Neuromodulation and Rehabilitation with Brain-computer Interfaces and Spinal Cord Stimulation

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To my mum, Margaret.

Declaration

I hereby declare that except where explicit reference is made to the contribution of others, this thesis is the result of the work of the named and has not been submitted for any other degree at the University of Glasgow or any other institution.

Ciarán A. McGeady
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Ciarán McGeady, Aleksandra Vučković, and Sadasivan Puthusserypady. “A hybrid MI-SSVEP based brain computer interface for potential upper limb neurorehabilitation: A pilot study." In *2019 7th International Winter Conference on Brain-Computer Interface (BCI)*, pp. 1-6. IEEE, 2019.

Abstract

Consequences of spinal cord injury (SCI) are often severe and life-altering. Recovery of hand and arm function is consistently reported by SCI individuals as their greatest priority in terms of rehabilitation. Yet current strategies provide poor-to-modest outcomes. Innovation is required to improve traditional approaches to upper limb rehabilitation. The current view is that, due to the multi-faceted nature of SCI pathology, effective treatment will take a combinational approach. This thesis brings together two emerging and promising technologies—transcutaneous spinal cord stimulation (tSCS) and brain-computer interfaces (BCIs)—in order to judge their complimentary nature as tools for neurophysiological assessment and rehabilitation following SCI.

There is growing evidence that cervical tSCS combined with intensive physical training can lead to lasting functional improvements in individuals with chronic SCI. The mechanisms underpinning tSCS-facilitated recovery, however, are still a matter of ongoing research, with conflicting reports of the impact of tSCS on cortical and spinal excitability. Evoked potentials and reflexes have so far been the primary method of quantifying corticospinal excitability. The research undertaken in this thesis first explores electroencephalography (EEG) as a potential complementary method for assessing neuromodulation following tSCS. Due the novelty of the research, a preliminary investigation was undertaken to establish the feasibility of EEG monitoring during cervical tSCS. In a cohort of twenty-one able-bodied individuals, it was demonstrated that tSCS presented as low-latency, high-amplitude artefacts in EEG time series, at a rate equal to the stimulation frequency. Descriptive statistics were used to characterise the impact of tSCS, and judge the effectiveness of noise-attenuation techniques. Results showed that, with artefact-suppression, EEG recorded during tSCS could be returned to levels statistically similar to that of EEG acquired without tSCS interference. Additionally, it was established that neural components, such as the individual alpha frequency, were recoverable, demonstrating the feasibility of EEG as a tool for tracking cortical activity during tSCS.

A subsequent study was conducted to investigate the neuromodulatory potential of tSCS on cortical activity. EEG was recorded during upper limb movements in 30 individuals both with and without concurrent cervical tSCS. Stimulation was delivered to the cervical region of

the neck at intensities matching the individual's highest tolerance without causing pain. It was found that cortical oscillatory dynamics were unaffected over a cohort of neurologically intact participants. However, a weak inhibitory effect was measured amoing individuals who received the highest stimulation intensities.

A final study was devised to explore the potential of movement priming for tSCS-facilitated upper limb therapy in an individual with chronic AIS A cervical SCI. Movement priming was achieved by encouraging the participant to engage in repetitive bimanual hand movements with respect to their sensorimotor cortical activity as measured with EEG. A BCI provided real-time feedback of the participant's motor engagement in the form of a computer game, allowing them to actively engage regardless of impairment level. The participant first underwent an initial phase of 15 sessions of tSCS training alone followed by a second phase of 15 sessions of BCI priming and tSCS training. The participant's strength and dexterity improved across both phases of the study. BCI priming may have contributed to an enhanced effect in some measures such as improved bilateral finger strength, but due to mixed results across functional measures no firm conclusions can be drawn. Nevertheless, the functional improvements lend greater credibility to cervical tSCS as a strategy for upper limb rehabilitation.

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Nomenclature

Roman Symbols

A	Amps
N	Newtons
V	Volts

Greek Symbols

Ω	Ohms

Acronyms / Abbreviations

AIS	American Spinal Injury Association Impairment Scale
ASIA	American Spinal Injury Association
CSP	Common Spatial Pattern
EEG	Electroencephalography/Electroencephalogram
EMG	Electromyography/Electromyogram
ERD	Event-related Desynchronisation
ERS	Event-related Synchronisation
GRASSP	Graded Redefined Assessment for Strength, Sensibility, and Prehension
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
LDA	Linear Discriminant Analysis
LT	Light Touch

MAS	Modified Ashworth Scale
MDD	Minimum detectable difference
NLI	Neurological Level of Injury
NMES	Neuromuscular Electrical Stimulation
PP	Pin Prick
PRM	Posterior root-muscle
SCIM	Spinal Cord Independence Measure
SCI	Spinal Cord Injury
SCS	Spinal cord stimulation
SMA	Superposition of Moving Averages
tACS	Transcranial Alternating Current Stimulation
tSCS	Transcutaneous Spinal Cord Stimulation
UEMS	Upper Extremity Motor Score
ZPP	Zone of Partial Preservation

Chapter 1

Introduction

1.1 Rationale

Spinal cord injury (SCI) often results in a disruption to the brain's ability to convey sensory and motor information to the rest of the body, resulting in weakness or complete paralysis of the upper and lower limbs. Loss of function can have severe consequences on affected individuals as they lose the ability to independently undertake activities of daily living. In the United Kingdom, there are around 1270 new cases of traumatic SCI every year [3]. The lifetime cost of a single case can range from £0.47 million to £1.87 million depending on the extent of the injury. Beyond economic factors, SCI can have a devastating, life-altering impact on the injured and their families. Due to the important role upper limb function plays in carrying out everyday tasks, its recovery is consistently reported as the highest priority of SCI individuals. Yet current rehabilitation strategies offer modest outcomes at best. This thesis aims to explore emerging strategies for promoting upper limb recovery after SCI.

The following chapter provides context to the research undertaken. It begins by outlining the nature of SCI, its pathology and classification, and current approaches to rehabilitation; also introduced is the concept of motor priming, a potential strategy for enhancing rehabilitation outcomes; electrophysiology and its relation to brain-computer interfaces and neurorehabilitation; and finally, transcutaneous spinal cord stimulation, a novel strategy for improving upper limb rehabilitation.

1.2 Spinal cord injury

The spinal cord is a tubular structure of nervous tissue that conveys nerve signals between the motor cortex and the muscles of the body, and between sensory organs and the sensory cortex [4]. The spinal cord is enclosed in bony vertebra as it extends from the medulla oblongata in the brainstem to the lumbar region of the vertebral column. There are 31 nerve segments of the human spinal cord; eight cervical, 12 thoracic, five lumbar, five sacral, and one coccygeal. Pairs of sensory and motor nerve fibres branch off at each segment (with the exception of the coccygeal segment), forming the peripheral nervous system [4].

SCI is typically acquired through physical trauma—from a car accident, violence, falls, or recreational activities [5]. Traction and compressive mechanical forces damage the neural tissue of the spinal cord, leading to cell death around the site of injury, including neurons, astrocytes, microglia, olgiodentrocytes, and endothelial cells. Critically, long axonal projections are damaged, limiting or ceasing the ability of ascending and descending pathways to convey information between the brain and the rest of the body. Secondary damage occurs in the months-to-years following injury, as damaged cells, axons, and blood vessels release toxic chemicals that attack healthy neighbouring cells, worsening the initial pathology [6, 7].

SCI can affect nearly every physiological system: musculoskeletal, respiratory, sympathetic, cardiopulmonary, urinary, and reproductive. Pathology varies widely across the population and depends on factors such as spinal level affected and completeness of injury [5]. Cervical SCI, which occurs following damage to one of the cervical spinal segments (C1–C8), may lead to tetraplegia, impairment of all four limbs.

Classification schemes have been created to quantify the consequences of SCI in order to guide treatment. The American Spinal Injury Association (ASIA) developed what is now the gold standard for SCI classification: The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), which includes the ASIA Impairment Scale (AIS) [8]. The assessment consists of a myotomal-based motor examination, dermatomal-based sensory examination, and anorecal examination (Figure 1.1; see also Appendix A.1). This information informs the assigned level of injury. The sensory examination involves grading 28 dematomes using a three-point scale (between zero and two) for light touch and pin prick sensation. The motor examination uses a six-point scale (between zero and five) to grade strength in five muscles in the upper extremities and five muscle in the lower extremities. Deep anal pressure is also measured to determine completeness of the injury. The neurological level of injury (NLI) is defined as the most caudal spinal segment with intact sensation and muscle function (of at least three points) provided there is normal sensory and motor function rostrally.

AIS then distinguishes between a complete and incomplete injury. A complete SCI is defined as the total absence of motor and sensory function below the spinal level of injury, including sacral roots and deep anal pressure. These injuries are known as Grade A, or AIS A, and are often the most severe and life-altering. Where there is some spared motor or sensory function below the level of injury, the injury is classified as incomplete. AIS B to AIS E are potential incomplete classifications. AIS B reflects some spared sensation below the neurological level of injury but no motor function. AIS C injuries have preserved motor function below the neurological level of injury, with more than half of key muscles scoring fewer than three points. Whereas, AIS D injuries have greater control with at least half of key muscles having a score of at least three. AIS E patients have normal motor and sensory function but display some sort of pathological neurological function. Lastly, ISNCSCI defines a further metric for injuries with absent motor or sensory function in lower spinal segments called the Zone of Partial Preservation (ZPP). It refers to the dermatomes and myotomes caudal to the sensory and motor levels that remain partially innervated.

Although the ISNCSCI has become a standard method for classifying SCI, it does not give an indication of motor ability beyond strength, nor does it always provide the sensitivity necessary to document subtle changes in functional outcomes. For research seeking to specifically evaluate upper-extremity recovery after cervical SCI, other metrics are often used in parallel with the ISNCSCI. The Graded Redefined Assessment for Strength, Sensibility, and Prehension (GRASSP) was created to address this lack of sensitivity and provide a robust measure of neurological status in order to substantiate neurological recovery [9]. GRASSP is organised into three domains central to upper extremity function: Strength, Sensation, and Prehension. Similar to ISNCSCI's motor category, the Strength sub-test grades the strength of key upper extremity muscles. The sensibility sub-test measures sensation on the dorsal and palmar side of the hands using Semmes-Weinstein monofilaments. Lastly, Prehension grades the SCI individual's ability to perform functional tasks–pouring water from a bottle, placing a key in a lock, inserting coins into a slot, to name a few. Summing scores across each domain gives an indication of the individual's hand and arm function. The GRASSP worksheet is provided in Appendix A.2.

Other metrics have been devised to measure other facets of SCI pathology. The Modified Ashworth Scale (MAS) is used to quantify spasticity by passively moving muscles through a range of motion and grading the quality of movement [10]. A score of zero is awarded where no spasticty is detected, whereas a score of four is given under velocity-dependent resistance to movement (See Appendix A.3 for MAS worksheet). Finally, the Spinal Cord Independence measure (SCIM) is a questionnaire completed by the SCI individual to quantify their level

of independence in the home environment. Categories include self-cafe (feeding, bathing, dressing etc.), and mobility (ability to transfer from bed to a chair, reliance on walking aids or wheelchairs etc.) [11]. See Appendix A.4 for SCIM worksheet.

