a 7-minute training period continuously, with short rest periods permitted.

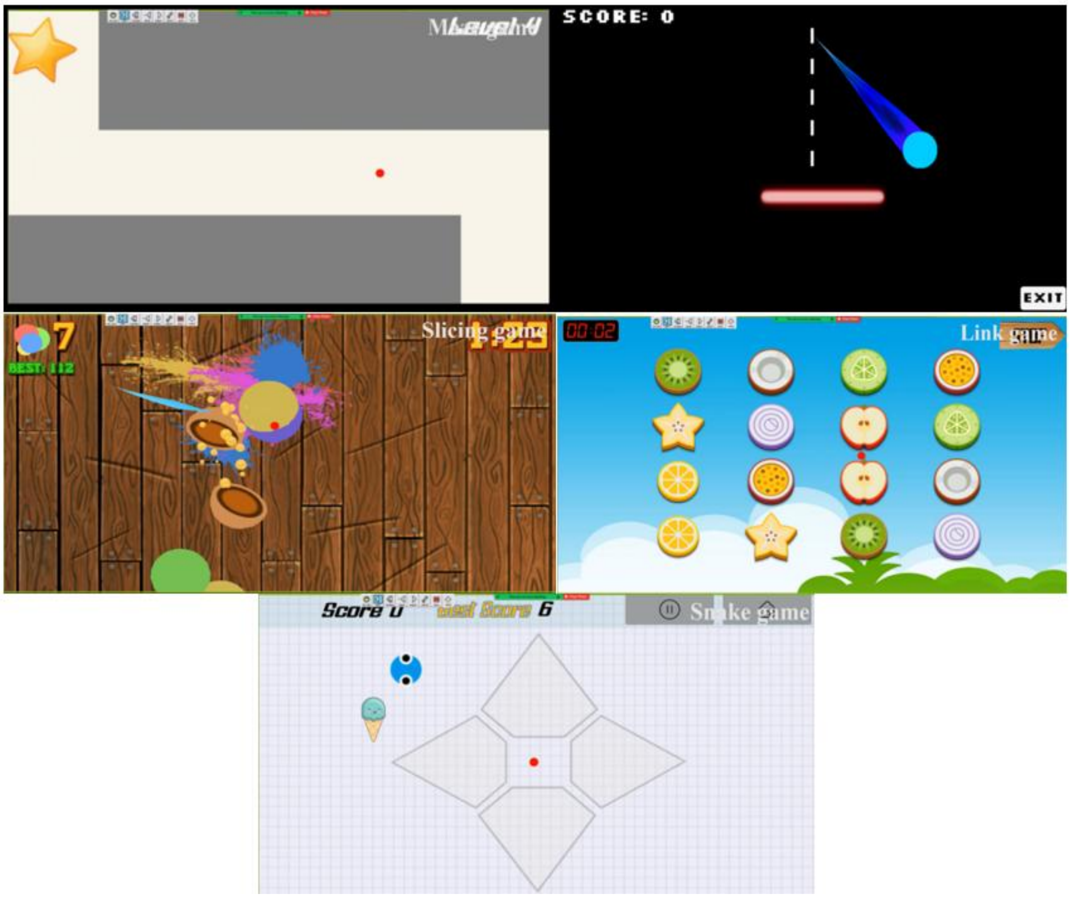
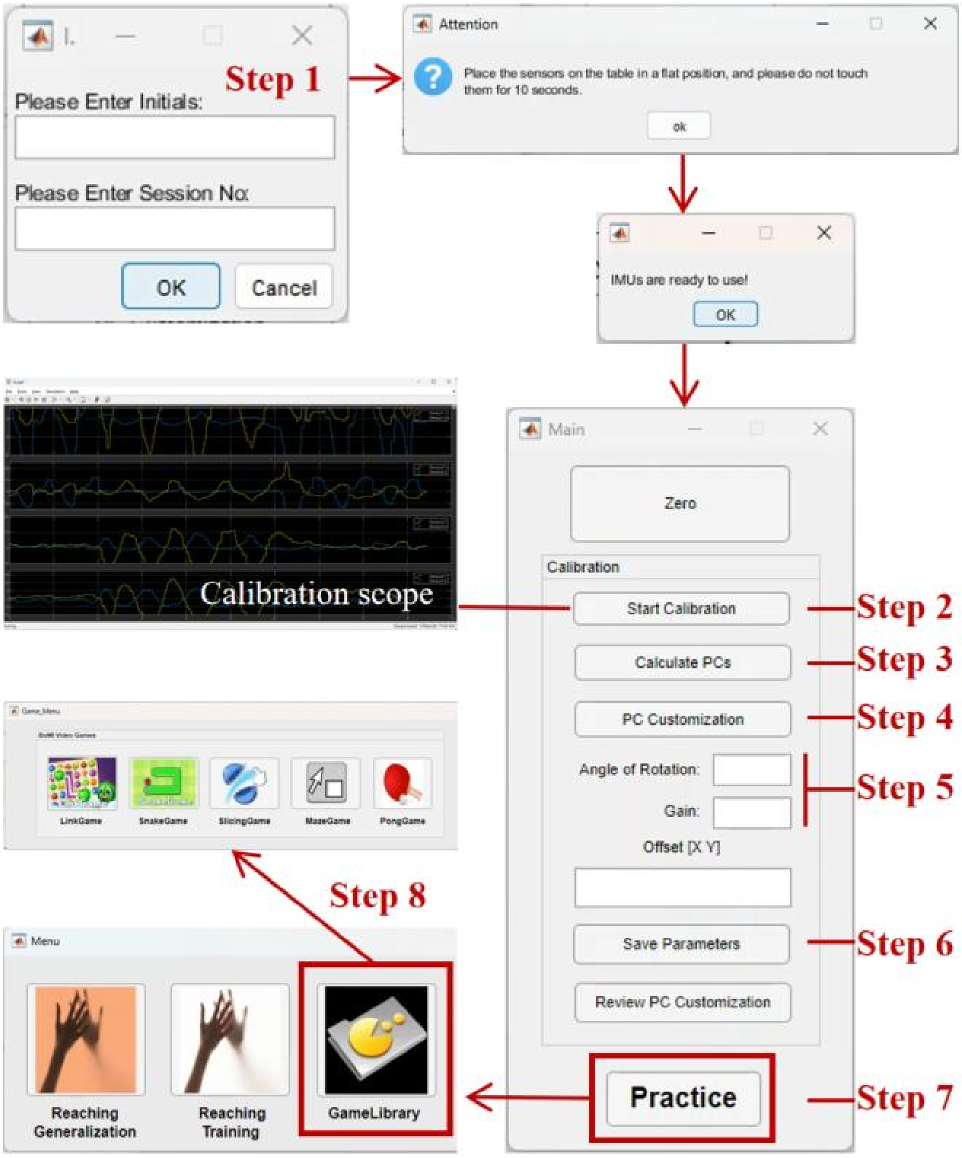


Figure 2.8 The illustration of five 2D video games.

2.5.6 Overall Workflow of BoMI

In Figure 2.9, the overall workflow of the BoMI GUI is illustrated. The first step was to launch the application file called 'Main_App' in MATLAB for participant information registration, where the participant ID and session number were filled out following the specified format (Figure 2.9, step 1). After clicking the ‘OK’ button, an attention page appears, reminding participants to hold their body still for 10 seconds in their comfortable zero position. After 10 seconds, the system indicates that the IMU sensors are ready for use, indicating that the sensors have successfully connected with the computer workstation. Participants can then proceed to the ‘main’ page to start the calibration process, which includes a scope for visualizing the two Euler angles for each IMU sensor (Figure 2.9, step 2). After calibration, the ‘Calculate PCs’ button was clicked to calculate the PCA using the data obtained from the calibration (Figure 2.9, step 3). The ‘PC customization’ button was then clicked to further modify and customize the control parameters of the cursor based on the participant's self-reported feedback and familiarization performance (Figure 2.9, step 4). The ‘Angle of Rotation’ and ‘Gain’ parameters can be set accordingly to realize the modification and customization above (Figure 2.9, step 5). The ‘Save Parameters’ button was clicked to save the adjustment parameters (Figure 2.9, step 6), and the ‘Practice’ button was clicked to begin the training and assessment of BoMI control (Figure 2.9, step 7). If the participants were required to perform different center-out reaching tasks, the ‘Reaching Generalization’ or ‘Reaching Training’ button was clicked. Clicking the ‘Game Library’ button displays a new ‘BoMI Video Games’ page to choose different 2D video games (Figure 2.9, step 8). Finally, clicking the ‘End Practice’ button closes the Simulink simulation and saves the data when the experiment with BoMI was done.



Please Enter Initials:

Please Enter Session No:

Place the sensors on the table in a flat position, and please do not touch them for 10 seconds.

IMUs are ready to use!

Angle of Rotation:

Gain:

Offset [X Y]

Figure 2.9 The step-by-step workflow of the BoMI based on MATLAB.

2.5.7 Event Stamps in BoMI Practice

To capture and analyze the performance of center-out reaching tasks, it is necessary to record the different states of each trial in real time within one block of reaching tasks, for instance, the time when the cursor entered the center circle, the time when it moved out of the center circle, and the time when it entered the target circle, etc. The same applies to 2D video games and other tasks in

BoMI. To achieve this, a numerical stamp for each state is displayed in different constant blocks in real time through the Simulink simulation. These constant blocks correspond to different environment states in the BoMI, such as the reaching state and game state, and the subcategories of each state are represented by Arabic numerals in order. For instance, in the reaching state, ‘0’ represents that the cursor is on the fly, ‘1’ means that the cursor is in the center circle, ‘2’ means that the cursor reaches the target successfully, and ‘3’ means that the specified arrival time of 2 seconds has been exceeded. To quantify the performance of center-out reaching tasks more accurately, the event stamps and sampling data are combined to calculate the cursor movement time, speed, and other factors.

The figure below (Figure 2.10) also illustrates how the event stamps change during one ideal reaching trial state change. By classifying the real-time event stamps, it is possible to identify the timing of BoMI events such as the entry and exit of the cursor into the center circle or target circle. The number of occurrences of these event stamps can be used to calculate the time of a specific period of the BoMI event. For example, to determine the time taken for a single reaching trial from the point the cursor leaves the center circle to when it reaches the target circle, we can count the number of times stamp 0 falls between labels 1 and 2 and divide it by the BoMI sampling frequency. This method allows for accurate measurement of time intervals during each BoMI trial, providing valuable data for further analysis and interpretation.

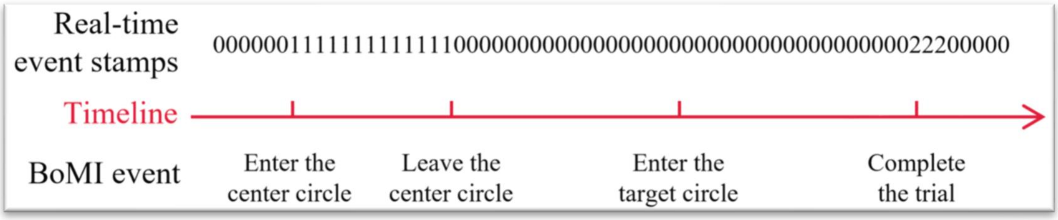


Figure 2.10 The dynamic changes of state stamps during one ideal reaching trial.

These stamps representing different event statuses were recorded as a data set in real-time at a sampling rate of 50 Hz and saved for post-test data processing and analysis, along with other data, such as Simulink time, CPU time, cursor coordinates, IMU angles, etc. The table below (Table 2.3) shows the selected structure of the data set and the corresponding meaning of each event stamp.

Table 2.3 The selected structure of the data set and the corresponding meaning of each stamp.

Data rows number	Items / States	Event stamps	Meaning
1	Simulink time		-
2	CPU time		-
3	Cursor-X		-
4	Cursor-Y		-
5	Main Menu States		
		0	Main menu
		1	Reaching training
		4	Game menu
		6	Generalization
6	Reaching States		
		0	On the fly
		1	Center
		2	Target
		3	Time over
7	Game States		
		0	Main menu
		1	Pong game
		3	Link game
		4	Snake game
		5	Slicing game
		6	Maze game
12-19	IMU data		8-dimensional data from four IMUs

2.6 Synchronization of the Data Stream from Multiple Systems

As multiple recording systems, including BoMI, EMG, and 3D motion capture systems, collect data simultaneously during various training movements, labeling their data streams synchronously is essential for facilitating the analysis of different evaluation factors (including BoMI, muscle activities, and kinematics) generated by the same task. To synchronize the EMG sensors and the 3D motion capture system, we used a trigger pulse generator to send a trigger analog signal that was recorded by both systems simultaneously. This ensured that both recording systems could be synchronized in the analysis process, and the collected data was accurately time-stamped. To solve the synchronization problem between BoMI and the 3D motion capture system, we used a data acquisition board (NI USB 6009, National Instruments, USA) to send TTL pulse from the BoMI workstation to the 3D motion capture system, generating accurate timestamps between the start and end of the specific task. The input end of the data acquisition board was connected to the computer workstation via a USB cable, and the output end was connected to the QTM analog signal adapter via a BNC cable. We used analog signals with different amplitudes and a duration of 0.01 seconds to categorize the start and end of different reaching tasks and video games. For instance, a 1V analog signal indicates the start and end of reaching task for training, a signal at 2V denotes the start and end of center-out reaching tasks for generalization, and signals ranging from 3-7V indicate the five different video games respectively.

2.7 Overview of the Full Study Protocol

The frame diagram of the full study protocol is shown in Figure 2.11. To minimize confounding situations caused by factors such as muscle fatigue or habituation, this experiment was conducted over the course of four sessions on separate days. The first day focused on testing the performance of tSCS in eliciting lower extremity muscle responses to assess the reliability of stimulation electrode placement. The position of the stimulation electrodes was manually fine-tuned based on the reflection of the muscles of the lower limbs to achieve better muscle responses. In addition, on the first experiment day, a study was conducted to measure the ankle, knee, and hip range of motion. Participants were instructed to perform three movement blocks, each of which will include five flexions and extensions of each joint to measure their respective range of motion. Three blocks were conducted under three different stimulation conditions, respectively, including tSCS, sham tSCS, and non-tSCS.

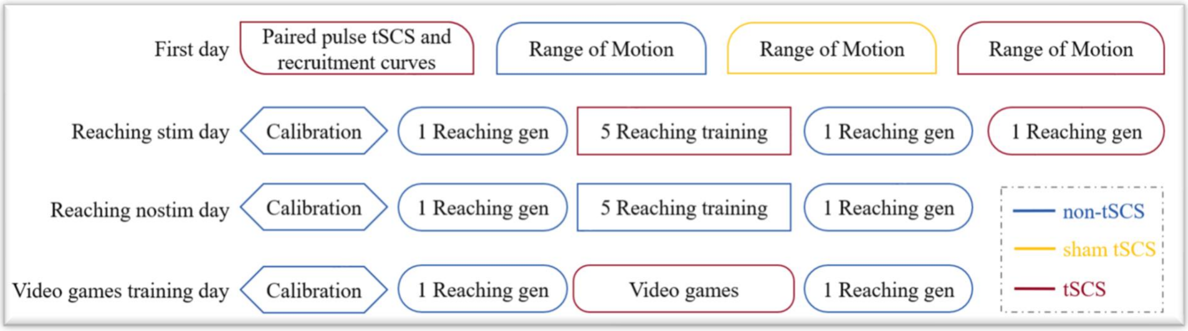


Figure 2.11 The frame diagram of the full study protocol

The remaining three days of the experiment were referred to as reaching stim day, reaching nostim day, and video games training day. For unimpaired control participants, the order of the three-day experiments was randomized, while for participants with SCI, the order of the three days was performed sequentially according to the task and stimulation conditions (i.e., reaching nostim, reaching stim, and video games training day).

(1) On the reaching nostim day, participants completed one block of generalization task after completing the calibration, then completed five blocks of reaching training tasks within 45 minutes, and finally completed one block of generalization task without tSCS again.

(2) On the reaching stim day, participants completed one block of generalization task with tSCS after calibration, then completed five blocks of reaching training tasks with tSCS within 45 minutes, and finally completed two blocks of generalization tasks, one with tSCS and one without tSCS.

(3) On the video games training day, participants completed one block of generalization task without tSCS after calibration, then played five video games with tSCS within 45 minutes, and finally completed one block of generalization task without tSCS again. In addition, there was a prescribed order and duration for playing video games. Participants first completed the first block of the maze game in 8 minutes, followed by the 7-minute pong game, 7-minute slicing game, 8-minute snake game, 7-minute link game, and the second block of the 8-minute maze game.

EMG was exclusively used for recording muscle activity during the paired pulse tSCS and recruitment curves, whereas a 3D motion capture system and EMG sensors were employed for recording kinematic data and muscle activity, respectively, during other experimental sessions.

2.8 Evaluation Metrics of Motor Performance

2.8.1 Performance Metrics Based on Simulink and MATLAB

Multiple performance metrics were computed from the Simulink output datasets and event stamps to quantify the performance BoMI for functional training, including smoothness, movement time, endpoint error, and straightness.

(1) smoothness: also known as the dimensionless jerk, was calculated by normalizing the time derivative of acceleration with respect to movement amplitude, duration, and mean speed. A movement with lower dimensionless jerk values indicates smoother and more efficient control of the movement.

(2) movement time: it is the time taken by participants to move the cursor from the center circle to the target circle for each reaching trial, which reflects the speed and accuracy of movement execution.

(3) endpoint error: it was defined as the Euclidean distance between the cursor and target positions 2 seconds after the target circle appears. A smaller endpoint error indicates more accurate movement and better performance.

(4) straightness: or path length, was calculated by the sum of the Euclidean distance between the starting and ending cursor positions, normalized by the straight-line distance between center and target positions. A lower path length value denotes a straighter line from the center circle to the target circle.

2.8.2 Performance Evaluated using EMG and 3D Motion Capture Systems

The use of EMG sensors and 3D motion capture systems provides valuable information about muscle activity and kinematic data during different motor tasks. Muscle signals can be recorded in real-time using EMG sensors to capture the muscle activity elicited during the reaching trial and identify muscle activation patterns. In addition, the 3D motion capture system can be utilized to capture the kinematics of the trunk, and bilateral upper and lower limbs, such as ankle angles, knee angles, hip angles, foot pitch angles, and movement amplitudes for range of motion tasks, BoMI calibration, video games training, and each trial of center-out reaching tasks.

2.8.3 Performance Evaluated using 2D Video Games

Given that participants play various video games by manipulating a 2D cursor through body movements, the game scores serve as a direct indicator of motor performance enhancement before and after training. Specifically, for the Maze and Link games, the time taken to finish the whole trial was documented, whereas a shorter time reflects better performance. If the participants don’t complete all levels within the allotted time (8 minutes), the time or performance of this Maze game block will be counted as 8 minutes. In addition, for the Pong, Slicing, and Snake games, the scores obtained within a limited duration were recorded. A higher score represents a better ability to manipulate the cursor accurately.

2.9 Data Processing and Analysis

Data processing and analysis were conducted using custom programs developed in MATLAB and R studio (RStudio, Inc., USA). The raw BoMI data were saved as .mat files in MATLAB under the folder designated for each participant based on subject number and session number. Raw motion capture data recorded by QTM was processed using Theia software (Theia Markerless, Inc., Canada), which is designed to handle motion capture data and provides advanced processing, filtering, and analysis tools. After the data was processed using Theia, it was then imported into Visual3D (C-Motion, Inc., USA) software automatically for further analysis and visualization. The raw kinematic data can be selected, checked, and viewed in Visual3D, along with the raw muscle activity data of muscle activities since the 3D motion capture system and EMG system were synchronized before. Finally, the muscle activity data from EMGs, analog data from BoMI, and kinematics data from the 3D motion capture system were able to export together in a .txt format using a specific pipeline via Visual3D for further processing and analysis.

2.9.1 Reconstruction of Cursor Trajectory on Reaching Tasks

As previously discussed, during each block of the center-out reaching task, it is possible to obtain the state of the cursor (e.g., on the fly, leave the center circle, enter the target circle) for every trial within the block by examining the event stamps. Consequently, cursor trajectories for each trial can be reconstructed by the calculation using the BoMI sampling frequency, event stamps, and two-dimensional cursor coordinates. For instance, when a participant attempts to move the cursor from the central circle to the target circle located at the top of the screen, the system automatically detects whether the cursor coordinates align with those within the target circle's area. If a match occurs, it signifies that the cursor has successfully entered the target circle, prompting the generation of a new event stamp to document the stage transition. By identifying alterations in these stamps and integrating them with concurrently recorded cursor coordinates, a trajectory extending from the central circle to the target circle can be reconstructed.

By replicating this process, cursor trajectories associated with each trial in a reaching block can be reconstructed and differentiated using unique colors to denote trajectories leading to each target circle. Through this reconstruction of cursor trajectories, the control performance of individual reaching blocks can be assessed and compared with other blocks of reaching tasks. Additionally, this method facilitates the implementation of various metrics for assessing the BoMI performance, including the time required for the cursor to complete each trial, trajectory length, and cursor movement speed to further quantify the BoMI performance.

2.9.2 BoMI Performance

In this study, four performance metrics were employed to evaluate the BoMI control performance based on the IMU sensors and MATLAB. The metrics included movement time, smoothness, endpoint error, and straightness(56,76). For an individual participant, the minimal task unit utilized for documenting BoMI performance is a single trial (e.g., a complete block of reaching training task consisting of 24 single trials. However, a complete block of generalization tasks consisted of 6 single trials because only visible trials were considered and analyzed at this time). Consequently, each trial was assessed using these four metrics of BoMI performance. When comparing the performance across different reaching blocks for the same participant, all trials within each block were collectively considered as a comprehensive data set.

When comparing the performance of various reaching blocks within a group of unimpaired control participants, the performance metrics dataset for each participant was averaged across trials within each block. Therefore, the movement time performance of the unimpaired control group during the first reaching training block comprises these values calculated for all unimpaired control participants. In addition, for participants with SCI, differences in placement of IMU sensors and experimental protocols between individual participants result in each participant being considered separately in subsequent data processing and data analysis.

2.9.3 Learning Rate of BoMI Control

The learning rate for BoMI control was defined as the change in performance metrics for the first and last block of the same type of center-out reaching on each experimental day(77). For example, the learning rate of reaching training was the difference in performance between the first and last blocks, and the learning rate of generalization was the difference in performance between the first and second blocks without tSCS. Consequently, the learning rate of individual unimpaired control participants was derived by subtracting the different evaluation metrics of the two reaching tasks after the performance metrics data of each participant had been summed and averaged by trial number. In addition, the learning rate of individual participants with SCI was calculated separately and was defined as the difference between the sum of each metric for the first reaching block and the sum of the corresponding performance metrics for the last reaching block.

Chapter 3: The Effect of tSCS on Center-out Reaching Training Performance

3.1 Motivation and Objective

Spinal cord injury (SCI) can result in long-term loss of motor and sensory function, which can significantly impact patients' ability to move, function independently, and engage in activities of daily living(1). In response to these challenges, various rehabilitative strategies have been developed(40,61,66). For instance, center-out reaching tasks are commonly used in functional training to improve motor function in individuals with neurological disorders such as SCI(23). Additionally, tSCS is a neuromodulation technique that has shown promise in improving motor function and neural plasticity when combined with other exercise training tasks(38). Therefore, the technological platform combining center-out reaching training and tSCS could be a promising rehabilitation strategy for people with SCI. However, the specific effect of tSCS on motor learning and function, measured through center-out reaching training performance, remains unclear, which highlights the need for further investigation into this matter.

Therefore, the primary object of this chapter is to address the research question of the potential impact of tSCS on the performance and learning rate of center-out reaching. Furthermore, we aim to investigate the effects of this motor training platform on intact and impaired neural pathways by conducting experiments with both control participants and individuals with SCI. By addressing this question, we hope to contribute to a better understanding of whether the tSCS can enhance the performance of center-out reaching tasks, which has the potential to inform the development of more effective rehabilitation strategies for individuals with SCI and improve their motor function and overall quality of life.

3.2 Methods

3.2.1 Study Design

In this study, a two-day experiment was conducted with both control participants and individuals with SCI to investigate the impact of tSCS on center-out reaching training performance based on training with vs. without tSCS. Participants were prepared for stimulation electrodes, EMG sensors, and IMU sensors before sitting on a stable chair positioned at 120° from a projector screen to perform the calibration procedure and control a 2D computer cursor. During each day, participants were asked to perform five blocks of center-out reaching tasks for training (i.e., reaching training) in the training session, lasting 45 minutes each. If needed, participants could take rest breaks after completing any training block, with tSCS being turned off at the same time. The only difference between the two days was the presence of tSCS during the reaching stim day, while there was no tSCS during the reaching nostim day. Each block of reaching training task consisted of 24 trials, with a detailed schedule of reaching training presented in Table 3.1.

Table 3.1 The schedule of center-out reaching tasks for training.