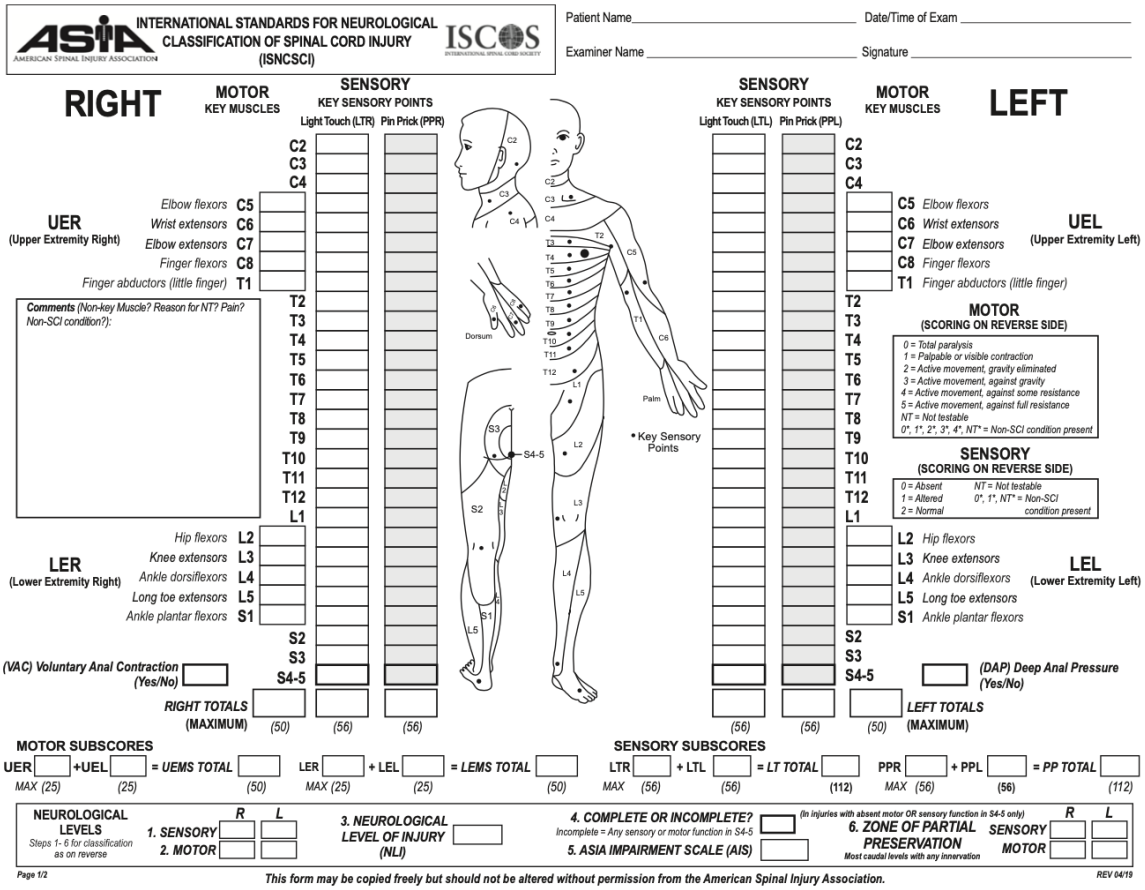

Fig. 1.1 The American Spinal Injury Association International Standards for Neurological Classification of Spinal Cord Injury worksheet used to evaluate spinal cord injury. (American Spinal Injury Association. International Standards for Neurological Classification of Spinal Cord Injury. Atlanta, GA, Revised 2011, Updated 2015. Published with permission of the American Spinal Injury Association, Richmond, VA, USA.)

1.3 Current approach to rehabilitation

In the acute stages of a SCI, focus is placed on minimising further neurological damage to the spinal cord and optimising recovery. The spine is stabilised with bed rest or surgery in order to reduce traction or compressive forces [5]. Once a SCI patient is medically stable—which may take days to weeks, depending on any other injuries the patient may have sustained—a

rehabilitation program follows. The precise goals of this rehabilitation is dependant on the particulars of the individual but ultimately a return to a productive and satisfying life is the main focus. The expectations of physiotherapists and patients on realistic outcomes plays a large part in guiding rehabilitation programs. For example, whether a patient can regain the ability to walk at one year post-injury can be predicted by five variables recorded in the weeks following injury: age, quadriceps strength, light touch sensation at L3, and light touch sensation at S1 [12]. Typically, after stability has been reached, focus is placed on passive exercises to prevent muscle atrophy, joint contractures, stiffness and reducing pain, and muscle strengthening exercises to help with transfer between bed and wheelchair [13]. SCI rehabilitation may not target restoration of movement as a goal. Instead training compensatory strategies to perform tasks, for instance, practicing a tenodesis grasp.

In general, traditional rehabilitation of the upper limbs following SCI has modest outcomes at best [13, 14]. There is a great need to explore emerging technologies as potential strategies for devising new or augmenting traditional rehabilitation approaches. Following a period of spontaneous recovery, further meaningful recover is rare [14]. Research has shown, however, that even in cases of complete SCI, there are often intact descending neurons that pass the site of injury [15]. This is termed discomplete SCI and occurs in 80% of complete injuries. Spared pathways represent an opportunity for further recovery and indeed partially form the basis for much activity-based restorative therapies.

1.4 Motor priming

The notion of priming to facilitate motor learning is a relatively novel concept in the area of rehabilitation. Originating in the field of psychology, priming is a phenomenon whereby one stimulus influences the response to a second stimulus [16]. In the context of neurorehabilitation, priming refers to interventions that seek to perturb the central and/or peripheral nervous system into a state more pliable to a subsequent restorative therapy [17, 18]. Priming strategies which closely resemble the subsequent therapy are known as modal-specific priming. For example, movement-based priming may have an individual perform repetitive movements with their weakened limbs before engaging in conventional physical practice. Cross-modal priming, on the other hand, is where interventions are dissimilar. For example, semantic priming, the reading of words related to movement, can have a positive effect in producing movement in neurologically-intact individuals [19]. However, it is understood that cross-modal priming offers smaller effects than modal-specific applications.

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Priming is predicated on the understanding that elevated neural activity immediately prior to, for instance, physical practice, can promote mechanisms like long-term potentiation (LTP), or long-term depression (LTD). The precise neural mechanisms depend on the form of priming, but generally, priming seeks to increase corticospinal excitability or normalise inhibition, in order to facilitate motor function. Priming strategies most pertinent to motor rehabilitation include stimulation-based priming [20], motor imagery and action observation priming, manipulation of sensory input, movement-based priming, and pharmacologically-mediated priming.

Stimulation-based priming uses magnetic (repetitive transcranial magnetic stimulation: rTMS), or electrical (transcranial direct current stimulation: tDCS; peripheral nerve stimulation: PNS) stimulation, or a combination of both (paired associative stimulation: PAS) to alter the excitability of corticospinal networks. Although rTMS has been shown to induce long-term after effects on cortical excitability, studies have not found it to be effective at enhancing the effects of conventional physical therapy [21]. On the other hand, tDCS, which passes a low-intensity electric current through electrodes on the scalp, has been reported to enhance the efficacy of stroke rehabilitation training when administered immediately before therapy [20]. Priming protocols have targeted upregulation of the ipsilesional hemisphere and/or downregulation of the contralesional hemisphere and functional effects have been reported up to 3 months after the intervention [20, 22].

Motor imagery is a form of mental practice that involves representing a motor action in the 'mind's eye' without overt motor output, and has been shown to increase cortical activity in the motor areas responsible for the action [23]. Studies have shown that motor imagery is specific to the imagined muscle movement; that is, excitability is elevated between the cortical representational area and imagined musculature only, facilitating only training involving that particular muscle. This has been demonstrated using transcranial magnetic stimulation (TMS) [24]. A Cochrane review concluded that motor imagery appeared beneficial in improving the effects of upper limb training after stroke [25]. It was highlighted, however, that the reviewed studies tended to have small sample sizes, with heterogeneous intervention designs. In addition to motor imagery, which may be termed explicit motor imagery, implicit motor imagery—for example, the mental rotation of the hand—has also been shown to activate similar sensorimotor brain regions [26].

Movement-based priming involves any form of repetitive or continuous attempted or actual movement that is intended to facilitate the effects of a subsequent therapy [18]. Movement-based priming is not task-orientated, instead it involves non-functional repetitions of movement. Movements may be unimanual, bimanual, active or passive, and single or multi-jointed. The most widespread form of movement priming concerns bimanual upper limb priming combined

with traditional physiotherapy for post-stroke rehabilitation [27–29]. This consists of the unaffected wrist driving mirror-symmetric movements of the paretic limb via an assistive device [30]. A randomised controlled trial by Stinear *et al.* split 57 individuals with a first-ever subacute ischemic stoke into two groups: A priming group that involved device-assisted mirror-symmetric bimanual wrist flexion-extension before upper limb physiotherapy, and a control group which received placebo-like cutaneous electrical stimulation before physiotherapy [29]. The work concluded that the primed participants were three times more likely to reach a motor function recovery plateau by 12 weeks post-stroke [29].

Recent research suggests that gamification, the structuring of priming to resemble a game, with elements such as competition or point-scoring, can encourage participants to fully engage with a movement priming task, and limits physical and mental fatigue [31]. Some studies have reported that a gaming paradigm that hinges on synchronised visuomotor control can itself contribute to increased corticomotor excitability due to increased visual attention and procedural learning [32, 31]. Lim *et al.* had stroke survivors participate in game-based movement priming of the lower limb. Using a wearable motion tracking system, ankle movement was used to control a computer game. Corticomotor excitability, as measured by TMS, was found to have increased by 25% following 20 min of priming but remained unchanged following 20 min of rest, however, no change in motor performance was measured, likely because a subsequent physical training was not performed.

In conclusion, combining priming and task-orientated upper-extremity training appears a promising avenue of research for motor rehabilitation. Although the majority of studies reported above pertain to rehabilitation following stroke, owing to far greater prevalence of stroke compared to SCI, the research may also be applicable in a SCI rehabilitation context. Methods for enhancing corticospinal excitability through voluntary engagement can have a positive impact on SCI rehabilitation protocols, hence the studies reviewed can serve as a basis in which to approach motor restoration following SCI.

1.5 Electrophysiology

Following SCI, motor commands are partially or completely disrupted from reaching their target muscles. The cortical substrate which instantiate these commands, however, remains functional. Electrophysiology allows for brain activity to be monitored and can provide insight of underlying neural processes. One of the most common techniques to monitor brain activity is electroencephalography (EEG). EEG uses electrodes to record the electrical activity on the scalp which is used to infer neurophysiological processes. Brain activity measured through

EEG can provide valuable clinically relevant information, and can be used as a control signal to control with external devices.

EEG signals arise, in part, from the action of neurons [33]. Neurons are cells that possess electrical properties that allow them to convey information over long distances via their axonal processes. They are electrically polarised by around -60 mV relative to the extra-cellular environment. This resting potential is supported by the balance of ions both inside and outside of the cell. Specifically, potassium (K^+) and chloride (Cl^-) ions are found in high concentrations within the neuron, while sodium (Na^+) and calcium (Ca^{2+}) ions are typically kept outside. The resting potential is perturbed by the influx and efflux of ions through small pores within the neuronal membrane. For example, when Na^+ channels open, Na^+ enters the neuron, resulting in a linear increase in membrane potential, called depolarisation. After a critical volume of Na^+ enters the neuron, however, additional Na^+ channels will open, causing a rapid and non-linear increase in Na^+ entering the neuron. This rapid influx results in the transmembrane potential quickly depolarising to around 20 mV. This fast spike in electrical membrane potential is the rising phase of what is known as the action potential. The positive voltage level triggers the closing of Na^+ channels, followed by the removal of Na^+ from inside the neuron, and the return to a resting state. To return to the resting potential more rapidly, K^+ channels open to allow K^+ efflux, which quickly repolarises the neuron, and results in the falling phase of the action potential. Once initiated, the action potential can extend throughout the entire neuron which may traverse long distances and influence other neurons to fire action potentials. Despite the action potential creating a relatively large electric and magnetic field across the neuron, its contribution to EEG is considered negligible [33, 34].