Days	Training Sessions				
Reaching nostim day	5 blocks of reaching training				
Block #	Block1	Block2	Block3	Block4	Block5
Numbers of trials	24	24	24	24	24
Stimulation status	OFF	OFF	OFF	OFF	OFF
Reaching stim day	5 blocks of reaching training				
Block #	Block1	Block2	Block3	Block4	Block5
Numbers of trials	24	24	24	24	24
Stimulation status	ON	ON	ON	ON	ON

3.2.2 Statistics

Statistics analyses were conducted using custom programs developed in MATLAB and R studio (RStudio, Inc., USA). An unpaired t-test was employed to examine the difference in BoMI performance between the first and last reaching training blocks in a training session under two different tSCS conditions (tSCS or non-tSCS). A representative participant from the unimpaired control group (S008) was included in this test to investigate whether a significant improvement in BoMI performance occurred after the training session with different tSCS for this individual impaired participant. Moreover, a paired t-test was applied to the unimpaired control group (N=14) to assess group differences between the first and last blocks of reaching training performance with or without tSCS (i.e., the first block with tSCS vs. the fifth block with tSCS, the first block without tSCS vs. the fifth block without tSCS), as well as the group difference in performance between training with and without tSCS for the first or last block of reaching training task (i.e., the first block with tSCS vs. the first block without tSCS, the fifth block with tSCS vs. the fifth block with tSCS). By doing so, we can investigate the potential improvement in BoMI performance following training and investigate whether there is a difference in the performance of the first or last block on the two experimental days under different tSCS conditions for the unimpaired control group. Additionally, a paired t-test comparing the learning rate generated by training with two different tSCS conditions for the unimpaired control group was employed to test the effect of tSCS on the improvement of BoMI performance of reaching training tasks.

Also, an unpaired t-test was applied to data from participants with SCI separately (BMS001 and BMS002) to test the difference between the first and last blocks of reaching training performance with or without tSCS (i.e., the first block with tSCS vs. the fifth block with tSCS, the first block without tSCS vs. the fifth block without tSCS). This unpaired t-test also analyzed the difference in performance between training with and without tSCS for the first or last block of reaching training task (i.e., the first block with tSCS vs. the first block without tSCS, and the fifth block with tSCS vs. the fifth block with tSCS). This method of comparison was analogous to using the paired test for unimpaired group described above, but an unpaired test was employed here because the data within these compressions for participants with SCI were not in a one-to-one correspondence.

3.3 Results

3.3.1 BoMI Performance of the Unimpaired Control Group Improved after Training with Reaching Tasks and Was Unrelated to tSCS

In order to investigate the potential impact of tSCS application during exercise on motor control performance in the unimpaired control group, we analyzed and compared the performance of five blocks of reaching training tasks with and without tSCS on reaching stim day and reaching nostim day, respectively. The performance of the first and fifth blocks, based on four BoMI evaluation metrics, was calculated and presented to display the difference before and after training under different tSCS conditions. First, a representative single control participant (S008) was selected to demonstrate the potential effects of tSCS on motor training in unimpaired control individuals. Figure 3.1A and Figure 3.1C depict the performance of the tSCS and no tSCS training sessions, respectively. The first and last reaching training blocks of each experimental day were marked and displayed with cursor trajectory reconstruction and tangential velocity for 24 single reaching trials.

These figures show that regardless of the tSCS application, the cursor movement trajectories in the fifth block after training appeared more organized and orderly compared to the disordered and chaotic first block. Simultaneously, through the visualization of the tangential velocity of each reaching trial, it was also observed that the movement became faster and more stable after training, converging towards a fixed and narrow range. This intuitive information suggests that cursor control in this representative control participant became more adept and stable after training, with or without the application of tSCS.

The statistical analysis is depicted in Figure 3.1B and Figure 3.1D. Figure 3.1B tested the difference in performance between the first and last block of reaching training tasks using tSCS. The results indicate a significant difference between the first and last block of reaching training tasks with tSCS for all performance metrics, including movement time ($p = 0.00087$), smoothness ($p = 0.00023$), straightness ($p = 0.015$), and endpoint error ($p = 0.019$). Additionally, Figure 3.1D demonstrates a significant difference between the first and last block of reaching training tasks without tSCS in movement time ($p = 0.0019$), smoothness ($p = 0.0091$), error ($p = 0.0071$), but not in straightness ($p = 0.29$). Notably, the significant differences in movement time, smoothness, and straightness between the first and last reaching training blocks were more pronounced with tSCS than without tSCS. These results may suggest that tSCS has a potential facilitative effect on the performance of this single participant, or simply that the initial performance with tSCS was worse than without tSCS, but the participant was able to achieve a similar level of the final performance. Consequently, we employed a larger sample size of the unimpaired control group to further explore the impact of tSCS on BoMI performance within this population.

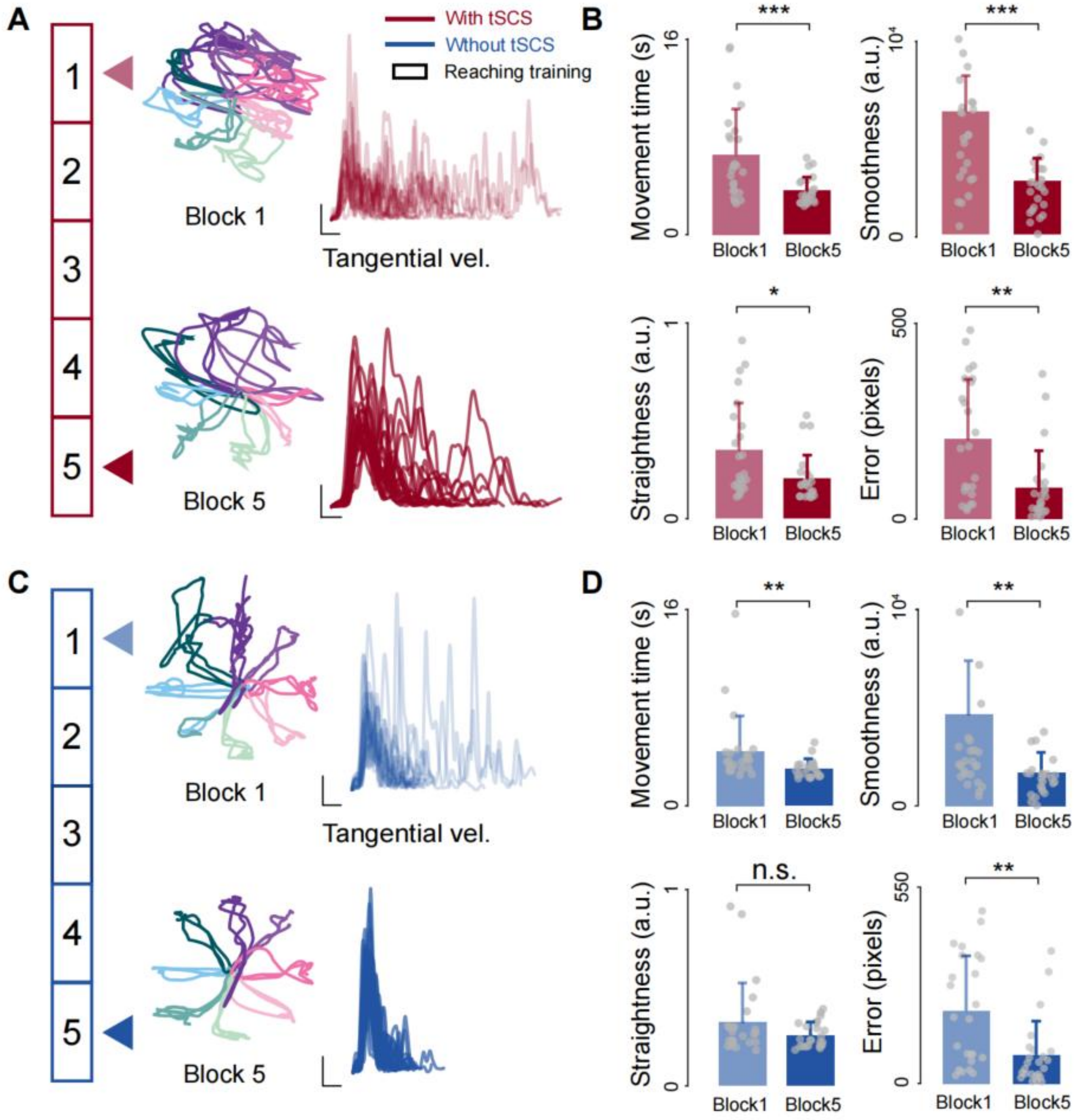


Figure 3.1 The performance of the first and last blocks of reaching tasks within the training sessions for an unimpaired participant. **(A)** The reconstruction of cursor trajectory and trial-based tangential velocity of the first and last blocks of reaching tasks during the training session with tSCS. Five rectangles symbolize five reaching training tasks within a training session, with numbers indicating the order. The rectangle with the red border signified that tSCS was applied throughout the entire training session, while the blue indicated that tSCS was not applied. **(B)** The quantified performance of the first and last blocks of reaching tasks during the training sessions with tSCS based on four evaluation metrics. Light red bar: the first block, dark red bar: the last block. **(C)** The reconstruction of cursor trajectory and tangential velocity of the first and last blocks of reaching during the training session without tSCS. **(D)** The quantified performance of the first and last blocks of reaching tasks during the training sessions without tSCS. Light blue bar: the first block, dark blue bar: the last block.

Figure 3.2A presents the performance of the five blocks of reaching training tasks under each tSCS condition for the unimpaired control group (N=14) in a line graph format. The line graph's trend illustrates the change in performance across five blocks of reaching training tasks. The two solid lines in the graph generally exhibit a downward trend, with the performance of the two tSCS conditions remaining relatively close. This observation suggests that motor training under different conditions led to a gradual improvement in the BoMI performance of this group, regardless of tSCS application. Another intriguing phenomenon was observed in Figure 3.2A, where the average performance of all evaluation metrics in the last block of a training session for the unimpaired control group, both with and without tSCS, is remarkably close, with a smaller standard deviation than in the first training block. This observation may indicate that participants reached a temporary but similar saturation point of performance at the last block of the reaching training, irrespective of tSCS usage.

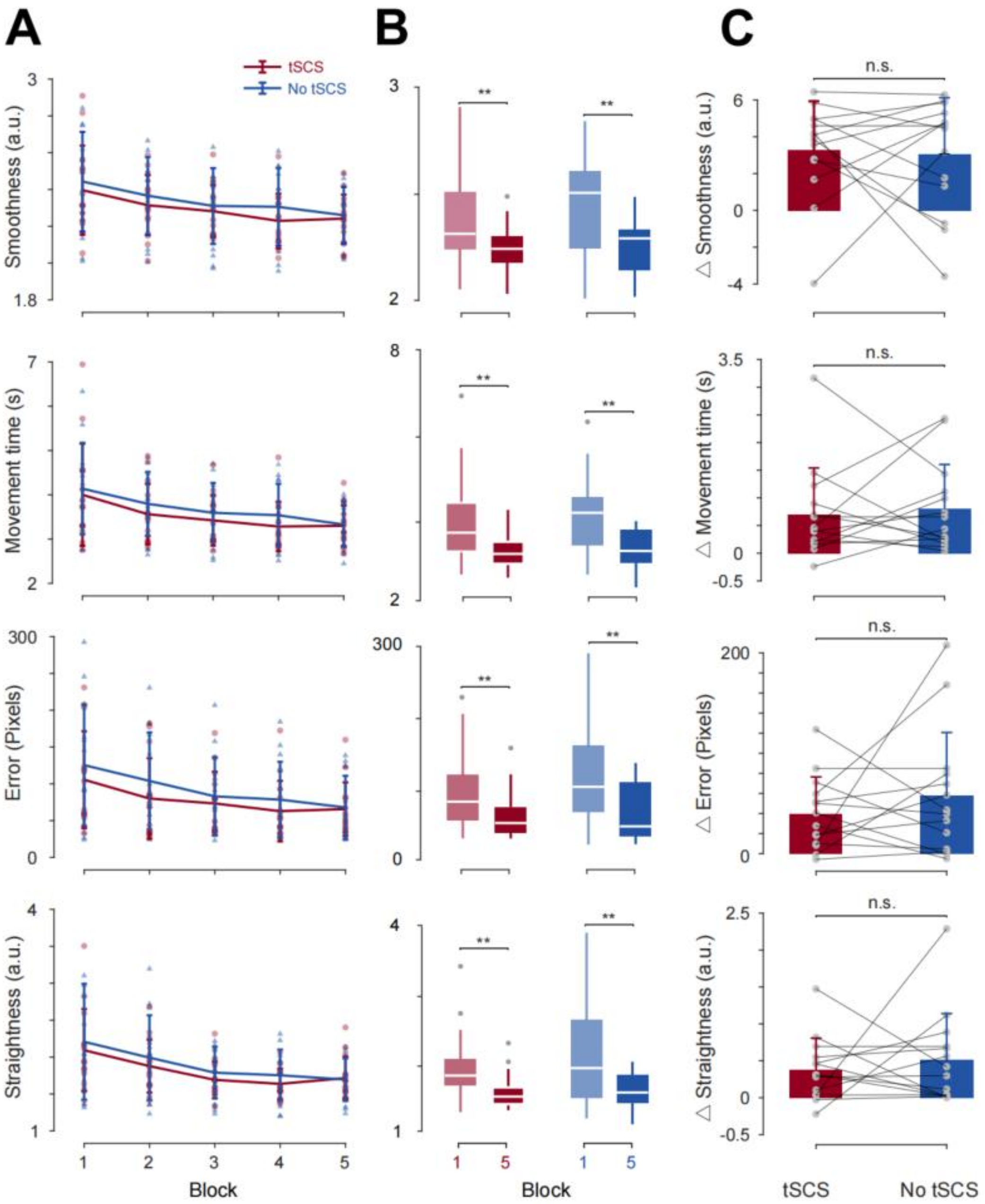


Figure 3.2 The performance and learning rate during the training sessions under different tSCS conditions within the unimpaired control group. **(A)** The quantified performance of five blocks of reaching tasks during the training session based on four metrics. X-axis: the sequence of training blocks, Y-axis: different values of BoMI performance metrics, red solid line: training with tSCS, and blue solid line: training without tSCS. **(B)** The BoMI performance comparison between the first and last blocks of reaching training tasks under different tSCS conditions and comparison between the first block with tSCS and first block without tSCS or the last block with tSCS and last block without tSCS. Light red box: the group performance of the first block of reaching task with tSCS, dark red: the last block with tSCS, light blue: the first block of reaching without tSCS, dark blue: the last block without tSCS. **(C)** The learning rate during the training sessions with or without tSCS. Red bar plot: the learning rate of training with tSCS, the blue bar plot: the training without tSCS, Y-axis: the change of performance between the first and last block of reaching tasks.

The statistical analysis results presented in Figure 3.2B display the differences between the first and last blocks of reaching training performance with and without tSCS (i.e., the first block with tSCS vs. the fifth block with tSCS, the first block without tSCS vs. the fifth block without tSCS), as well as the group difference in performance between training with or without tSCS for the first and last block of reaching training task (i.e., the first block with tSCS vs. the first block without tSCS, the fifth block with tSCS vs. the fifth block with tSCS). The results reveal that significant statistical differences in performance were found between the first and the fifth blocks within each experimental day. However, regardless of tSCS usage during the training sessions, no significant statistical difference in performance was observed between the two first or fifth blocks of the two experimental days. This finding suggests that there was no difference in BoMI performance when participants began training with tSCS or without tSCS, nor did they perform differently after training. Consequently, it can be inferred that training with tSCS did not have a significantly better effect on improving the performance of reaching tasks than training without tSCS in unimpaired control group, but it also did not interfere with participants' ability to learn the task. Nonetheless, it is noteworthy that training with and without tSCS resulted in significant improvement by the end of the training session.

Comparing the difference in learning rate between training with and without tSCS in unimpaired control group, Figure 3.2C also demonstrates that training under both tSCS conditions yielded a positive learning rate. However, there were no significant statistical differences in learning rate between reaching training with vs. without tSCS. In Figure 3.2C, it is also observed that not every participant in the unimpaired control group achieved a positive learning rate during both two days of a training session with different tSCS conditions, but they did so for at least one day. This observation probably suggests that individual participants' motor control might be enhanced to some degree or disturbed, reducing their BoMI performance e when using tSCS.

3.3.2 tSCS Has a Potential Facilitation Effect on the BoMI Performance for BMS002 but not for BMS001

Figure 3.3A presents the performance of the three blocks of reaching training tasks under each tSCS condition for participant BMS001 in a line graph format. Due to the participant completing only three blocks within the allocated 45 minutes, the training session analysis includes only these three reaching training blocks. From the overall line graph, it is apparent that training without tSCS generally achieved better performance in most reaching blocks. A more specific statistical analysis was further utilized to quantify the difference in BoMI performance produced by the two tSCS conditions.

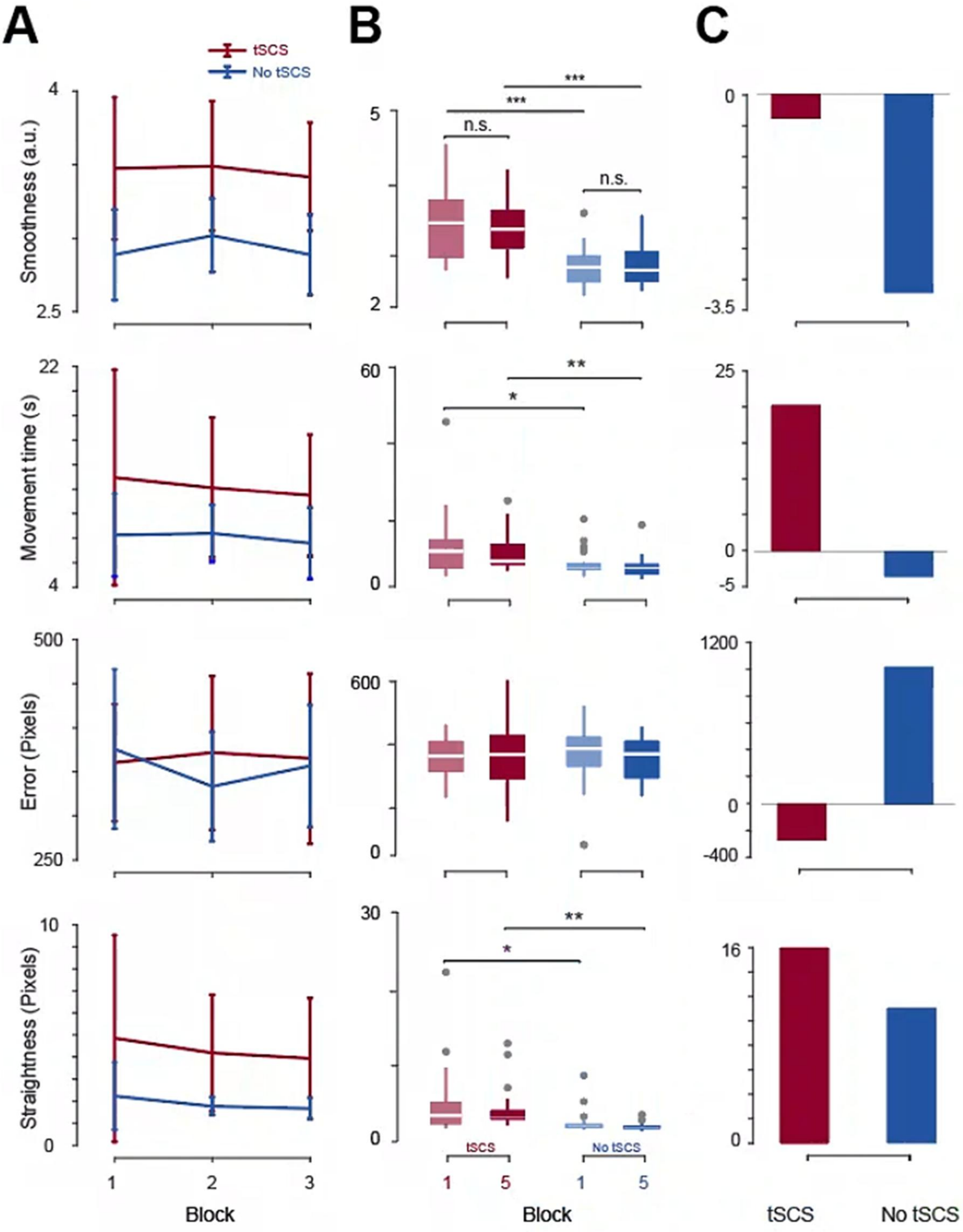


Figure 3.3 The performance and learning rate during the training sessions under different tSCS conditions in participant BMS001. **(A)** The quantified performance of three blocks of reaching tasks during the training session based on four metrics. **(B)** The BoMI performance comparison between the first and last blocks of reaching task under different tSCS conditions and comparison between the first block with tSCS and first block without tSCS or the last block with tSCS and last block without tSCS. **(C)** The learning rate during the training sessions with or without tSCS.

Figure 3.3B displays the significant differences in performance between the first and last training blocks under different tSCS conditions in smoothness, movement time, and straightness, but not in endpoint error. This result indicates that the performance of the first and last training with tSCS is consistently worse than training without tSCS in smoothness, movement time, and straightness. We also observed that reaching training with or without tSCS produced no significant change in performance at the last block of training in any metric. This finding suggests that exercise training did not allow this participant to achieve significant improvements in BoMI performance.

The learning rate between the first and last blocks under different tSCS conditions, shown in Figure 3.3C, demonstrates that the application of tSCS did not result in a consistent improvement in BoMI performance. However, it is observed that the learning rate in some assessment metrics produced by motor training in certain blocks was greater than the regression value in other blocks, such as the movement time and straightness metrics. This suggests that exercise training has a potential effect on the motor learning of this participant with SCI.

However, another participant with SCI (BMS002) exhibited quite different performances and results. Figure 3.4A presents the performance of the five blocks of reaching training tasks under each tSCS condition for participant BMS002 in a line graph format. From the overall line graph, it is evident that motor training with and without tSCS generally achieved improved performance across the five blocks of reaching training tasks. Furthermore, training with tSCS generally yielded better performance during the training session in smoothness, movement time, and endpoint error. In addition, a marked convergence and saturation of BoMI performance were also observed in the metrics of movement time and straightness of the fifth training block.

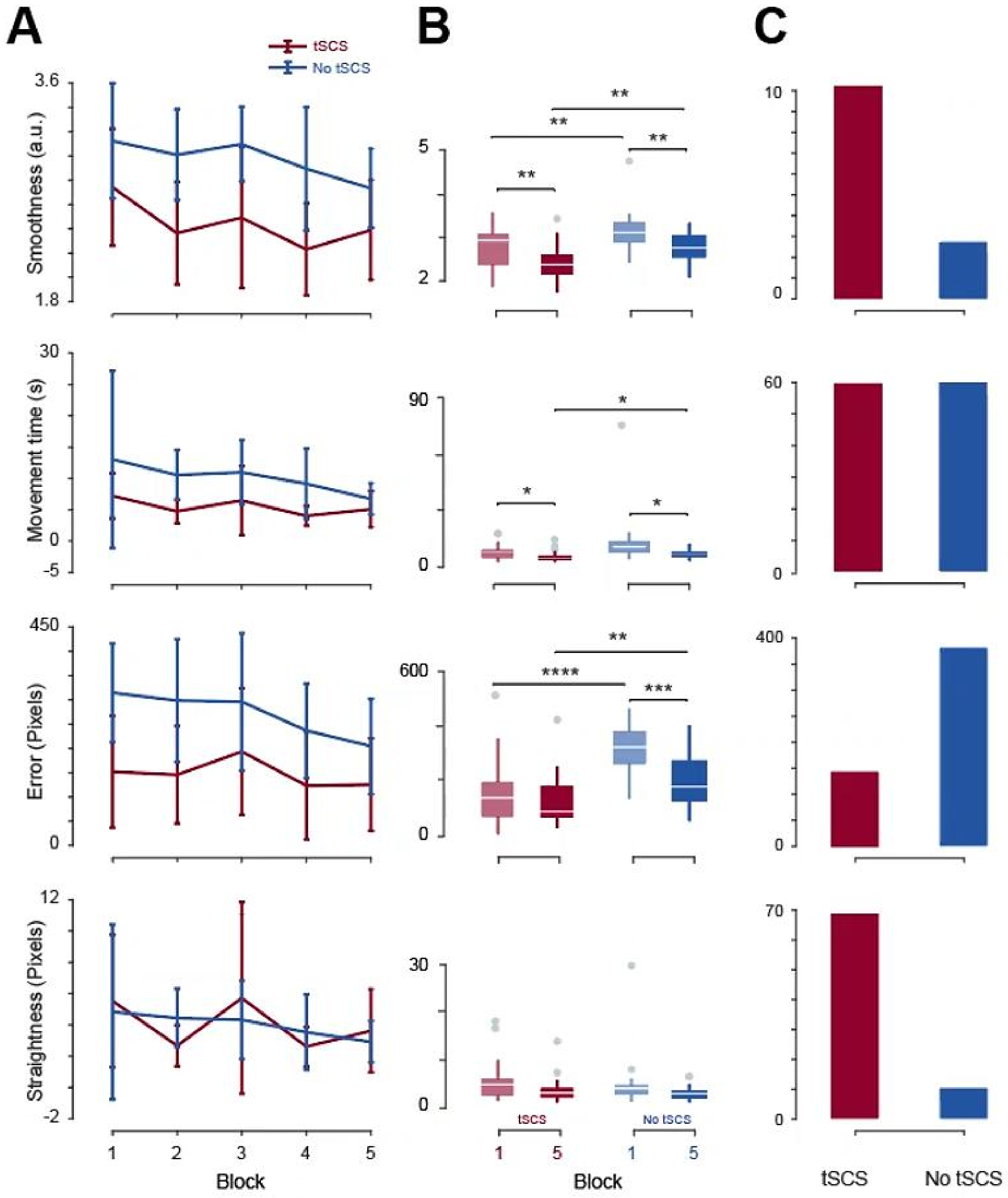


Figure 3.4 The performance and learning rate during the training sessions under different tSCS conditions in participant BMS002. **(A)** The quantified performance of five blocks of reaching tasks during the training session based on four metrics. **(B)** The BoMI performance comparison between the first and last blocks of reaching task under different tSCS conditions and comparison between the first block with tSCS and first block without tSCS or the last block with tSCS and last block without tSCS. **(C)** The learning rate during the training sessions with or without tSCS.