When an action potential fires it results in neurotransmitters being released into a thin gap between the end of one neuron and beginning of another. This interface, called the synapse, is composed of the presynaptic membrane of the neuron which has undergone an action potential, and the postsynaptic terminal of a target neuron. The presynaptic terminal releases neurotransmitters which bind to receptors on the surface of the postsynapic terminal. Neurotransmitters affect the ion channels present on the postsynaptic terminal, which in turn will disturb the resting membrane potential and may lead to the triggering of an action potential. Cortical pyramidal neurons release a neurotransmitter called glutamate, termed an excitatory neurotransmitter, as it depolarises a target neuron. Conversely, the opposite effect occurs when GABA, an inhibitory neurotransmitter, hyperpolarises the post-synaptic resting membrane. An excitatory postsynapic potential (EPSP) results from depolarisation follows the release of neurotransmitters, and an inhibitory postsynaptic potential (IPSP) results from hyperpolarisation. Compared to the action potential, EPSP and IPSP are smaller in amplitude

but, crucially, they last much longer (tens of milliseconds, compared to the < 1 millisecond duration of an action potential). It is for this reason that their contribution to EEG is so significant [33]. It is the linear sum of the vast number of overlapping fields generated by EPSP and IPSP that can be measured inside and outside of the brain.

An EEG signal is a complex waveform (see Figure 1.2A) consisting of the superposition of multiple oscillating components. It can be decomposed into an appropriate combination of sine waves using a technique called Fourier analysis. The amplitudes of these constituent waves can be represented in a form illustrating their relative spectral contribution to the overall signal; this is known as the power spectrum (see Figure 1.2C). This method allows the signal to be transformed from the time domain to the frequency domain, allowing subsequent analysis. The frequency representation of EEG loses its connection to time information, however. To address this, Fourier analysis typically divides EEG into multiple short, often overlapping, temporal epochs before transforming into the frequency domain. Both temporal and spectral (frequency) information can be visualised (See Figure 1.2D). EEG is generally understood in terms of its main frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (13–30 Hz), and gammma (30–100 Hz) [35]. The alpha and beta bands are most pertinent to this thesis due to their relationship to movement-related activities [36].

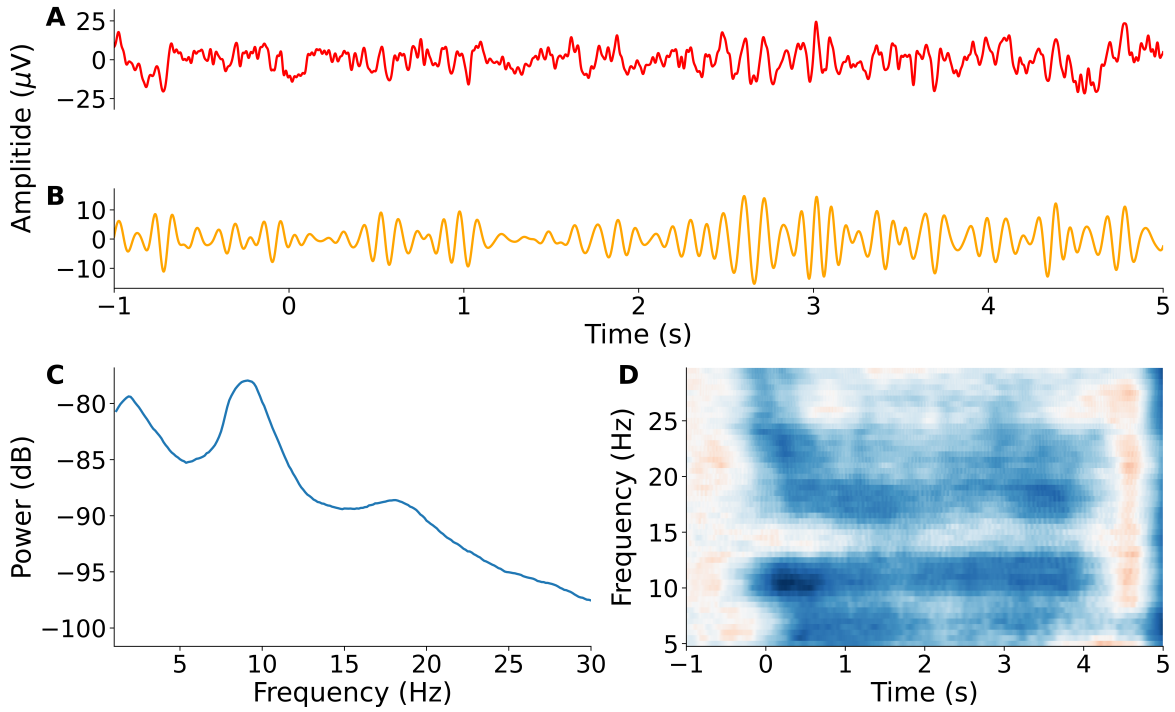

Fig. 1.2 Example of author's electroencephalogram. **(A)** Raw EEG from the sensorimotor area during a movement task. **(B)** Filtered EEG between 8 and 12 Hz, isolating the alpha frequency band. **(C)** Power spectral density between 1 and 30 Hz. Notice the '1/f' shape and prominent oscillatory power at around 10 Hz. **(D)** Time-frequency representation of alpha- and beta-band event-related desynchronisation during hand movement. Repetitive finger flexion-extension begins at $t = 0$ s, causing a reduction in alpha- and beta-band power (indicated in blue) relative to a pre-movement rest period ($t < 0$). Red indicates a power increase compared to baseline, known as event-related synchronisation (ERS). Notice ERS occurs immediately after movement cessation at $t = 4$ s.

The power spectrum of EEG typically follows a '1/f' shape, where f is frequency; that is, the amplitude of brain oscillations tend to be negatively correlated with their frequency. This shape is usually interrupted by a prominent peak at around 10 Hz. This is known as the individual alpha frequency, and is one of the most studied components of EEG, having been discovered in the 1930s by Hans Berger [37]. The alpha frequency has been associated with a wide range of neurophysiological phenomena—this thesis is interested in its connection to motor activity. The alpha and beta rhythms are typically considered to extend from around 8 to 12 Hz, and 13 to 30 Hz, respectively [36, 35].

It has been well established that the movement—and indeed, imagined movement—results in alpha- and beta-band power modulation over sensorimotor areas [36]. Sensorimotor rhythm suppression has been reported to begin up to 2 seconds before movement onset in a process

known as event-related desynchronisation (ERD). ERD reflects cortical areas losing synchrony as they engage in specific motor-related task processing. ERD is therefore considered a correlate of cortical activation [38]. As well as being frequency-band specific, ERD displays distinct spatial patterns depending on the type of movement. For instance, alpha-band ERD is most prominent over the contralateral sensorimotor area during unimanual wrist flexion-extension. Following movement cessation, beta activity is seen to increase, termed event-related synchronisation (ERS), and reflective of cortical inhibition, before returning to baseline [39]. Beta ERD/ERS has been characterised as slow and spatially diffuse, often when viewed as an average across trials. It has recently been observed, however, that beta oscillations are not a continuous signal but appear in sporadic short-lived bursts at the trial level [40]. It has been suggested that beta activity should therefore be understood in terms of a probability distribution, where the likelihood of beta activity is lower before and during movement and higher post-movement. Nevertheless, its correlation with movement-related processing is clear despite its presentation and precise functional role being a matter of ongoing research [40, 41].

Following SCI, the cortical structure tends to undergo reorganisation, which can result in pathological oscillatory signatures. ERD in tetraplegics has been shown to be diminished compared to healthy counterparts [42–44]. This has been corroborated by other neuroimaging techniques such as functional magnetic resonance imaging (fMRI), which has shown that persistent paralysis following SCI results in decreased cortical activation across cortical regions representing the lost movement [45]. Despite reduced activity during attempted movement, cortical sensorimotor representation is still observed, and can even be reactivated following some forms of BCI training [43].

1.5.1 EEG electrode placement

EEG is measured from electrodes placed on the head, usually at locations abiding to an international standard, for instance the 10-20 system [46]. Under this system, electrodes are positioned relative to two geodesic arcs connecting cranial landmarks. The first line lies on the median plane and connects the nasion (the indentation between the nose and forehead) and the inion (a bony protuberance at the posterior side of the head). The second line joins the left and right preauricular points (an indentation anterior to the ear). Electrodes are placed along these line in intervals of either 10 or 20% the line's length. Locations are labelled alphanumerically. Electrodes located over the frontal, parietal, temporal, and occipital lobes, are denoted with an F, P, T, and O, respectively, while centrally located electrodes are given the letter C. Additionally, electrodes above the left hemisphere are labelled with an odd number and those on the right

are given even numbers. For example, electrode F3 lies above the left frontal lobe, while T8 sits over the right temporal lobe. Electrodes that lie on the midline are denoted with the letter Z and are not numbered. The 10-20 system describes a total of 19 electrode locations. For recordings of higher spatial resolutions, extensions have been devised, for instance, the 10-10 system allows for up to 74 electrode locations [47].

1.6 Brain-computer interfaces

The electrophysiological knowledge outlined above has allowed for the creation of brain-computer interfaces, or BCIs. BCIs allow an individual to interact with a computer through cortical activity alone, establishing a channel of communication between the brain and environment that bypasses the peripheral nervous system [1]. BCIs have promising potential for tetraplegic individuals as their use depends on brain activity and has little bearing on extent of injury [42, 48]. Applications have been developed to allow tetraplegics to use their brain rhythms to control a cursor on a screen, an electric wheelchair, a prosthetic limb, a functional electrical stimulator [49], among others [50].

To control devices, BCIs rely on the quasi real-time decoding of EEG signals (see Figure 1.3 for a common BCI pipeline). Typically, two steps are involved: 1) Feature extraction, and 2) Feature classification [51]. Feature extraction takes a raw EEG signal and transforms it into a more compact form; that is, it converts a time series of voltages into a single value called a feature. BCIs typically record EEG from multiple EEG electrodes, hence features are extracted from each electrode or 'channel' simultaneously. Features must capture the information embedded within EEG in order to characterise the current mental state (e.g. whether a user is resting or imagining movement). Motor-imagery based BCIs tend to use band-power features. Control may be achieved by first band-pass filtering incoming EEG to isolate the alpha band (8–12 Hz), then squaring the signal to estimate power, followed by taking the temporal average. The brain state can then be predicted by feature classification. Many BCIs utilise supervised machine learning algorithms for classification [51]. Classifiers work by using training data (EEG data gathered from a calibration session) to model a boundary within a feature space. New unseen EEG can then be fed to this model and labelled based on which side of the boundary it lies. Linear discriminant analysis (LDA) classifiers are typically used for this purpose.