The statistical analysis in Figure 3.4B demonstrates that in smoothness and movement time, training with and without tSCS both generated a significant improvement in performance at the last reaching training task compared to the first block. In addition, training with tSCS resulted in a significantly better final performance than without tSCS in smoothness, movement time, and error. However, in error, training with tSCS did not produce a significantly better outcome by the last block of reaching training sessions. As for straightness, no significant difference was shown in each comparison, indicating that training with and without tSCS did not generate any significant change between the first and last block of reaching training sessions. From a bar plot in Figure 3.4C, comparing learning rates for the first and last training blocks, training with tSCS produced faster learning rates in terms of smoothness, movement time, and straightness than without tSCS.

Chapter 4: The Effect of Training with Video Games Compared to Reaching Tasks on BoMI Control Performance

4.1 Motivation and Objective

Video games and center-out reaching tasks performed by body movement using a novel body-machine interface represent two different rehabilitation tools for motor training(56,78). Both tools specifically target motor learning and motor control, involving the direct practice and repetition of body movement, which allows participants to develop and refine their movement skills, muscle coordination, and proprioceptive feedback. However, video games may further enhance attention, problem-solving skills, visuospatial processing, decision-making, and reaction time by engaging participants in dynamic environments, providing a more enjoyable and immersive experience that could lead to increased motivation and adherence to the functional training program(66,68,78). Furthermore, video games can be easily adjusted to match individual skill levels, allowing for tailored training experiences and gradual progression in difficulty(66). However, the effectiveness of video games compared to center-out reaching tasks based on a body-machine interface for motor training remains to be fully explored and determined.

This research question aims to investigate whether 2D video games can serve as a viable alternative to traditional center-out reaching training tasks in neural rehabilitation for individuals with SCI. By examining the differential effects of these two training strategies, researchers and clinicians can develop evidence-based and optimal rehabilitation interventions. If video games are proven to be equally or more effective than center-out reaching tasks, it is possible to offer a more engaging and enjoyable approach for people with SCI to enhance their motor function and abilities of daily living in the future.

4.2 Methods

4.2.1 Study Design

In this research question, a two-day experiment involving reaching stim day and video games training day was performed with both unimpaired control participants and individuals with SCI to investigate the effect of training with video games compared to training with center-out reaching training tasks (i.e., reaching training) on the performance of motor control. The motor control performance was evaluated by a generalization center-out reaching task (i.e., generalization). During each day, participants performed one block of generalization without tSCS before the training session and another block of generalization without tSCS after the training session. The only difference between the two days was the presence of five blocks of reaching training tasks with tSCS during the training session on the reaching stim day, while a 45-minutes video games training session with tSCS was performed during the video games training day. Each block of generalization consisted of 6 visible trials. In this study, the difference between training with reaching tasks and video games was evaluated by comparing and analyzing the performance metrics of the 6 visible trials in a single block of generalization before and after the training session. A detailed schedule of generalization tasks for training is presented in Table 4.1.

Table 4.1 The schedule of center-out reaching tasks for generalization.

Days	Evaluation	Training sessions	Evaluation
Reaching stim day			
Task types	Generalization	Reaching training	Generalization
Block #	Block a	5 blocks in 45 mins	Block b
Numbers of trials	6	24 trials for each block	6
Stimulation status	OFF	ON	OFF
Video games training day			
Task types	Generalization	Video games	Generalization
Block #	Block a	5 video games in 45 mins	Block b
Numbers of trials	6	N/A	6
Stimulation status	OFF	ON	OFF

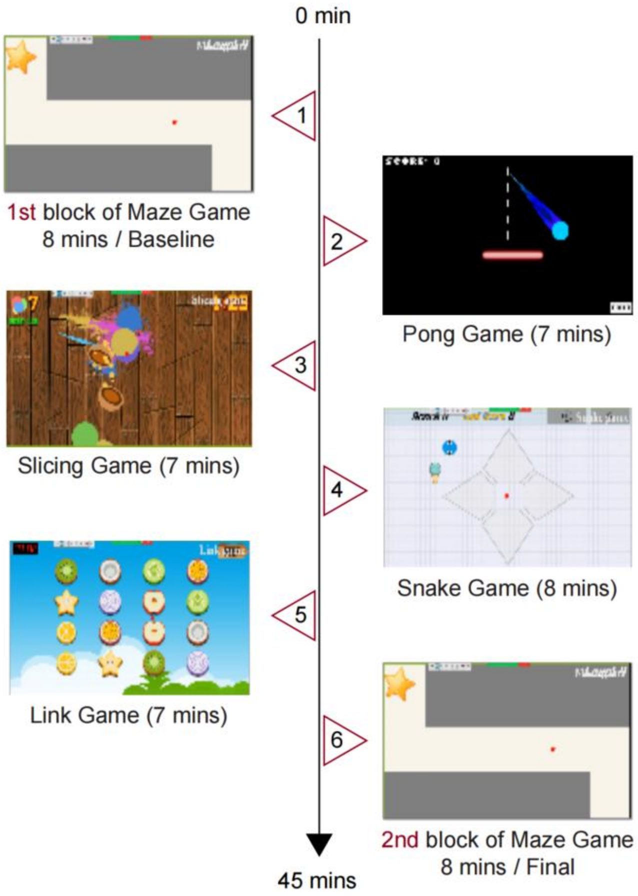


Figure 4.1 The schedule of training sessions using five video games in 45 minutes.

During the training session, participants played five distinct video games that were within a 45-minute time frame (Figure 4.1). The participants started by controlling the 2D cursor in a block of Maze game for eight minutes, followed by a seven-minute session of Pong game, a seven-minute of Slicing game, an eight-minute of Snake game, and a seven-minute of Link game. The training concluded with an additional eight-minute block of the Maze game. Prior to the initiation of the game-based training, we provided the participants with comprehensive instructions regarding the rules of each game, ensuring they were familiar with the gameplay mechanics and could optimize their performance throughout the training session.

4.2.2 Statistics

Statistics analyses were conducted using custom programs developed in MATLAB and R studio. An unpaired t-test was employed to examine the difference in BoMI performance in a single representative participant (S008) between one block of generalization before and after training sessions using different training methods (reaching or video games). Moreover, a paired t-test was then applied to the unimpaired control group (N=14) to assess group differences in performance between the one block of generalization (block a) before the training session and one block of generalization (block b) after the training session while training with reaching or videogames, as well as the group difference in performance before and after training. In this way, we can study the specific changes in BoMI performance of generalization tasks following training sessions using different training strategies for an unimpaired group. Additionally, a paired t-test comparing the learning rates generated by two different training strategies for the unimpaired control group was employed to test the effect of reaching tasks and 2D video games on the improvement of BoMI performance.

For participants with SCI (BMS001 and BMS002), an unpaired t-test was applied to examine the difference between one block of generalization (block a) before the training session and one block of generalization (block b) after the training session while training with reaching vs. videogames. This test also analyzed the difference in BoMI performance between the first blocks and the last generalization blocks across conditions. This method of comparison was analogous to using the paired test for the control group described above, but an unpaired test was employed here since the data of the same subject on two days are not directly related.

Moreover, an additional paired t-test was conducted to compare the difference in performance between the first and last blocks of Maze games, as well as the difference in performance between the first and last trials of the Slicing game, Link game, Pong game, and Snake game within the unimpaired control group. This statistical analysis aimed to further explore potential improvements in performance as a result of training within each video game.

4.3 Results

4.3.1 Training with Reaching Tasks and Video Games in a Control Group Achieved Similar BoMI Performance but Reaching Training Results in More Consistent Improvements

In an effort to examine the potential influence of videogames applications during a training session on motor control performance in unimpaired individuals, we conducted an analysis comparing the performance of one block of generalization tasks before and after training sessions with different training protocols using tSCS: center-out reaching and gaming. Performance for the first and second blocks was assessed based on four BoMI evaluation metrics and presented to illustrate differences before and after training sessions with the respective tools.

A representative single participant (S008) was selected to demonstrate the potential effects of 2D video games on motor training in unimpaired control individuals. Figure 4.1A and Figure 4.1C illustrate the workflow of training and evaluation sessions. The first and second generalization blocks of each experimental day were marked and displayed with cursor trajectory reconstruction and tangential velocity for six single reaching visible trials. From these figures, we noticed that after motor training with reaching tasks, the cursor movement trajectories in the second block of generalization appeared more organized and orderly compared to the disordered first block, but not for trajectories after training with video games.

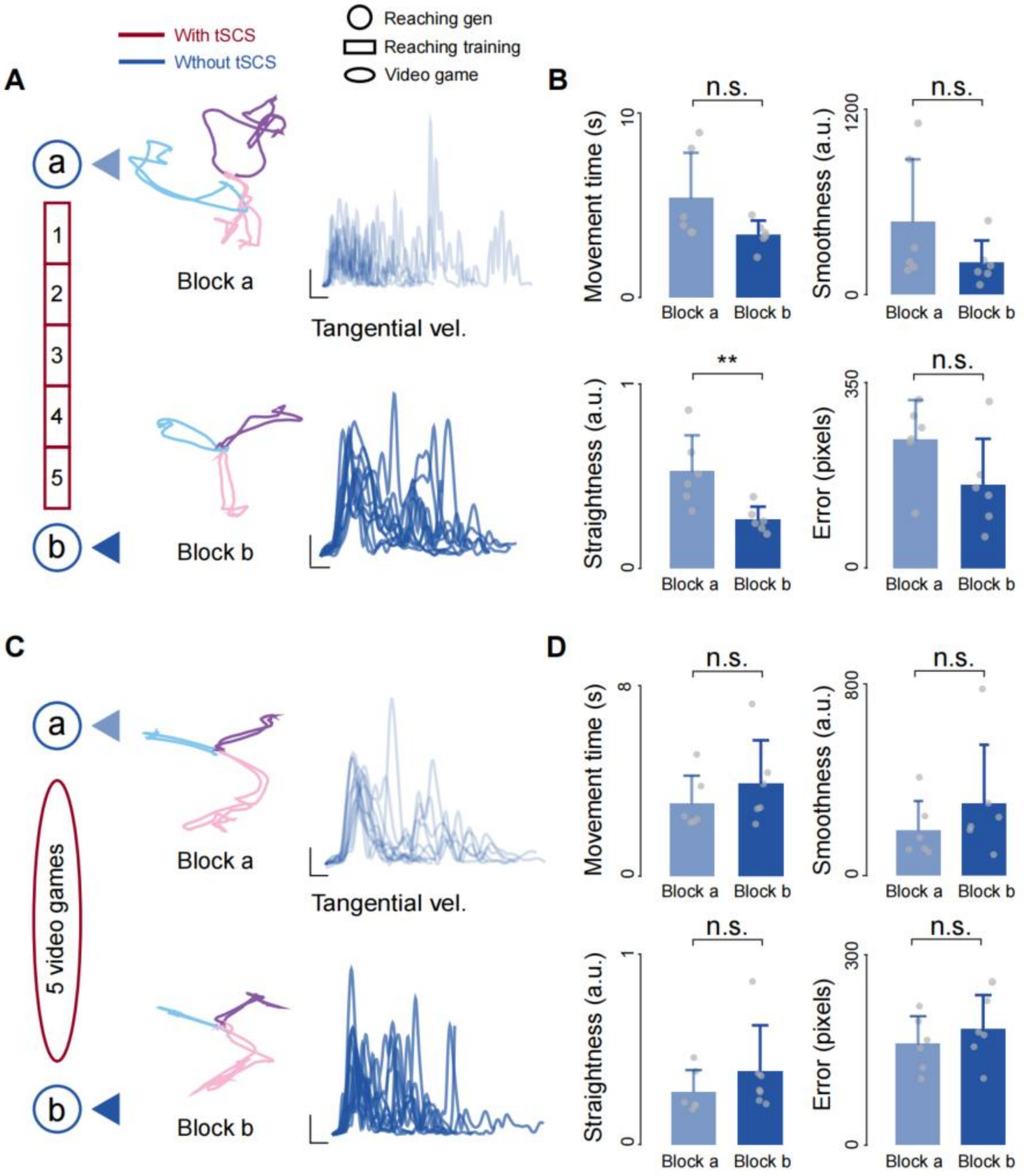


Figure 4.2 The performance of the one block of generalization before and after the training sessions for an unimpaired participant. **(A)** The reconstruction of cursor trajectory and tangential velocity of one block of generalization before and after the training session with reaching. Rectangles: five reaching training tasks within a training session, circles: one block of generalization before and after the training session, oval: the training session with video games. **(B)** The quantified performance of one block of generalization before and after the training sessions with reaching based on four evaluation metrics. Light blue bar: one block of generalization before a training session, dark blue bar: one block of generalization after the training session. **(C)** The reconstruction of cursor trajectory and tangential velocity of one block of generalization before and after the training sessions with 2D video games. **(D)** The quantified performance of one block of generalization before and after the training sessions with video games based on four evaluation metrics.

The statistical analysis is presented in Figure 4.2B and Figure 4.2D. Figure 4.2B evaluates the difference in generalization performance between different training strategies. The results reveal a significant difference between the first and the second generalization blocks while training with reaching tasks only in terms of straightness ($p = 0.0043$), but not in movement time ($p = 0.065$), smoothness ($p = 0.18$), and error ($p = 0.13$). In contrast, Figure 4.2D demonstrates that there is no significant difference between the first and the second generalization blocks while training with video games across all performance metrics, including movement time ($p = 0.39$), smoothness ($p = 0.49$), straightness ($p = 0.39$), and error ($p = 0.31$). This observation indicates that the unimpaired participant who trained with the reaching tasks exhibited improvement in only one metric of generalization performance while training with the video games did not result in any performance improvement between the first and second blocks of generalization tasks.

Consequently, to further investigate the impact of training with 2D video games on BoMI control performance within this unimpaired control population, we expanded our study to include a larger sample size of the unimpaired control group.

Subsequently, Figure 4.3A presents the performance at the pre-and post-training generalization blocks for both training with center-out reaching and training with video games. Both solid lines in the graph generally exhibit a downward trend, with the training performance generated by the two training strategies remaining relatively close. This observation suggests that motor training using different tools led to a gradual improvement in center-out generalization with unimpaired control groups, regardless of the different training strategies.

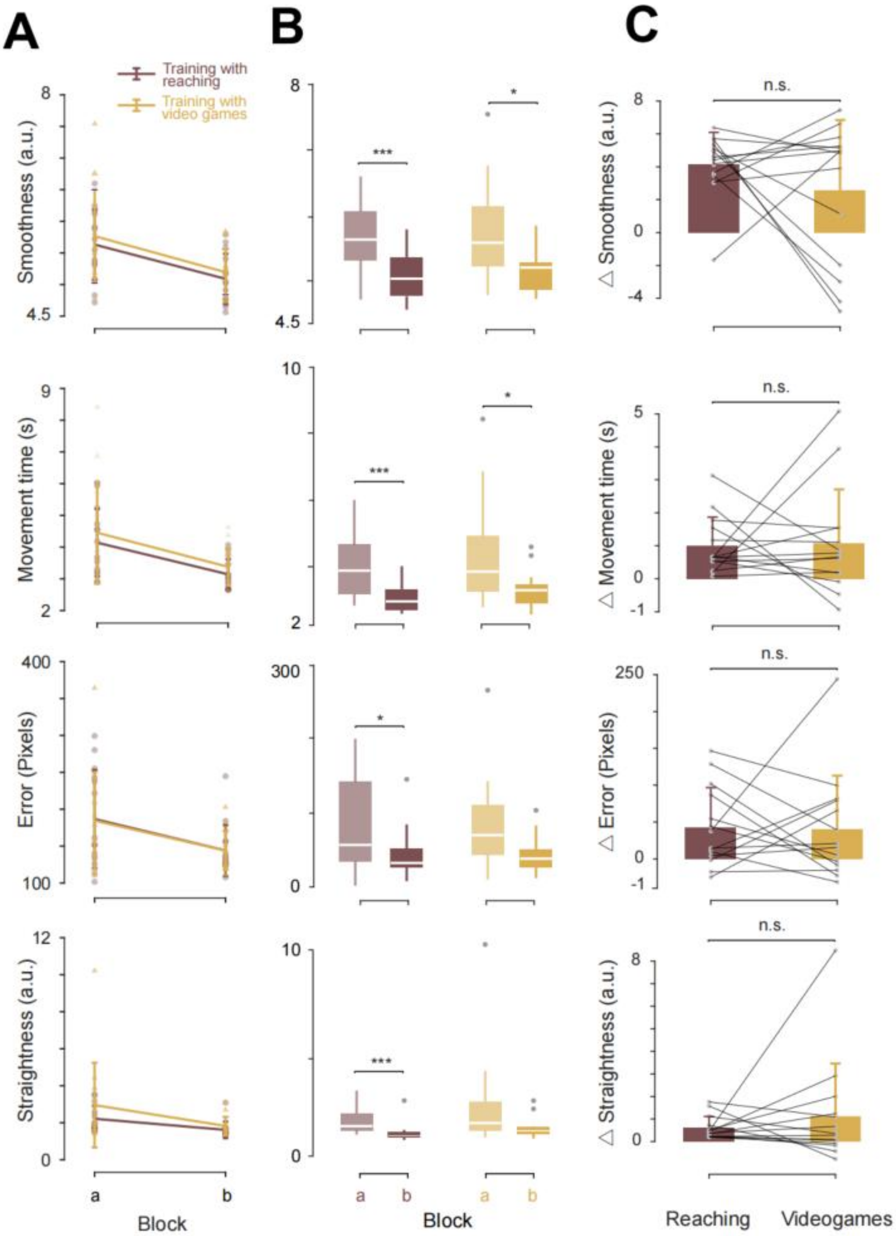


Figure 4.3 The performance and learning rate across the training sessions using different training tools in the unimpaired control group. **(A)** The quantified performance of one block of generalization before and after the training session based on four metrics. X-axis: the sequence of training blocks, Y-axis: different values of performance metrics, brown solid line: training with reaching tasks, yellow solid line: training with video games. **(B)** The BoMI performance comparison between the first and the second blocks of generalization training with different tools and the comparison between one generalization before training with reaching and one after training with video games, or one generalization after training with reaching and one after training with 2D video games. Light brown box: the performance of one generalization before training with reaching tasks, dark brown: one generalization after training with reaching, light yellow, one generalization before training with video games, dark yellow, one generalization after training with video games. **(C)** The learning rate across the training sessions with reaching tasks and video games. Brown bar plot: learning rate of training with reaching tasks, yellow bar plot: learning rate of training with video games, Y-axis: the change of performance metrics.

Figure 4.3B shows the within-condition comparison in reaching performance for both training strategies. The statistical analysis results presented in Figure 4.3B revealed a significant difference in generalization performance across all performance metrics when training with reaching tasks, including smoothness ($p = 0.00054$), error ($p = 0.00089$), movement time ($p = 0.012$), and straightness ($p = 0.00078$). In addition, there is a significant statistical difference in generalization performance after training with video games, only in smoothness ($p = 0.026$), but not in movement time ($p = 0.055$), error ($p = 0.56$), or straightness ($p = 0.094$). The results reveal that both reaching tasks and video games contribute to a significant improvement in performance of generalization tasks after the training session. However, training with reaching tasks results in a more substantial and more statistically significant enhancement compared to training with video games within this unimpaired control group.

In addition, Figure 4.3C compares the difference in learning rate generated between two blocks of generalization generated by different training strategies in the control group. The result indicates that training with both tools yielded a positive learning rate. However, no significant difference was observed in the learning rate when training with reaching tasks compared to video games.

4.3.2 Training with Video Games Generated a Significantly Better BoMI Control Performance in Participant BMS001

The performance for the first and last blocks of generalization tasks generated by different training strategies is shown in Figure 4.3. From Figure 4.3A and 4.3C, it is evident that the performance of generalization after training with 2D video games exhibited a consistent improvement across all performance metrics, whereas only minor improvements or even regressions were observed in generalization performance after training with reaching.

The statistical analysis results presented in Figure 4.3B display that there is a significant difference in performance between one generalization block before training with reaching and another block after training with video games in specific performance metrics, including smoothness (p = 0.012), movement time (p = 0.015), and straightness (p = 0.039), but not in error (p = 0.18). However, no significant differences were found in BoMI performance between one generalization block before training with reaching and another block after training with reaching in all performance metrics, including smoothness (p = 0.075), movement time (p = 0.32), error (p = 0.94), and straightness (p = 0.37). These results demonstrate that although training with reaching tasks and video games achieved a similar final generalization performance, training with video games generated a better and significant improvement task than training with reaching tasks within participant BMS001.

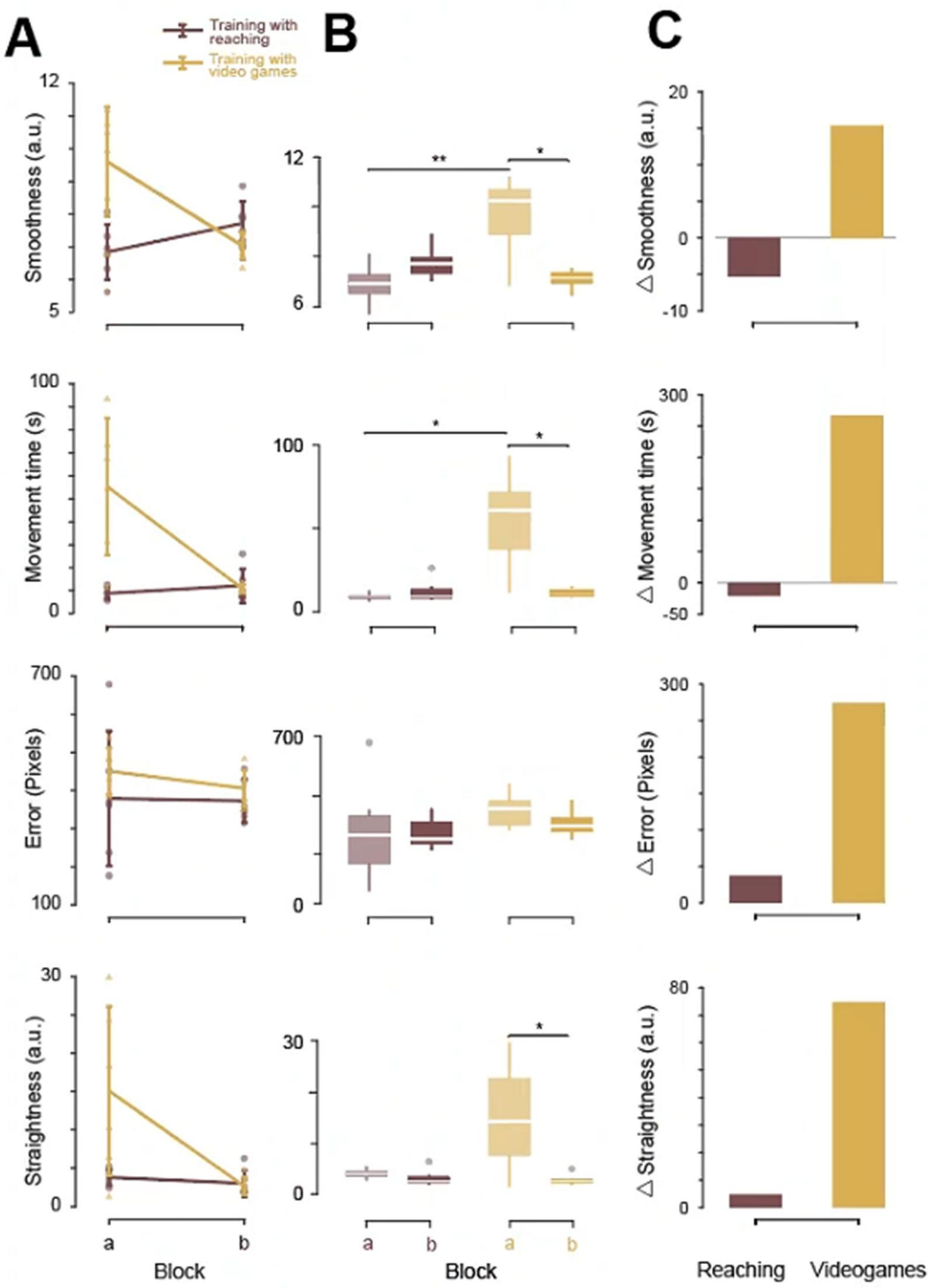


Figure 4.4 The performance and learning rate across the training sessions using different training tools in BMS001. **(A)** The quantified performance of one block of generalization before and after the training session based on four metrics. **(B)** The BoMI performance comparison between the first and second blocks of generalization training with different tools and the comparison between one generalization block before training with reaching and one after training with 2D video games, or one generalization after training with reaching and one after training with video games. **(C)** The learning rate across the training sessions with reaching tasks and video games.