The current gold standard for oscillation-based BCIs use a common spatial pattern (CSP) filter and linear discriminant analysis (LDA) classifier [51]. A CSP filter leverages the fact that different movement-related brain states (say, left v. right hand motor imagery) produce different spatial patterns in multi-electrode EEG. For example, right-hand motor imagery produces a

lateralised ERD over the left sensorimotor area, whereas ERD during left-hand motor imagery tends to be distributed over the right sensorimotor area. An effective CSP algorithm will yield spatial filters such that the variance of filtered EEG is maximised for one brain state and minimised for the other, boosting the discriminability between different brain states [52, 53]. CSP algorithms tend to extremise the following function:

$$J_{CSP}(w) = \frac{wX_1X_1^Tw^T}{wX_2X_2^Tw^T} = \frac{wC_1w^T}{wC_2w^T} \tag{1.1}$$

where T denotes the transpose operator, X_i denotes band-pass filtered training data of condition i, and C_i is the covariance matrix of class i. Here, wX_i is the spatially filtered EEG from class i, and $wX_iX_i^Tw^T$ is the variance of the spatially filtered signal; that is, the band power of the spatially filtered signal. It follows, therefore, that if $J_{CSP}(w)$ is maximised and minimised, it leads to spatially filtered EEG that is maximally different between conditions. The equation can be solved by generalised eigenvalue decomposition. The spatial filters w that maximise and minimise J_{CSP} are the eigenvectors corresponding to the largest and lowest eigenvalues. N channel EEG will generate N spatial filters. In practice, two to six pairs of filters will be used, corresponding to the largest and lowest eigenvalues. For this reason CSP filtering acts as a dimensionality reduction tool. For instance, sixty-four electrode EEG is transformed into six surrogate-channels after CSP filtering. In sum, CSP features are derived from band-pass filtered EEG through the following transformation:

$$f = \log\left(w\mathbf{X}\mathbf{X}^Tw^T\right) = \log\left(w\mathbf{C}w^T\right) = \log\left(var(w\mathbf{X})\right) \tag{1.2}$$

Note that X is unlabelled here as it represents unknown incoming EEG. Features are then compared against an LDA classifier, labelled, providing an output to an application.

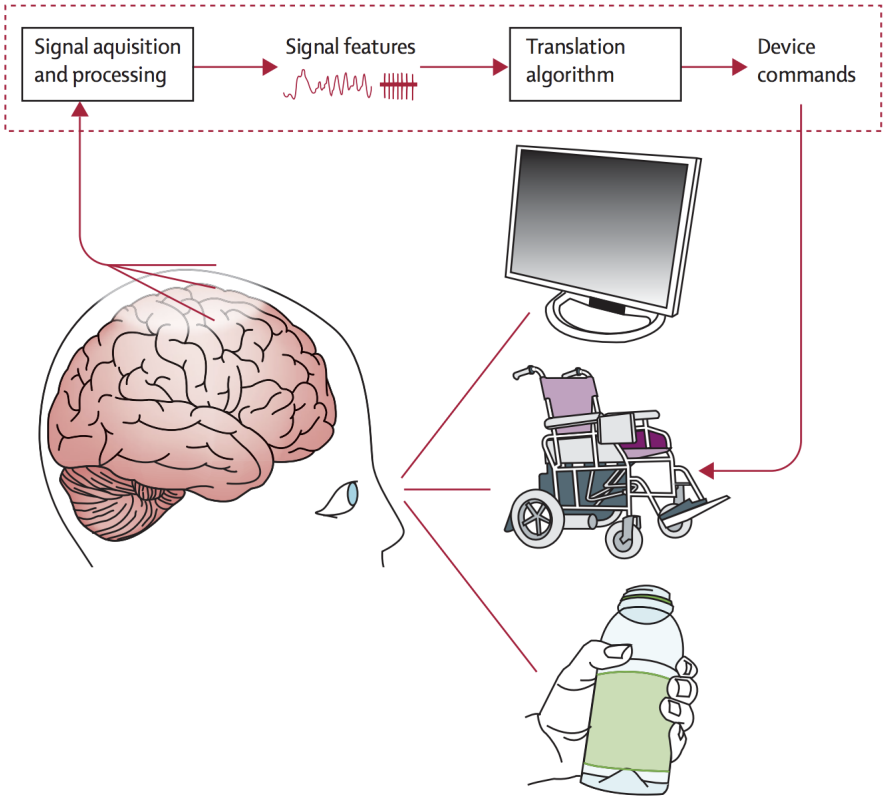

Fig. 1.3 Schematic of a typical BCI. Brain activity is acquired (e.g, via EEG), signal features are extracted and translated into a control signal for a given application. Reproduced from Daly et al. (2008) [1].

1.7 Spinal cord stimulation

As outlined above, the nervous system is composed of electrically active substrate. In addition to the monitoring of electrophysiological signals, exogenous electrical stimulation can be applied to perturb homeostatic processes, and has been shown to have therapeutic potential following SCI. Electricity as a means of neuromodulation has long history [54], and has resulted in a field with an array of techniques for perturbing the physiological stasis of the nervous system. Spinal cord stimulation is a form of electrical neuromodulation that seeks to recruit spinal structures for therapeutic and/or neurophysiological assessment purposes. Therapeutic SCS typically applies sub-threshold, high frequency currents through implanted or surface electrodes, such that interneurons and motor neurons are pushed closer to their firing threshold, making acts of motor volition easier for individuals with weakened post-injury descending drive [55]. Stimulation for neurophysiological assessments applies single pulses of supra-

threshold currents in order to evoke posterior root-muscle (PRM) reflexes [56]. Recording PRM responses with electromyography (EMG) from target musculature can give insight into sensorimotor transmission and the functioning of spinal circuits [57, 58].

With a track record spanning over five decades, implanted epidural stimulators have become a *bona fide* neuomodulatory treatment for intractable chronic pain [59, 60]. More recently, epidural spinal cord stimulation (eSCS) has been used to facilitate motor control in people with motor-complete SCI, owing to the discovery that high frequency stimulation of the dorsal roots of the spinal cord may generate patterns of locomotion [61, 62]. Owing to its invasive nature, however, eSCS is associated with a great deal of risk. Stimulators must be surgically implanted in the epidural space, carrying a high complication rate, either occurring intraoperatively or in the early-to-late postoperative period [63]. In summary, eSCS is invasive, expensive, and sparsely available. However, the mechanisms underpinning eSCS have recently been understood to derive from activation of posterior-root fibres, and not necessarily direct interaction with grey matter, suggesting that spinal cord stimulation may be achieved transcutaneously [64, 56]. Requiring no surgery, transcutaneous SCS (tSCS) can be applied cheaply, safely, and with materials and expertise that are far more accessible than eSCS [56]. Its use, when combined with upper limb exercises, has been shown to lead to lasting functional improvement following SCI [65, 66].

1.7.1 Parameters of tSCS

In general, tSCS is delivered through round adhesive cathode electrodes of around 2–3 cm in diameter that are placed on the midline over the vertebral column (see Figure 4.1 for an illustration) [67, 68, 65, 69, 2]. Applications which seeks to facilitate lower-limb control would typically place electrodes over T11–T12 and/or L1–L2 inter-vertebral space, while upper limb studies have most commonly placed the stimulating electrodes at C3–C4 in parallel with C6–C7 or C7–T1 [66]. Often placement is made relative to the neurological level of injury, with placement above and below. Recent research suggests that tSCS alters the excitability of multiple segments of the spinal cord [2]. Some studies determined electrode placement by using single-pulse stimulation to maximise an evoked response in the EMG of a target muscle. The anode electrodes tend be bigger than the cathodes and rectangular in shape, they are normally inter-connected and placed symmetrically over the anterior superior iliac spine or iliac crests, while other studies chose the anterior side of the neck [70, 71].

In addition to electrode placement and size, the waveform delivered through this material may be adjusted depending on the application. Parameters include pulse width, current intensity,

and frequency, as illustrated in Figure 1.4. For therapeutic applications, stimulation is typically delivered in rectangular mono- or biphasic pulses of around 0.4–2 ms in duration at a frequency range between 1 and 90 Hz at a stimulation intensity up to 170 mA. More recent studies have used modulated stimulation, that is, stimulation which incorporates a high frequency component (up to 10 kHz) within a single pulse [72]. The rational is linked to research claiming that modulated waveforms can deposit higher current intensities without causing as much pain. An example of a modulated waveform is shown in Figure 1.4c. Here, a 1 ms burst is composed of a train of ten 100 μs biphasic pulses; or in other words, it is modulated with a 10 kHz carrier frequency.

1.7.2 Mechanisms of tSCS

Although *spinal cord stimulation* implies interaction between current flow and the spinal cord, it is most likely that the principle mechanism of tSCS results from recruitment of large sensory afferent fibres within the dorsal root and dorsal columns of the spine (Figure 1.5) [73, 69]. These fibres have mono- and polysynapic connections to spinal motor neurons, conveying volleys of excitatory postsynaptic potentials to motor neurons and interneurons. As stimulation intensity is increased, smaller diameter afferent fibres such as group Ib, and deeper intraspinal circuits and interneurons are recruited, bringing interneurons and motor neurons closer to their firing threshold. This increases the likelihood of them responding to weakened post-injury descending drive. It has also been suggested that stimulation of the skin itself contributes to elevated neural excitability [74]. Recruitment of cutaneous mechanoreceptors surrounding the electrode may contribute a neuromodulatory effect to tSCS through polysynaptic connections [75]. It is also likely that the excitability of multiple levels of the spinal cord are altered by stimulation through interneuronal connections [2].

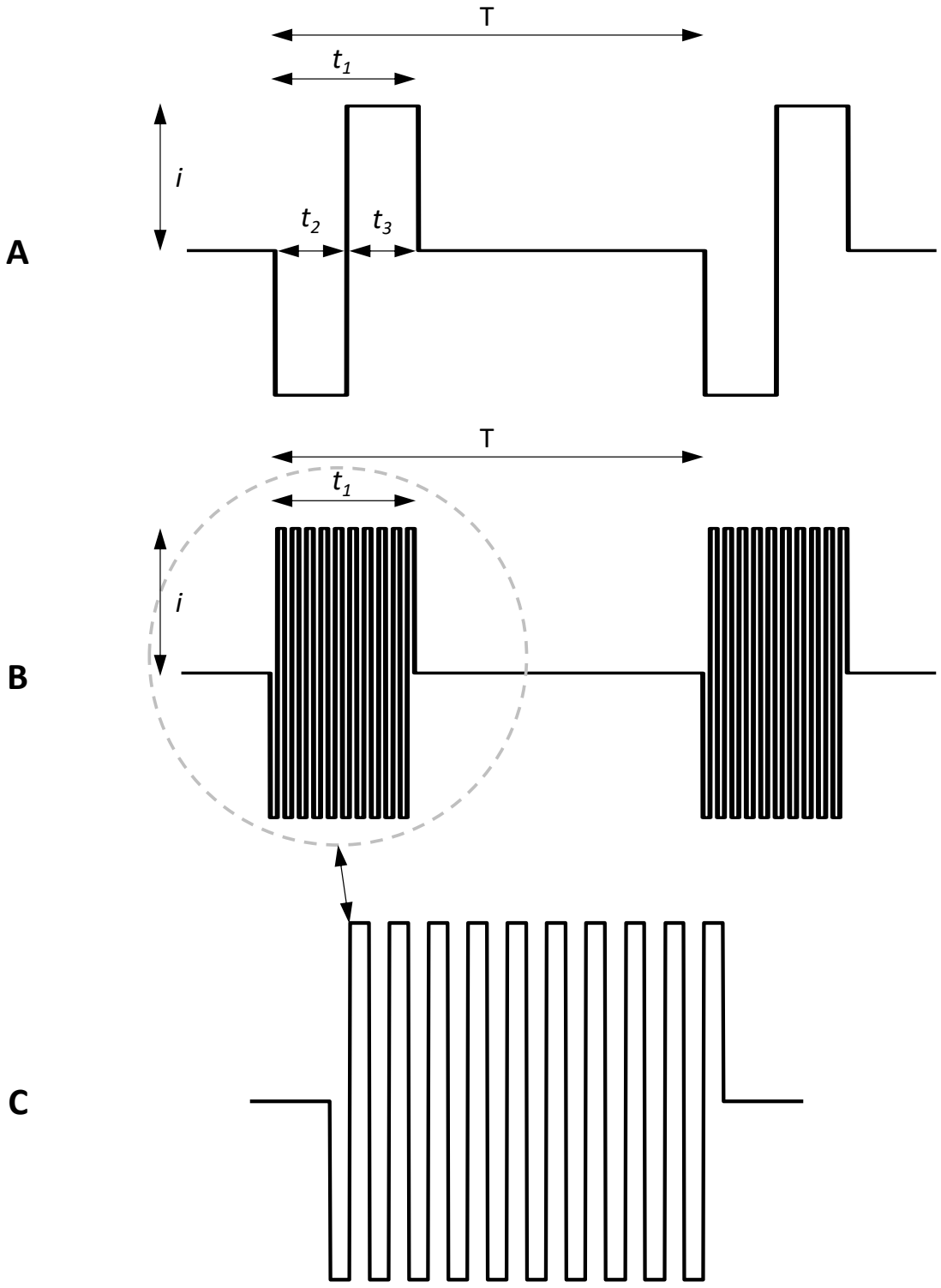

Fig. 1.4 Illustration of tSCS waveform. **(A)** Two biphasic pulses with t_1, t_2, t_3, T, and i denoting pulse width, positive phase duration, negative phase duration, pulse interval, and stimulation intensity, respectively. **(B)** Two pulses modulated with a 10 kHz carrier frequency. **(C)** Enlarged view of modulated burst showing 10 biphasic pulses.

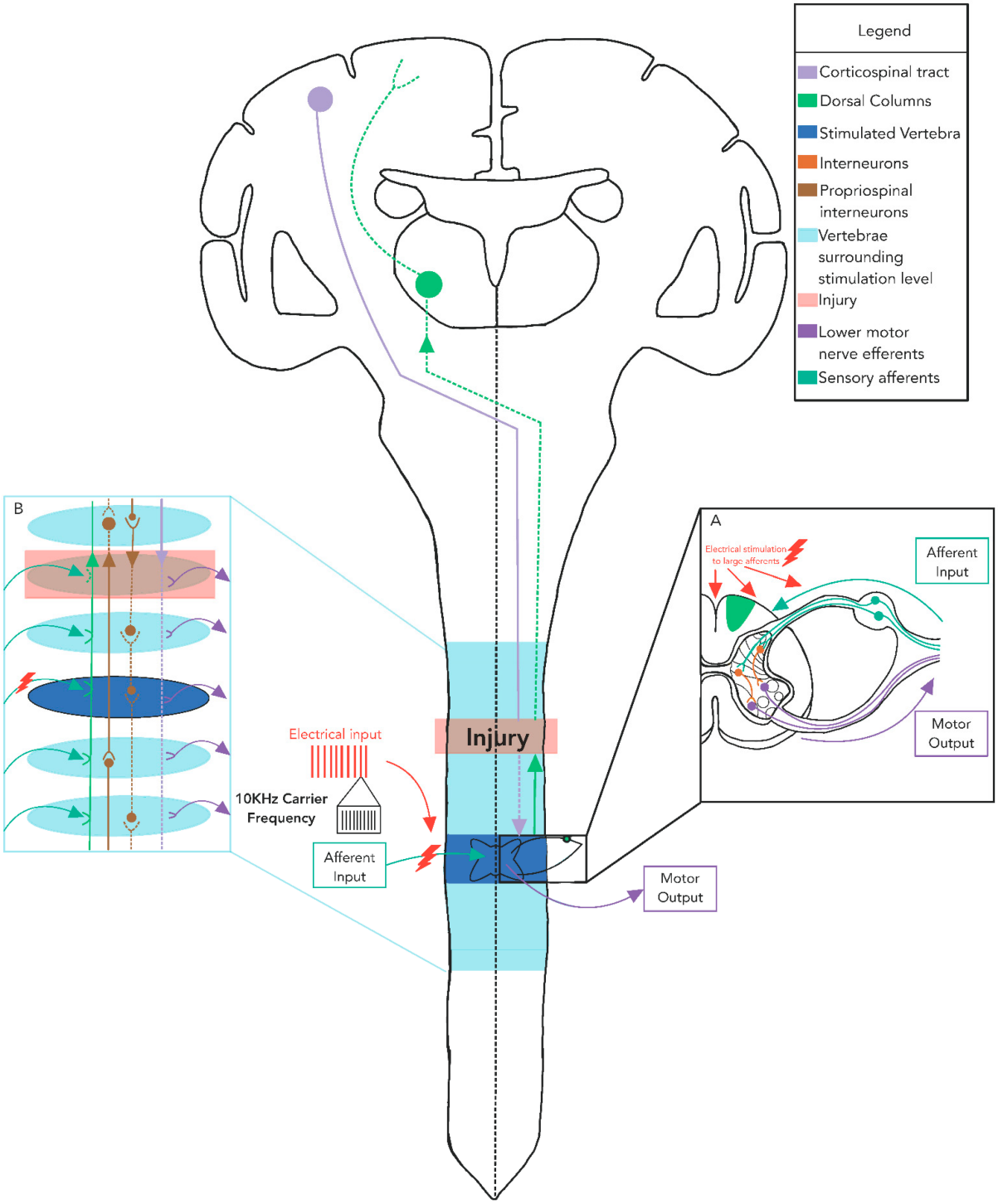

Fig. 1.5 Schematic of the spinal circuits potentially modulated by tSCS. **(A)** Medium-to-large diameter afferent fibers in the dorsal column/roots are likely activated, which transsynaptically activates interneurons, facilitating descending drive. **(B)** Transmission likely extends to multiple spinal segments. Solid lines indicate that transmission remains intact to the point of injury, whereas dashed lines indicate transmission that could potentially be augmented by tSCS. Figure reproduced from Barss et al. (2022) [2].

Chapter 2

Literature review

2.1 Neuromodulation with cervical tSCS

In order to determine the neuromodulatory effect of tSCS on the nervous system, studies have used evoked potentials and reflexes to measure corticospinal and spinal excitability. There are many examples of this in research investigating spinal locomotor circuits [76, 58]. Few studies, however, have focused on cervical tSCS in order to modulate upper limb spinal circuits [72, 77, 71]. Benavides et al. used transcranial magnetic stimulation (TMS) and cervicomedullary electrical stimulation to elicit evoked potentials in order to measure corticospinal and spinal excitability, respectively [72]. In 17 SCI patients (AIS A, n=4; AIS B, n=3; AIS C, n=2; AIS D, n=9) and 15 age-matched control subjects, tSCS was delivered to the cervical region of the neck (between C5 and C6 spinous processes). Stimulation was delivered in 200 μs biphasic pulses with a 5 kHz carrier frequency at 30 Hz for 20 min. Recorded in the biceps brachii, the amplitude of motor-evoked potentials (MEPs) and cervicomedullary evoked potentials (CMEPs) were compared before and after tSCS. The amplitude of CMEPs were enhanced for up to 75 min after cessation of stimulation in both groups, whereas MEPs elicited by TMS were suppressed, suggesting facilitated excitability at the spinal level but an inhibitory effect at cortical networks. They posited that this suppression may be attributable to tSCS-activation of inhibitory cortical circuits projecting onto corticospinal neurons. Indeed, it has been shown in animal models that cortical activity can be affected by afferent input via dense intracortical projections between the motor cortex and somatosensory cortex [78]. Interestingly, the same experiment performed again with the 5 kHz carrier frequency removed showed facilitated MEPs and CMEPs, suggesting that cortical inhibitory effects were attributable to the carrier frequency [72]. This is a matter of contention, however, as a similar study by Kumru et al. demonstrated facilitated spinal and corticospinal expression using 1 ms pulses with a 10

kHz carrier frequency. In a cohort of 10 able-bodied volunteers they applied cervical tSCS intermittently in 20 s intervals followed by an 80 s resting period for 30 min. This study also emphasised the value of concomitant voluntary motor engagement in order to promote neuromodulation. Among two experimental groups, one received tSCS alone, while the other received tSCS while performing hand training exercises, it was found that only the latter group increased spinal cord excitability as measured by the F wave, and corticospinal excitability measured by TMS. Here, spinal excitability, as measured by the F-wave at the abductor pollicis brevis (APB), was found to be enhanced before and after, emphasising that changes are dependent on voluntary hand training [77]

A further study, by Sasaki et al., contrasted with these reports, reporting a null effect of tSCS on either the corticospinal or spinal level. In 10 able-bodied volunteers, tSCS (400 μs bursts at 30 Hz, with no carrier frequency) was delivered at the cervical level for 10 min with participants in a relaxed supine position [71]. Intensity was tailored to the individual by ramping up the current until paresthesia was induced in the arm muscles. MEPs and posterior root-muscle (PRM) reflexes were unaffected after tSCS compared to baseline. They suggested that the disparity with other reports may stem from the differences in experimental protocol. It may be that stimulation duration, or voluntary involvement, or electrode configuration plays an important role in promoting neuromodulation with tSCS.

Measures of corticospinal and spinal excitability have tended to use motor evoked potentials as measures of neuromodulation. Other measures, such as cortical oscillations, may offer an alternative perspective on the physiological effects of tSCS. Although MEP and oscillation amplitudes have both been associated with motor cortical excitability, they are not strongly correlated, and likely reflect different neural processes [38, 79]. Where cortical oscillations tend to reflect the induced excitability of large populations of cortical neurons, MEPs are affected by the global excitability of corticospinal pathways [38, 36]. An understanding of how each measure is affected by tSCS will build a stronger foundation in which to guide future tSCS-based neurorehabilitation strategies. A further benefit is that, unlike posterior root-muscle reflexes, cortical oscillations can be measured during tSCS. As outlined above, ERD is a correlate of cortical activation during attempted movement and might serve as a useful marker of neuromodulation following tSCS. To date, it is unknown whether cortical activity can be modulated through spinal cord stimulation. Other stimulation-based techniques have been shown to enhance cortical activity as measured with EEG. For instance, Insausti-Delgado et al. showed that functional electrical stimulation of the wrist extensors induced stronger levels of ERD compared to imagined movement alone, likely due to activation of proprioceptive network [80]. Measuring EEG during concomitant electrical stimulation is not a trivial task,

however, as electromagnetic stimulation can present as high-amplitude noise, masking neural components. The final section of this chapter considers this issue.