4.3.3 Training with Video Games Generated Positive Improvement in BoMI Control and Achieved Similar Performance to Training with Reaching Tasks on BMS002

The generalization performance by different training strategies in BMS002 is shown in Figure 4.4. This figure indicates that although the generalization performance after training with two different strategies slightly improved, these improvements were not statistically significant. Moreover, there were no significant differences in generalization performance between training strategies before or after training session. This finding illustrates that training with both training strategies did not generate a significant improvement in performance of generalization tasks after training sessions for participant BMS002.

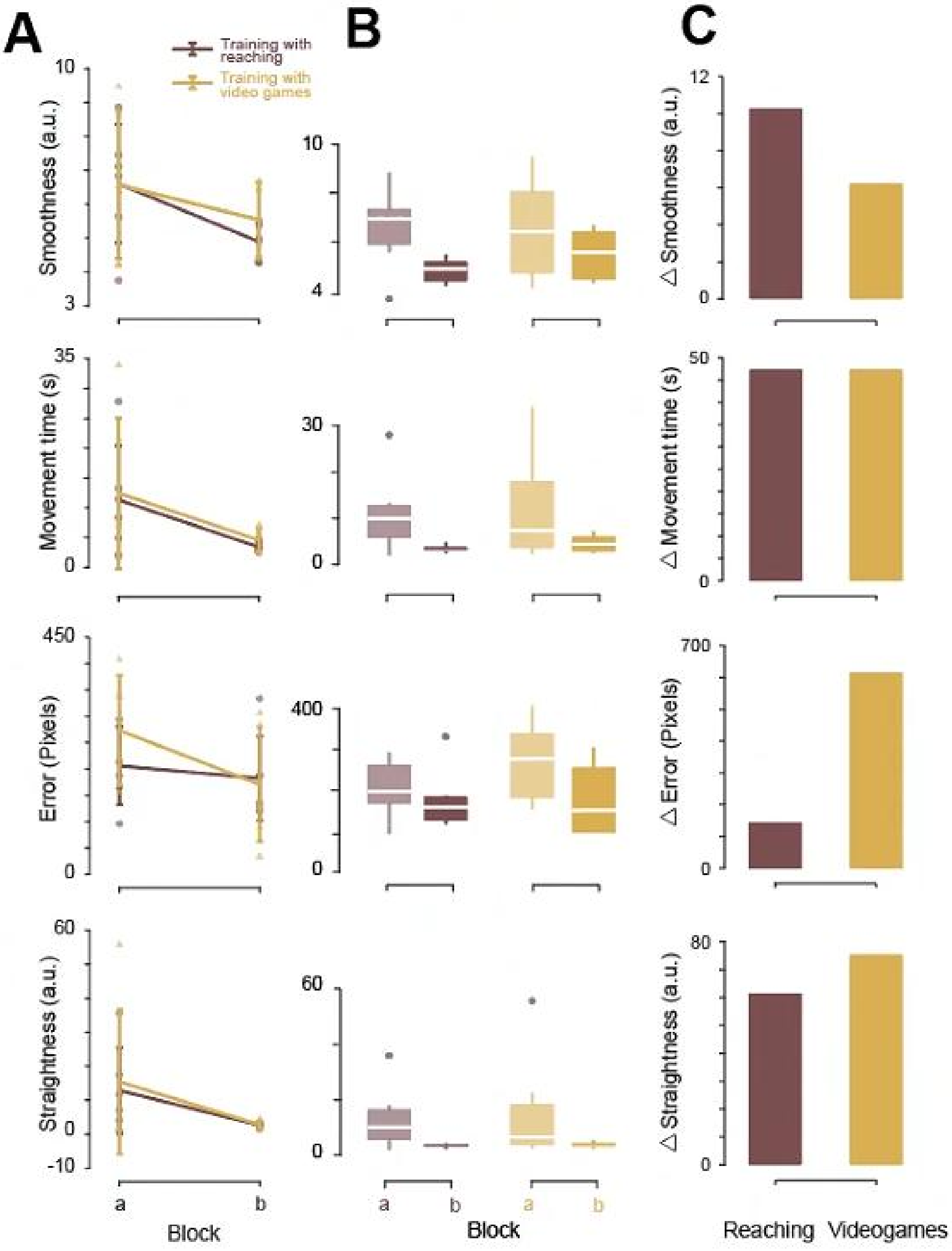


Figure 4.5 The performance and learning rate across the training sessions using different training tools in BMS002. **(A)** The quantified performance of one block of generalization before and after the training session based on four metrics. **(B)** The BoMI performance comparison between the first and second blocks of generalization training with different tools and the comparison between one generalization block before training with reaching and one after training with video games, or one generalization block after training with reaching and one after training with 2D video games. **(C)** The learning rate across the training sessions with reaching tasks and video games.

4.3.4 Both Unimpaired Participants and Individuals with SCI Improved Game Performance in tSCS-assisted Video Games Training

In order to examine the potential influence of tSCS on the improvement in video games play for both the unimpaired control group and individuals with SCI during the video game training day, we conducted a statistical comparison between the first and last trial/blocks for each game (Figure 4.5). From Figure 4.5, it can be observed that for the unimpaired group, participants demonstrated statistically significant improvements in the Pong ($p = 0.045$), Slicing (0.016), Link ($p = 0.00049$), and Snake games ($p = 0.011$). For the Maze games played at the start and end of the 45 minutes video game training session, we identified statistically significant differences in the performance of the Maze game between the beginning and end of the training session ($p < 0.001$). This finding suggests that these five video games contributed to significant improvements in game performance with the unimpaired control group.

Figure 4.6 illustrates the performance improvement of each game for the two participants with SCI. Neither participant exhibited improvements in the Maze game. However, BMS001 demonstrated enhanced performance in the Slicing game, Snake game, and Link game, while BMS002 showed improved performance in the Snake and Link games. Consequently, employing the combination of 2D video games and tSCS as a functional training tool can enhance game control performance over time for participants with SCI, and each participant may benefit from training with one type of video game vs. another.

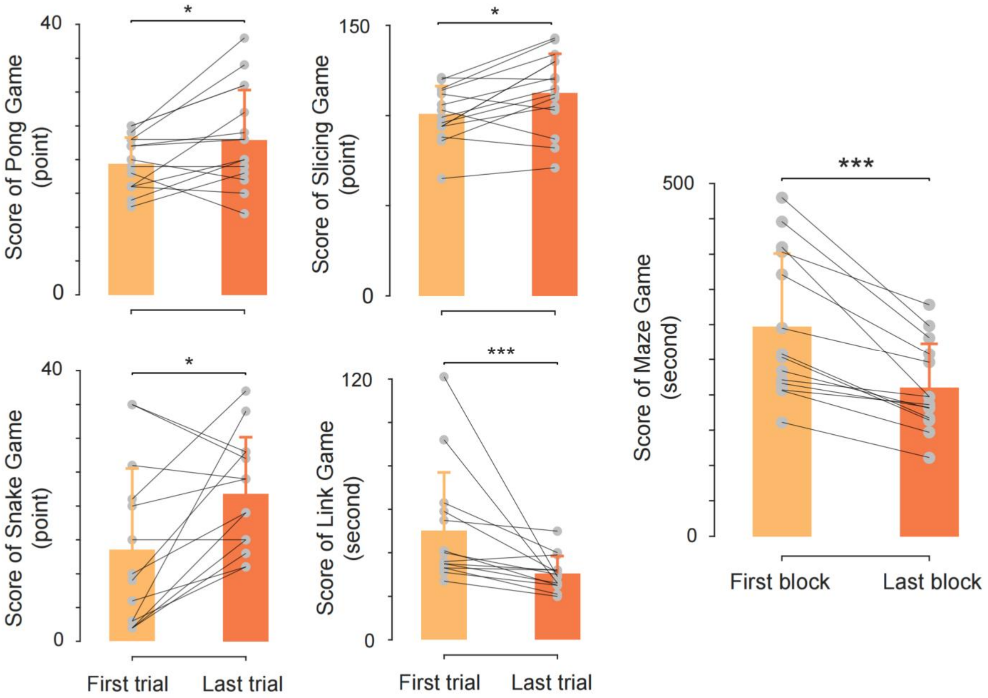


Figure 4.6 The performance comparison between the first block/trial and the last block/trial of five video games during the video games training day with tSCS in the unimpaired control group (N=14). Y-axis: the performance of different video games. Left light orange bar: the first block/trial of games, right dark orange bar: the last block/trial of games.

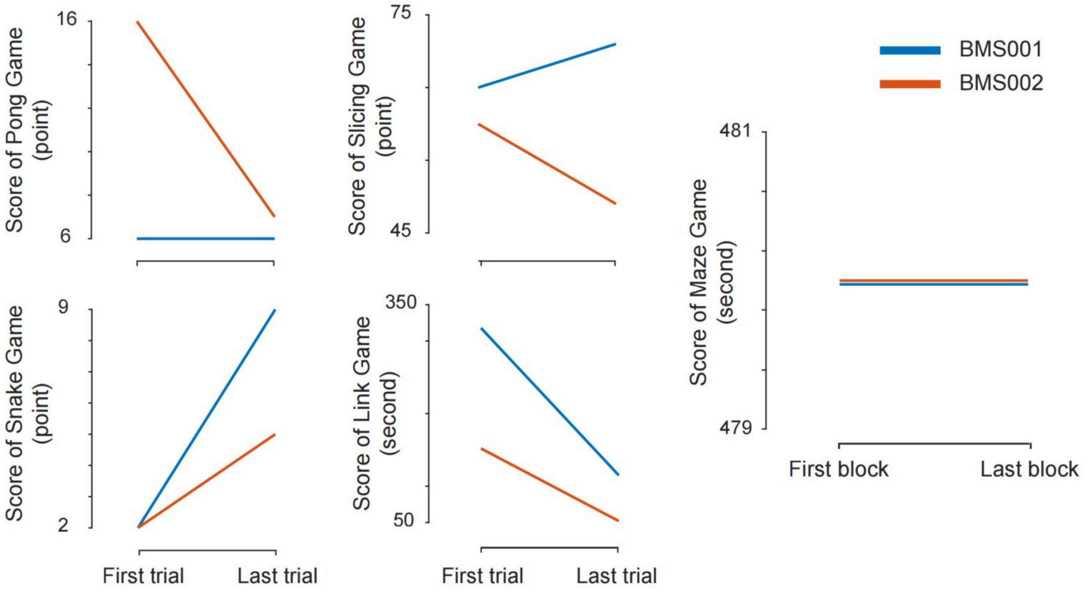


Figure 4.7 The performance comparison between the first block/trial and the last block/trial of five video games during the video games training day with tSCS for participants BMS001 and BMS002. Blue solid line: performance of BMS001, orange solid line: performance of BMS002.

Chapter 5: Discussion

In this work, we established and validated a technical framework for utilizing residual mobility in individuals with SCI for motor training and evaluated the additional potential of tSCS to further improve motor function. Our experiments further confirmed the stable, low-latency, and precise performance of a non-invasive body-machine interface in translating high-dimensional body motion data into 2D computer cursor control. The participants in this study successfully completed customized center-out reaching tasks and video games using the BoMI and tSCS. Overall, this study underscores the significance of utilizing residual mobility in individuals with SCI for motor training and the potential benefits of incorporating tSCS and video games during the motor training session along with BoMI.

5.1 BoMI Performance in the Unimpaired Control Group is Independent of Whether tSCS is Administered

In this study, unimpaired control participants were recruited to investigate the effects of tSCS on motor control in individuals with intact or injured neural pathways. The findings revealed that the learning rate was significant for unimpaired control participants, regardless of whether tSCS was used for motor training. Moreover, the learning rate was found to be independent of whether tSCS was utilized or not. In addition, we found that the comfortable amplitude of tSCS that unimpaired participants were able to tolerate during the training session was found to vary, with most being under 10 mA (8.43±4.59). Motor threshold amplitudes for tSCS were significantly higher than the amplitudes used for motor training. Analysis of the amplitude of tSCS used in training for the unimpaired control group divided by the motor threshold measured on the first experiment day versus the improvement in performance showed a low correlation between the two (Supplementary Figure 1). Additionally, some participants even regressed after training with tSCS, potentially because of the uncomfortable sensations during the application of tSCS(48), or because their motor learning abilities were not reflected in the training with specific center-out reaching tasks. Overall, the motor learning ability in the unimpaired control population was not mediated by tSCS. Which is consistent with previous research findings(79). One reason for this is that tSCS primarily affects the sensory and motor functions of the spinal cord. In unimpaired individuals, the spinal cord is functionally intact, with the unimpaired transmission of sensory and motor signals(80). Therefore, the application of tSCS does not lead to any significant improvement in motor function in healthy individuals.

5.2 The Transfer of the Effect of tSCS from Single Angle Movements to BoMI Performance Varies among Individuals with SCI

During this study, individual differences in the response to training with tSCS were observed in two participants with SCI. BMS002 showed superior BoMI control performance during training with tSCS, with evident improvement before and after training. This result directly indicates that tSCS has a positive effect on the motor control and learning rate of BMS002. This observed effect of tSCS on BoMI performance in BMS001 was found to be correlated with the range of motion test conducted on the first day of the experiment. Specifically, During the range of motion test, we found that the BMS001 had stronger muscle activity during the extension and flexion of his right hip with tSCS than without tSCS (Supplementary Figure 2). This finding shows that the facilitative effect of tSCS was successfully transferred from the individual joint angle into BoMI performance in BMS001. In contrast, BMS001 did not show significant improvement in BoMI performance at the end of the training session with and without tSCS, and the BoMI performance with tSCS was worse than without tSCS. We also didn't find an evident difference between the improvement in the range of motion test with and without tSCS for BMS001.

Overall, the impact of tSCS on motor function can vary from person to person, and it may depend on factors such as the severity and location of the spinal cord injury, as well as the individual's overall physical and other medical conditions(33,46,47,81).

5.3 Video Games are a Promising Approach for Motor Training

The 2D video game utilized in this study was designed to enhance the user's directional control, reaction time, and endurance, as well as their motor control abilities through repetition and gradually increasing difficulty levels. The results of the study demonstrated a significant improvement in BoMI performance for the unimpaired control group following both video games and reaching task training. However, the improvement was more pronounced with reaching task training, indicating its greater effectiveness for motor learning in unimpaired control participants. For individuals with SCI, both participants showed improvement after training with video games, but participant BMS001 clearly achieved a significant learning rate with video games.

There was no significant difference in the final BoMI performance achieved after training with reaching tasks and video games in either unimpaired control or SCI participants, indicating that both training methods were equally effective. This is beneficial for patients who require exercise training. Because both in the previous study and this experiment, the participants expressed that they were more motivated and patient to use video games for functional training than traditional training methods and content(82–84).

Notably, the improvement in one SCI participant's reaching task performance corresponded to the improvement seen within the 45 minutes of video games training. Participant BMS001 showed a significant learning rate in smoothness, movement time, and straightness during the reaching tasks, while also improving in the Slicing, Snake, and Link games. These video games also evaluated the participants' cursor movement speed and accuracy, indicating that the two training methods had equivalent effects.

The learning rate was observed to be higher in unimpaired control participants when training with reaching tasks compared to video games. This phenomenon may be attributed to the fact that the reaching tasks used for evaluation (generalization) and the reaching tasks used for training (reaching training) are two different types of center-out reaching tasks, but their underlying mechanisms are the same. As unimpaired control participants have an intact motor function, this similarity in assessment and training content facilitated proficiency and improvement, leading to a better learning rate during training with reaching tasks. However, this underlying similarity in the reaching task did not apply to participants with SCI. Their motor function has been partially impaired, and they may have to relearn and mobilize the residual mobility of the body to complete each task or even the same tasks. Therefore, participant BMS001 could demonstrate a significant learning rate after training with video games.

5.4 Limitations and Future Directions

The current study had a relatively small sample size of SCI participants, thus requiring the recruitment of a larger cohort to investigate the effects of tSCS and video games on this population more comprehensively. Additionally, due to the limited residual mobility of the individuals with SCI, it was challenging to transform their movements into two-dimensional cursor control. To address this, two of the four sensors were placed on the waist or shoulder to assist the lower limbs in gaining better 2D cursor control. However, this combination may also result in a partial loss of lower limb movement independence. Therefore, further modification of BoMI is needed to record this tiny residual mobility from individuals with severe SCI more sensitively and conveniently.

Although the study fully recorded the muscle activity and kinematics of all participants during training, this thesis only employed the BoMI metrics to evaluate and quantify motor control and the learning rate. Future analyses will focus on processing and analyzing data from EMG sensors and 3D motion capture systems to understand the patterns and characteristics of muscle activity during training. Lastly, this promising training framework can also be applied to other neurological disorders with motor challenges such as stroke, Parkinson's, etc., to further quantify the effect of BoMIs in other populations and develop more effective rehabilitation strategies based on study evidence and feedback.

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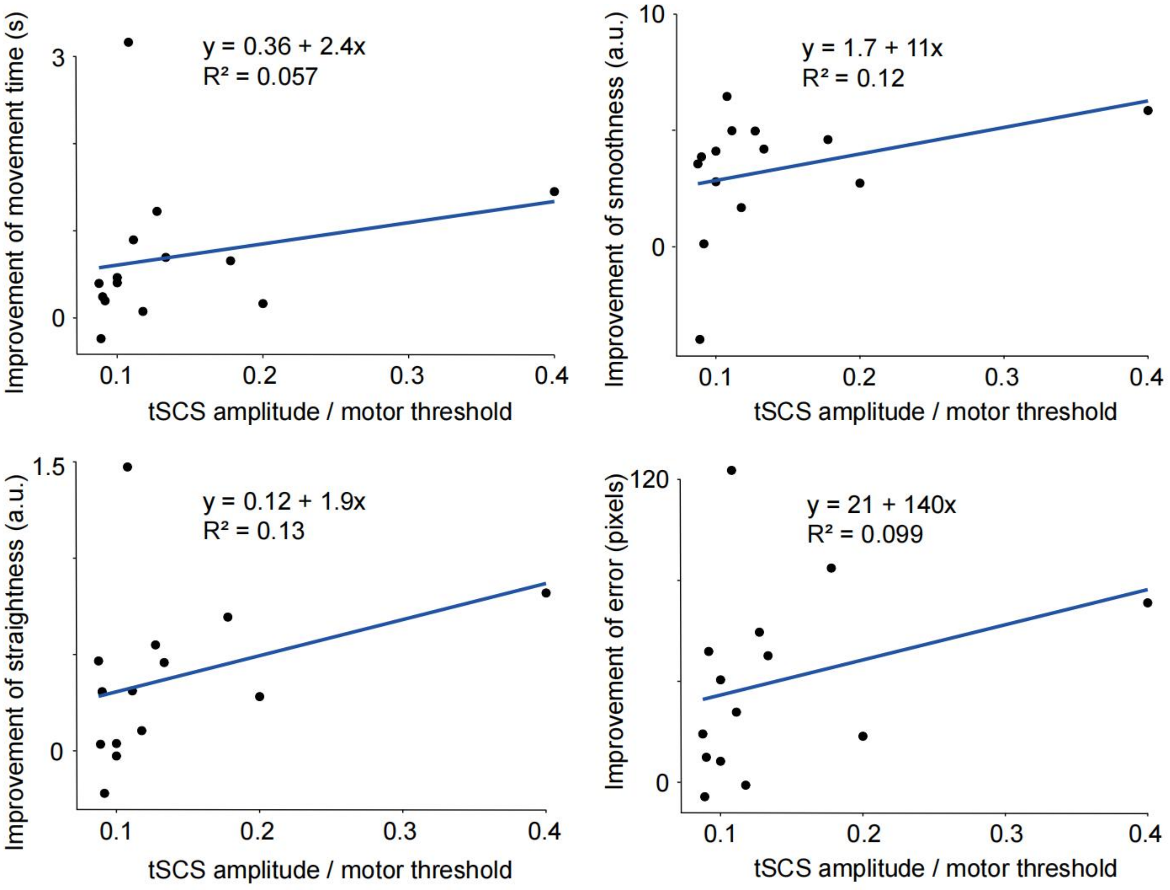
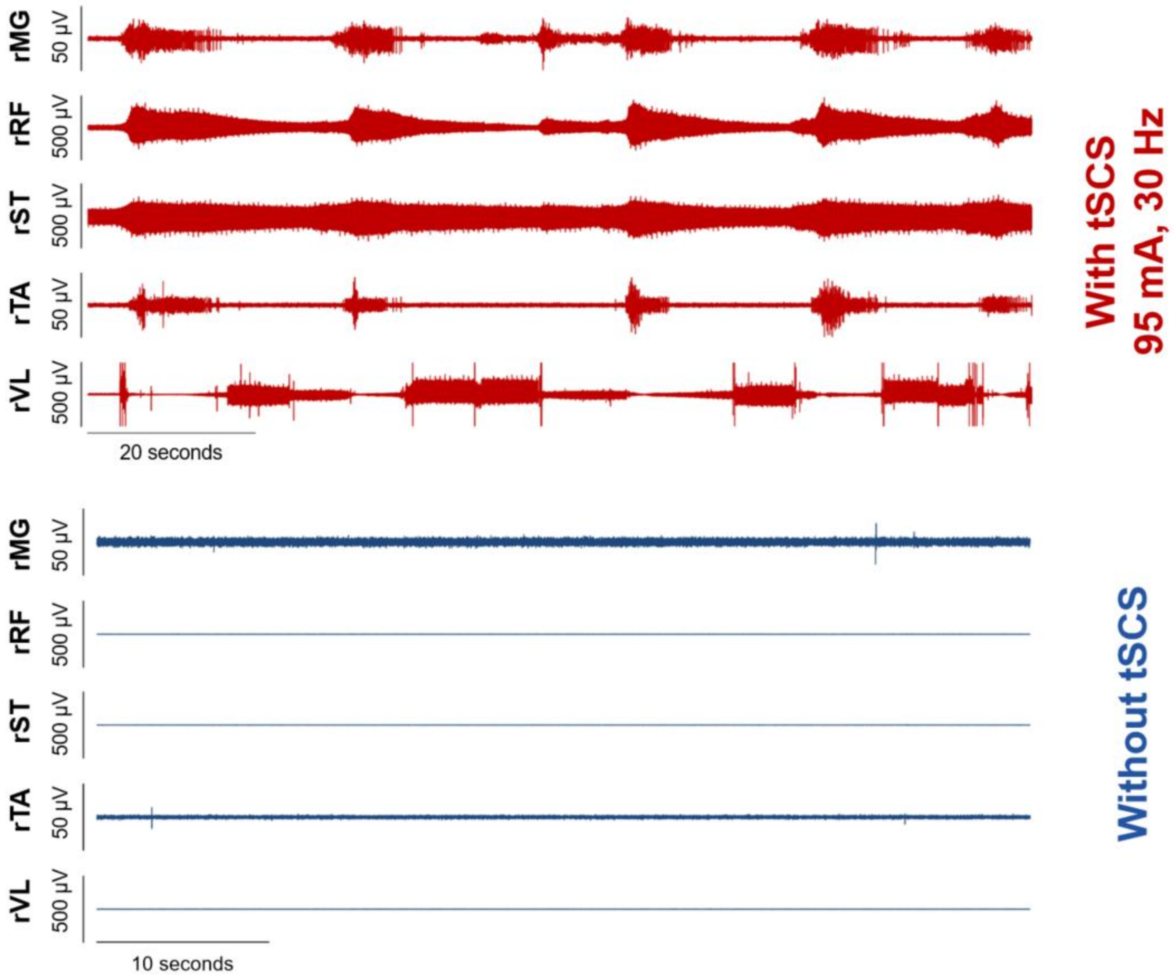
Appendix

Supplementary Figures



Supplementary Figure 1. The analysis of linear regression between the BoMI improvement and the ratio of motor threshold to motor threshold within the unimpaired control group.



Supplementary Figure 2. The muscle activity during the range of motion test of right hip with and without tSCS in BMS002. rMG: right medial gastrocnemius, rRF: right rectus femoris, rST: right semitendinosus, rTA: right tibialis anterior, rVL: right vastus lateralis, red line: muscle activity with tSCS at 95 mA (30Hz), blue line: muscle activity without tSCS.