2.2 Upper limb rehabilitation with tSCS

Upper-limb rehabilitation is one of the greatest priorities for individuals with SCI, yet most studies utilising non-invasive SCS have focused on improving lower-limb function. This may, in part, be due to early research showing that high frequency spinal stimulation could trigger locomotion in the lower limbs through activation of central pattern generators [81]. In recent years, there has been a small but increasing number of studies seeking to improve upper-limb function, see Table 2.1 for a summary. In 2018, two studies sought to investigate cervical stimulation's impact on hand and arm function [67, 65]. The first of these reports was from Gad *et al*. which reported that maximum voluntary hand grip force increased 2-fold after four weeks of stimulation combined with hand grip exercises among a cohort of eight chronic cervical SCI participants (AIS B, n=3; AIS C, n=5) [67]. When grip strength was tested in the presence of simultaneous stimulation, this increase was 3-fold above baseline measurements. Some participants self-reported improved autonomic function, lower extremity motor function and sensation below the level of injury. Being a proof-of-concept, the study lacked rigour, for instance it was unblinded and uncontrolled. The study's significance lay in its suggestion of neuromodulation with no adverse affects, specifically that stimulation did not alter hemodynamic parameters or cause undue discomfort to the participants. The second report came the same year from Inanici *et al.*, which reported a case study with a 62 year old individual with a chronic SCI (AIS D) that combined functional physical therapy and tSCS [65]. This study used more clinically relevant outcome measures, such as the Graded Refined Assessment of Strength, Sensibility, and Prehension (GRASSP), and the Spinal Cord Independence Measure (SCIM). The study used a more robust design in that it had two phases: the first lasted four weeks and had the participant undergo intensive hand and arm exercises while stimulation was applied above and below the neurological level of injury; the second phase lasted a further four weeks and involved hand and arm training only, allowing the participant to serve as their own control. The participant responded well to the intervention, with a 31-point and 20-point increase in total GRASSP score following each phase, respectively. Improvements tended to derive from the strength category of the GRASSP, and gains appeared more pronounced following the first phase with tSCS. The self-care component of the SCIM increased by a single point, reflect the participant's renewed ability to self-feed. Given the study's design and that it included only one participant, it is difficult to draw any firm conclusions as to the efficacy of

tSCS on physical training. Without multiple cross-over phases, it cannot be ruled out that the gains were not a product of intensive hand training alone. On the other hand, the study reported immediate functional improvements following stimulation onset, characterised by more smooth and coordinated upper-limb movements. It may be concluded that cervical tSCS has the ability to advantageously modulate spinal circuits but whether this translated to lasting improvements in upper-limb function remained to be seen.

The same group later reported a more comprehensive investigation with a larger sample size and more robust study design [82]. Six chronic cervical SCI participants (AIS B, n=2; AIS C, n=2; AIS D, n=2) were recruited to undergo a two-arm, cross-over study. They extended their previous protocol of four weeks of intensive functional task training and four weeks of training and stimulation, by having participants repeat the protocol again in a random order, allowing each individual to act as their own control. This enhanced study used GRASSP and pinch force to track motor function and showed that training combined with stimulation was significantly more effective than training alone, as indicated by a paired-samples T-test ($p<0.025$). An immediate effect of stimulation was also reported for some participants, which is claimed to have made it easier for them to engage with training exercises, and allowing them to recruit plasticity mechanisms unavailable without stimulation. Upper extremity motor scores, a category of the ISNCSCI examination, improved by up to eight points at the end of stimulation, but only two points following training alone. Interestingly, one participant was reclassified as AIS D from AIS C after the intervention, and some participants were able to continue with hobbies that had been impossible since their injury, for example, playing musical instruments. A case study by Zhang *et al.* reached similar conclusions with an individual with a more severe SCI (AIS A): immediate and lasting functional improvements were made following hand and arm training coupled with cervical tSCS [83].

Another 2018 study, by Freyvert *et al.*, took a different approach to cervical tSCS by introducing the monoaminergic agonist buspirone to tSCS training in six chronic SCI participants (AIS B) [84]. Their rational for this approach came from the successful facilitation of lumbar spinal stimulation therapies with pharmacological agents [55]. Indeed, they reported that a combined stimulation and drug intervention led to clinically meaningful improvements of upper-extremity function as measured by hand grip force, upper extremity muscle strength (UEMS). Again, no adverse effects were reported. During high stimulation intensities, tingling sensations in the arms were reported.

A 2021 review by Taylor *et al.* appraised the majority of papers described here [66], with the exception of the 2021 study by Inanici *et al.* [82]. They used the Downs and Black (D & B) checklist to evaluate the following criteria: reporting, internal validity (bias), internal

validity (confounding factors), external validity, and power. They found that the studies were of poor quality. This was attributed to lack of balanced protocols stemming from SCI participants tending to differ in terms of classification, and insufficient descriptions of their recruitment protocols. A systematic review of tSCS on motor rehabilitation by Megía Garcia *et al*. highlighted the feasibility of tSCS as a neuromodulatory strategy but emphasised the need for statistically powered controlled clinical trials [85].

Stimulation parameters

The studies reviewed above tended to share stimulation parameters with some difference. All the reviewed studies—with the exception of the report by Freyvert *et al*., which used single-site stimulation—delivered stimulation with two cathodes, positioned above and below the neurological level of injury, citing that multi-site stimulation had proven more reliable in lower-extremity applications [55]. Every report used inter-connected anodes placed over the anterior superior iliac spine or iliac crest. Further, the studies stimulated with a 1 millisecond pulse width delivered at 30 Hz. Freyvert *et al*. were again an exception as they explored a range of frequencies between 5 and 30 Hz, and selected that which maximised voluntary hand grip force. The majority of studies also used a 10 kHz carrier frequency, owing to its association with reduced painful sensations.

Some studies explored biphasic and monophasic waveforms in order to optimise motor function [67, 65]. Inanici et al. claimed that monophasic stimulation tended to aid in strength-dependent activities, whereas biphasic stimulation better facilitated tasks requiring fine motor skills [82]. Other studies used monophasic stimulation only [83].

Stimulation intensity was tailored to each participant and reevaluated at the beginning of each session. From a low-intensity starting point, the current was gradually increased until a functional task—for example, maximum grip strength—was optimised without inducing discomfort. It was, in all cases, applied below motor threshold. Some studies verified this by ensuring evoked potentials were not detectable in EMG [65]. Typically tSCS was applied at intensities between 20–220 mA. However, comparisons between studies are difficult due to differences in electrode shapes and sizes, which has an impact on the participants' perception of the stimulation.

Table 2.1 Studies reporting investigations of cervical tSCS for upper-limb motor rehabilitation.

Study	Design	Subjects	Intervention	Intensity	Stimulation parameters	Electrode locations	Outcomes
Gad *et al.* 2018 [67]	CR	8 SCI	Hand grip training	2 1-2 h sessions/week, 4 weeks	bi or mono, 1 ms pulses at 30 Hz, 10kHz CF	Anodes: illiac crest; Cathodes: C3–C4, C6–C7	225% increase in maximum grip force
Inanici *et al.* 2018 [65]	CR, CT	1 SCI	Functional hand and arm training	2 h sessions, 4-5 times/week, 9 weeks	bi, 1 ms pulses at 30 Hz, 10 kHz CF	Anodes: illiac crest; Cathodes: C3–C4, C6–C7	UEMS increase by 10 points, pinch increase 2 (left hand) and 7 fold (right hand), 52 point increase in GRASSP
Freyvert *et al.* 2018 [84]	CS, CT	6 SCI	Buspirone and hand grip training	ns, 6 weeks	5–30 Hz	Anode: iliac spine; Cathode: C5	Improved max hand grip force
Zhang *et al.* 2020 [83]	CR	1 SCI	Functional hand and arm training	1 h, 18 sessions, 8 weeks	1 ms burst, 30 Hz, 10 kHz	Anodes: illiac crest; Cathodes: C3–C4, C7–T1	Increased hand grip force
Inanici *et al.* 2021 [82]	CS, CT	6 SCI	Functional hand and arm training	2 h, 3/week, 5 weeks	1 ms burst, 30 Hz, 10 kHz	Anodes: illiac crest; Cathodes: C3–C4, C6–C7	Significant functional improvement in tSCS+training group only

CS: case series; CR: case report; CT: crossover trial; CF: carrier frequency, ns: not specified

2.3 EEG monitoring during electrical stimulation

EEG monitoring during simultaneous electrical brain or muscular stimulation could provide insight into the behaviour of cortical processes during stimulation, and offer the ability to establish closed-loop BCIs where cortical activity informs stimulation parameters [49], or cortical activity can be self-regulated during stimulation. Electromagnetic stimulation often introduces undesirable noise which can distort the recorded signal rendering interpretation challenging or impossible. Techniques have been developed to over come this problem. For instance, to suppress the effects of functional electrical stimulation (FES) on EMG, blanking is a hardware solution which involves programming a recording device such that it temporarily rejects new data in step with the stimulation frequency [86–88]. Although an effective method of eliminating short-latency, high-amplitude artifacts, it leads to the creating of dead zones, which potentially eliminates useful neural information. An additional downside is that it cannot be applied retroactively on EEG already recorded data. Insausti-Delgado et al. used a median filter to attenuate FES in EEG such that such that event-related desynchronisation analyses could be performed [80]. They scanned a 10 ms window across the contaminated EEG time series, calculating the median value, and reconstructing EEG the artifact attenuated. It was found, however, that attenuation of neural components was also present, hence the 10 ms window size was used as a compromise as it reduced only 1.28%, 4.89% and 10.90% of the signal at 10, 20, and 30 Hz, respectively. Given that the filter effectively removed the FES artefact, this was deemed acceptable.

A median filter relies on a single parameter: the sliding window's width. This is tailored with reference to the stimulation artefact's width and amplitude. Stimulation artefacts present differently at different EEG channels, however, typically as a function of distance from the stimulation site, and hence would require individual tuning. Artefact suppression independent of the number of channels would benefit tSCS-EEG recording. This factor was considered by Kohli et al. when investigating techniques to suppress the contribution of transcranial alternating current stimulation (tACS) in EEG [89]. This study used descriptive statistics—for instance, complexity, kurtosis, root-mean square, and zero crossings—to characterise tACS's artefactual contribution to EEG and quantify the effect of stimulation-suppression techniques. They used an adaptive filter (AF) as it is time-varying; that is, its filtering coefficients change over time to reflect variations in EEG, such as changes in impedance. In addition, they proposed a superposition of moving averages (SMA) filter. This method has a low computational complexity and is channel count independent. It works by using a moving window to create a template approximating the stimulation artefact and subtracting it from the contaminated

EEG. Results showed that, after artefact removal, reconstructed EEG bore statistically identical descriptive statistics to uncontaminated EEG. They suggested that the SMA filter was superior to AF as it resulted in smaller contamination when tACS was applied at 40 Hz. It is likely that the approaches discussed here, particularly the SMA, would provide beneficial artefact-suppression in tSCS-EEG applications.

2.4 Research questions

There is growing evidence that upper limb rehabilitation following cervical SCI can be facilitated with transcutaneous spinal cord stimulation [66, 82]. There is, however, ambiguity around the precise corticospinal mechanisms underpinning this therapeutic effect, with contradictory reports of corticospinal and spinal network modulation following tSCS. The current work acknowledges that, in addition to the currently explored methods of TMS and PRM reflexes, EEG could provide insight into the nervous system's response to tSCS. Specifically, cortical oscillations from the sensorimotor cortex during movement may reveal important information about tSCS and its neuromodulatory potential. To date, no study has investigated the effect of tSCS on cortical oscillations. Indeed, it is also unknown whether the recording of meaningful EEG during high intensity/high frequency tSCS is feasible. In order to characterise a neuromodulation effect it is essential to first establish whether meaningful EEG can be extracted.

In addition to simultaneous tSCS-EEG, there may be an application for tSCS and EEG administered in series. Given that SCI pathology is multi-faceted, it has been predicted that future successful treatments will combine a variety of techniques in order to target different areas of pathology [90]. Where tSCS has been shown to target spinal circuits, an EEG-based brain-computer interface could target the cortical level, promoting neuromodulation at two levels of the central nervous system. Consequently, this thesis will partially explore BCI motor priming as a method of augmenting tSCS-facilitated upper limb rehabilitation.

2.5 Aims

This thesis aims to:

1. Characterise the instantaneous effect of tSCS on EEG.
2. Determine if meaningful neural components can be extracted from EEG during tSCS.
3. Investigate noise suppression of tSCS artefacts in EEG.
4. Determine if a brain-computer interface can be established during tSCS.
5. Investigate whether tSCS provides a neuromodulation effect on cortical activity.
6. Confirm whether cervical tSCS therapy promotes upper limb rehabilitation in a case of chronic AIS A SCI.

7. Explore whether a brain-computer interface can promote motor priming and enhance tSCS hand and arm training.

2.6 Thesis outline

Traditional approaches to upper limb rehabilitation following SCI provide modest benefits at best. New therapies must be developed to help individuals regain their independence and quality of life following SCI. The aim of this thesis is to bridge the use of transcutaneous spinal cord stimulation and brain-computer interfaces in order to better understand the potential complimentary nature of these technologies for use in neurorehabilitation. This investigation was undertaken from three perspectives: (1) Technical feasibility; (2) Potential for cortical neuromodulation; and (3) Potential as a restorative therapy following spinal cord injury. Chapters Three, Four, and Five explore these perspectives and are presented as articles of original research.

Chapter Three addresses the technical aspects related to simultaneous electroencephalography and transcutaneous spinal cord stimulation. Objectives include characterising the effect of concurrent tSCS on EEG recordings, deducing whether meaningful brain-related information can be derived, and whether stimulation artifacts could be suppressed with state-of-the-art filtering techniques. This research has been published in *Sensors* [91].

Chapter Four explores the potential for tSCS as a neuromodulatory tool in terms of physiological features of EEG. Brain activity was measured while able-bodied participants performed a movement task with and without cervical tSCS. This chapter explores whether brain activity is altered by the presence of tSCS. This research has been published in the *Journal of Clinical Medicine* [92].

Chapter Five describes a case study that sought to unify BCI technology with tSCS therapy in a motor rehabilitation context. A BCI was used to create a game-like paradigm to *prime* an individual with a chronic cervical SCI to better respond to tSCS upper limb therapy. This study used measures of upper-limb function to evaluate the participant's response to multiple therapy sessions over the course of 16 weeks. This research has been published in *Frontiers of Rehabilitation Sciences* [93].

Finally, **Chapter Six** summarizes the work presented, highlights contributions to the field of neurorehabilitation, and offers future directions for research.

Chapter 3

EEG monitoring is feasible and reliable during simultaneous transcutaneous electrical spinal cord stimulation

This chapter was written by Ciarán McGeady, with Aleksandra Vučković, Yong-Ping Zheng, and Monzurul Alam, and published in *Sensors* [91].

3.1 Abstract

Transcutaneous electrical spinal cord stimulation (tSCS) is a non-invasive neuromodulatory technique that has in recent years been linked to improved volitional limb control in spinal-cord injured individuals. Although the technique is growing in popularity there is still uncertainty regarding the neural mechanisms underpinning sensory and motor recovery. Brain monitoring techniques such as electroencephalography (EEG) may provide further insights to the changes in coritcospinal excitability that have already been demonstrated using other techniques. It is unknown, however, whether intelligible EEG can be extracted while tSCS is being applied, owing to substantial high-amplitude artifacts associated with stimulation-based therapies. Here, for the first time, we characterise the artifacts that manifest in EEG when recorded simultaneously with tSCS. We recorded multi-channel EEG from 21 healthy volunteers as they took part in a resting state and movement task across two sessions: One with tSCS delivered to the cervical region of the neck, and one without tSCS. An offline analysis in the time and frequency domain showed that tSCS manifested as narrow, high-amplitude peaks with a spectral density contained at the stimulation frequency. We quantified the altered signals

with descriptive statistics—kurtosis, root-mean-square, complexity, and zero crossings—and applied artifact-suppression techniques—superposition of moving averages, adaptive, median, and notch filtering—to explore whether the effects of tSCS could be suppressed. We found that the superposition of moving averages filter was the most successful technique at returning contaminated EEG to levels statistically similar to that of normal EEG. In the frequency domain, however, notch filtering was more effective at reducing the spectral power contribution of stimulation from frontal and central electrodes. An adaptive filter was more appropriate for channels closer to the stimulation site. Lastly, we found that tSCS posed no detriment to the binary classification of upper-limb movements from sensorimotor rhythms, and that adaptive filtering resulted in poorer classification performance. Overall, we showed that, depending on the analysis, EEG monitoring during transcutaneous electrical spinal cord stimulation is feasible. This study supports future investigations using EEG to study the activity of the sensorimotor cortex during tSCS, and potentially paves the way to brain–computer interfaces operating in the presence of spinal stimulation.

3.2 Introduction

Transcutaneous electrical spinal cord stimulation (tSCS) is a non-invasive neuromodulatory technique that has shown promise in recent years in promoting the motor recovery of spinal-cord injury patients [94, 65, 82]. The technique uses a surface electrode positioned over the site of spinal injury to deliver high-frequency currents, and has been associated with functional improvements in the upper limbs, the trunk [95], and the lower limbs [94], often when combined with physical practice. It has been postulated that tSCS elevates the motor threshold of dorsal root motoneurons, making volitional control easier through residual descending pathways [56]. The precise mechanisms underpinning recovery, however, are not fully understood. Recent studies have used various techniques to measure changes in corticospinal excitability, one even reporting changes to cortical excitability after tSCS [72]. Going forward it will be crucial to explore numerous research avenues, employing a range of techniques, such as electroencephalography (EEG), in order to establish the precise mechanisms of recovery.

As with other stimulation-based techniques—functional electrical stimulation [80], transcranial direct current stimulation [96], transcranial alternating current stimulation (tACS) [97], deep brain stimulation [98], for example—the introduction of EEG into an experiment may present a significant challenge when it comes to interpretation, owing to substantial stimulation artifacts in the recorded signal. Stimulation is often applied at intensities far exceeding the amplitudes associated with EEG. A pitfall may present itself in the frequency domain if the

stimulation frequency overlaps with a frequency range of interest, indeed cervical tSCS is often delivered at 30 Hz, within EEG's sensorimotor spectrum (7–40 Hz) [99]. Many tACS studies have overcome this conflict by limiting their EEG analysis to before and after stimulation. This removes the artifact problem but deprives the study of access to brain activity during stimulation. Recently, EEG during continuous tACS was monitored and artifacts were removed with artifact-suppression techniques [89], to an extent allowing the analysis of brain rhythms during stimulation. Transcranial alternating current stimulation (tACS) has as similar periodic waveform to tSCS. Artifact-suppression techniques developed for tACS are a good starting point for examining tSCS and EEG.

Whether tSCS complicates the extraction of neural information has not, to the best of our knowledge, been reported. This study aims to cast light on the way tSCS manifests on EEG during simultaneous acquisition, to quantify its effects and determine if artifact-suppression techniques can be used to minimise contamination. To address these questions we gathered an EEG dataset from healthy volunteers while stimulation was delivered transcutaneously to the cervical region on the posterior side of the neck. The location of stimulation and stimulation parameters—carrier frequency, burst frequency, pulse width, etc.—were chosen to reflect parameters typical of the current state-of-the-art in upper-limb rehabilitation using tSCS [65, 82]. We performed an offline analysis to illustrate how tSCS manifested in the time and frequency domain and considered the impact of EEG electrode location and stimulation intensity on artifact prominence. Our hypothesis was that, like other electrical stimulation techniques, tSCS would present in EEG as narrow, high-amplitude peaks and that artifact-suppression techniques could reduce the impact of stimulation. Overall, our results implied that extracting physiologically meaningful EEG during tSCS is possible, and paves the way to future research aimed at uncovering the sensorimotor neural mechanisms behind tSCS-based therapy.

3.3 Materials and methods

3.3.1 Participants

Twenty-one healthy volunteers (7 females, 14 males; 28 $\pm$ 5 years old) participated in this study, reflecting similar studies and the time constraints of the current study [89]. Exclusion criteria included previous neurological symptoms of the nervous or musculoskeletal systems, metal or electronic implants, medications influencing neural excitability (antiepileptic, antipsychotics, or antidepressants), allergy to the electrode material, epilepsy, and pregnancy.

Sessions were conducted at the same time of day to minimise baseline EEG variances and subjects were allowed to take breaks in between experiment runs to prevent fatigue. Written informed consent was obtained from all participants. This study was approved by the Human Subjects Ethics Sub-committee of the Hong Kong Polytechnic University, and conducted according to the principles and guidelines of the Declaration of Helsinki.

3.3.2 Experimental protocol

Participants underwent two EEG recording sessions on different days, based on a two-day crossover design. EEG and forearm EMG were measured as participants performed a movement task. Session A was performed with tSCS applied to the cervical region of the neck and Session B was performed without tSCS, on different days in order to minimise the potential of stimulation-induced brain activity changes. The order of sessions was balanced across participants.

Participants undertook two activities during each session: A resting state task, and a movement execution task. During the former task participants were instructed to sit still for 90 s while their EEG was recorded. This was repeated twice: with eyes opened and eyes closed.

To assess the effect of tSCS on event-related desynchronisation of sensorimotor rhythms during movement, participants were instructed to perform rhythmic right-hand or bimanual finger flexion when cued by a computer screen. A rightwards arrow cued right-hand movement and a double arrow pointing both left and rightwards cued bimanual movements. Each movement was performed for four seconds and repeated 30 times, with a randomised 1.5 to 2.5 s inter-trial interval. EMG was recorded from the forearm muscles simultaneously to measure movement onset.

3.3.3 EEG/EMG data collection

EEG was recorded at 1200 Hz with a g.USBamp biosignal amplifier (g.tec, Schiedlberg, Austria). Nineteen passive electrodes were used: Fz, FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, C4, CP3, CP1, CPz, CP2, CP4, Pz, POz, and Oz, according to the international 10-20 system. The ground and reference electrodes were placed at AFz and right earlobe, respectively. EEG was internally filtered with a band-pass filter at 0.01–100 Hz, and notch filter at 50 Hz to attenuate powerline noise. Special attention was given to ensuring that electrode impedance was below 5 kΩ throughout the recording session, and that participants minimised their body movements. This was important as conventional data-cleaning techniques were made challenging by the presence tSCS. For consistency, typical rejection thresholds on peak-

to-peak amplitudes were not used when processing either tSCS-off or tSCS-on data. EEG was pre-processed by applying a 3rd order Butterworth band-pass filter with a cutoff frequencies of 3 and 50 Hz.

Surface electromyography (EMG) was recorded from the left and right forearms to determine the beginning of movement onset and was used only in the movement classification analysis. Two electrodes (Ag/AgCl; F-301, Skintact, Innsbruck, Austria) were positioned on the belly of each extensor carpi radialis (ERC) muscle, with a 20 mm inter-electrode distance. Ground electrodes were attached to the lateral epicondyles. EMG was recorded simultaneously with EEG using a g.USBamp biosignal amplifier (g.tec, Schiedlberg, (Bandpass filter: 5–1200 Hz; notch filter: 50 Hz). Offline, a 20–500 Hz band-pass filter, and a 10 Hz low-pass filter were applied. Movement onset was defined as the moment the EMG signal exceeded the mean of the resting phase plus two times its standard deviation for at least 100 ms. EEG was epoched from -2 to 6 s relative to movement onset.

3.3.4 Transcutaneous spinal cord stimulation (tSCS)

Stimulation was delivered in trains of ten 100 μs long biphasic rectangular pulses at a frequency of 30 Hz with a DS8R Biphasic Constant Current Stimulator (Digitimer, Hertfordshire, UK). The cathode electrode (3.2 cm diameter; Axelgaard Manufacturing Co, Fallbrook, CA, USA) was positioned between the C5-C6 intervertebral space. Hypoallergenic tape fastened the cathode to the skin to ensure snug contact throughout the session. Inter-connected anode electrodes (8.9 $\times$ 5.0 cm; Axelgaard Manufacturing Co, Fallbrook, CA, USA) were placed symmetrically on the shoulders, above the acromion. The current was determined as the highest intensity tolerable to the participant (40 $\pm$ 10 mA).

3.3.5 Artifact suppression

To remove noise generated by tSCS we explored a number of artifact suppression techniques that could be implemented in real-time applications.

Superposition of moving averages (SMA)

First developed to attenuate the effects of transcranial alternating current stimulation in EEG the SMA filter creates a template approximating the stimulation artifact and subtracts it from the contaminated EEG [89]. With each channel split into N non-overlapping windows of a length equal to the stimulation frequency the SMA filter averages M windows and subtracts the

result from the current window, n. Hence, if $x(n)$ is a single channel split into N segments,

$$X(n) = x(n) - \frac{1}{M+1} \sum_{n-\frac{M}{2}}^{n+\frac{M}{2}} x(n), \tag{3.1}$$

where $X(n)$ represents the cleaned, or 'reconstructed', channel. The artifact template is updated as it slides across the time series, adapting to changes in artifact shape.

In this study, M was set to 5, which was heuristically found to maximise the classification accuracy as explained later. This analysis was performed with code from an open source repository [100].

Adaptive filter

We also explored an adaptive filtering technique. Unlike conventional filters with fixed coefficients the adaptive filter adjusts its filtering parameters over time to satisfy an optimization algorithm. Many adaptive filters rely on two inputs, the corrupted signal and a signal reflecting known noise, often the output of the stimulator itself. We, however, implemented a version of the adaptive filter that relies only on the corrupted signal. A similar technique was used to remove functional electrical stimulation (FES) artifacts from EMG [87, 88]. The method divides the incoming signal $x(n)$ into M non-overlapping windows of N samples and makes a prediction of the stimulation artifact by using a linear combination of the M previous frames, weighted by filter coefficients b. It is assumed that if the filter can remove true EEG then the energy of the resulting signal will have a minimal value. Coefficient b, therefore, is determined by a least-squares algorithm which minimises the energy of the current frame with respect to this coefficient. A detailed explanation of this procedure was described by Sennels et al. [87]. Next, the predicted artifact is subtracted from the current frame:

$$y(n) = x(n) - \sum_{j=1}^{M} b_j x(n - jN), \tag{3.2}$$

where N is the ratio of the stimulation frequency to the sampling rate, ensuring that the stimulation artifact is aligned in each window. The subtraction of the predicted artifact from the current frame, $x(n)$, aims to remove contributions from the stimulator, leaving behind a cleaned version of the signal, $y(n)$.

This study found that M of 6 was generally enough to eliminate the simulation artifact.

Median filter

Neuromuscular electrical stimulation (NMES) has been delivered to peripheral musculature and shown to manifest in EEG as short latency, high amplitude peaks. Insautsti-Delago et al. applied a short sliding window to each EEG channel while taking the median value to curtail the effects of NMES [80]. The current study applied a similar method with a sliding window of 7 samples, or around 6 ms long.

Notch filter

A 3rd order Butterworth filter was used to attenuate the stimulation frequency by setting the low and high cut-off frequencies to 29 and 31 Hz, respectively.

3.3.6 Stimulation artifact in the time domain

To illustrate the effect of tSCS on EEG in the time domain we plotted the pre-processed resting state EEG with eyes closed. In order to explore stimulation-intensity effects, we showed the EEG of the participants who were the most and least tolerant to tSCS. Furthermore, we investigated the impact of distance on artifact prominence by presenting data from the nearest and farthest channel to the stimulation site: Fz, and Oz, respectively. EEG from the tSCS-off condition is also shown for a better comparison.

3.3.7 Stimulation artifact in the frequency domain

As tSCS is delivered at a fixed location on the posterior side of the neck we expected artifacts to manifest in EEG as a function of distance. For simplicity, we considered only the midline electrodes as we did not expect a lateralised effect owing to the relative homogeneity of scalp composition. To observe the effect we considered the power spectral density (PSD) of resting state EEG with eyes closed at and around the stimulation frequency (28–32 Hz). We expected the posterior electrodes (Oz, etc.) to have a greater 30 Hz contribution than the frontal electrodes (Fz, etc.). PSD was estimated using the multitaper method with a bandwidth of 0.1.

3.3.8 Spatial distribution of tSCS contamination

Using the method outlined above, we found the PSD of resting state EEG with eyes closed at and around 30 Hz to determine the spectral pattern of stimulation on scalp topography. The average power of each channel during tSCS was subtracted from and divided by the power from

the tSCS-off condition, revealing the percentage power increase or decrease at the stimulation frequency. The process was repeated for the filtered EEG. Statistical differences in 30 Hz power between the tSCS-off and tSCS-on condition, and its filtered derivatives, were determined with a pairwise *t*-test where the data were found to follow a parametric distribution and a Wilcoxon signed-rank test where data were non-parametrically distributed. The *p*-values were adjusted using the Benjamini/Hochberg false discovery rate correction method.

3.3.9 Time domain: EEG descriptive statistics

To characterise the EEG signal quantitatively and assess the impact of tSCS and artifact-suppression techniques we used a number of descriptive statistics. Namely, kurtosis, root-mean-square (RMS), Higuchi fractal dimension, and zero-crossings. This approach was motivated by a method proposed by Kohli et al. to evaluate the effectiveness of removing transcranial alternating current stimulation artifacts from EEG [89]. Eyes open, resting state EEG was used for this analysis. The EEG from each channel was split into 10 s non-overlapping segments. The descriptive statistics were calculated for each segment and averaged. An average was taken again across all participants and was displayed graphically.

The descriptive statistics across each EEG condition and electrode position were compared for significant differences. Firstly, the Levene and Shapiro–Wilk tests were performed to determine the homogeneity of variance and normality of the data. Where these tests were satisfied a two-way analysis of variance (ANOVA) was used with the descriptive statistic as the dependent variable and EEG condition and electrode position as the independent factors. The Scheirer-Ray-Hare test was performed where statistical distribution assumptions were not satisfied. Post-hoc tests for multiple comparisons included the pairwise *t*-test for descriptive statistics following a parametric distribution, and the Wilcoxon signed-rank test for non-parametric statistics. The *p*-values were adjusted using the Benjamini/Hochberg false discovery rate correction method.

3.3.10 Frequency domain: effect on individual alpha frequency

The alpha rhythm is a prominent EEG feature which has been attributed to many cognitive processes [101]. To assess the feasibility of monitoring alpha rhythm expression during tSCS we extracted the peak frequency from the range of 8–12 Hz during the resting state task with eyes open and eyes closed. The PSD was calculated as outlined above. Normality and homogeneity were determined with the Shapiro–Wilk and Levene test, respectively. Where distribution assumptions were met we performed a one-way ANOVAs to determine if individual

alpha frequency was significantly affected by EEG condition (tSCS-off, tSCS-on, tSCS-on with filters). We carried out multiple one-way ANOVAs for electrode location (Fz, Oz) and resting state (eyes open, eyes closed) given the strong differences in individual alpha frequency expected from the normal EEG. Post-hoc tests for multiple comparisons were performed as outlined above.

3.3.11 Classification of sensorimotor rhythms

To determine the feasibility of classifying movements from sensorimotor rhythms during tSCS we used the current state-of-the-art: Band-pass filtering between 8 and 30 Hz, common spatial pattern (CSP) filtering, feature extraction and linear discriminant analysis (LDA) classification [52]. EEG was divided into 2 second segments, 0.5–2.5 s, relative to movement onset. Two conditions were considered for classification: Right hand versus bimanual rhythmic finger flexion. Thirty trials per condition were used for training and testing the CSP-LDA classifier. The CSP approach consisted of finding spatial filters w such that the variance of the filtered EEG signals were maximal for one class and minimal for the other. Spatial filters w were found by extremising the following expression through a generalised eigenvalue decomposition:

$$\frac{wX_1X_1^Tw^T}{wX_2X_2^Tw^T}, \tag{3.3}$$

where T denotes the transpose, and X_i is multi-channel, bandpass filtered EEG from class i. Filter w contains a number of eigenvectors (spatial filters) corresponding to the number of EEG channels. It is best practice, however, to select several eigenvectors from each end of the eigenvalue spectrum as spatial filters to aid classification. In this study, we used six pairs of filters. Next, the logarithmic variance of the CSP-filtered EEG signals was used as features to train a LDA classifier. We used 10-fold cross-validation to evaluate the performance of the trained classifier. The accuracy of the classifier was defined as the number of correctly classified trials compared to the total number of trials. A pairwise t-test was used to determine statistically significant differences between the mean accuracies. The p-values were adjusted using the Benjamini/Hochberg false discovery rate correction method.

As the procedure outlined above relies on the spatial distribution of broadband power across the scalp to characterise and classify movement-related cortical activity, scalp topographies during movement were obtained. This allowed for the noise-suppression techniques to be assessed for their ability to remove the tSCS artefacts without distorting characteristic spatial patterns.

3.4 Results

3.4.1 Stimulation artifact in the time domain

The time domain effects of stimulation intensity and electrode position on EEG are illustrated in Figure 3.1. Figure 3.1A,E show representative segments of eyes closed, resting state EEG from the participant whose EEG was least affected by tSCS, owing to them receiving only 10 mA of stimulation. The solid black line represents EEG recorded without tSCS and the grey dashed line is with tSCS. Visually, the signals in Figure 3.1A have a similar amplitude and both feature a 8-10 Hz component, typical of resting state EEG with eyes closed. It appears that at this intensity the frontal EEG channels are spared visually observable distortions. On the other hand, the posterior electrodes, represented by channel Oz (Figure 3.1E), show a clear 30 Hz component. The peak-to-peak amplitude at Oz is 120 μV during tSCS compared with 30 μV without tSCS, a 4-times increase.

At the other end of the intensity spectrum, Figure 3.1C,G show one second of resting state EEG from the participant who received the highest current intensity, 60 mA. In both Fz and Oz the EEG time series includes a substantial 30 Hz stimulation artifact, characterised as narrow high-amplitude peaks. It is most clearly visible in channel Oz. At 60 mA the stimulation condition increased the peak-to-peak amplitude 8.6-times, from 30 μV to 260 μV. The amplitude of the stimulation artifact at Fz is less intense, at around 4-times the size of normal EEG.

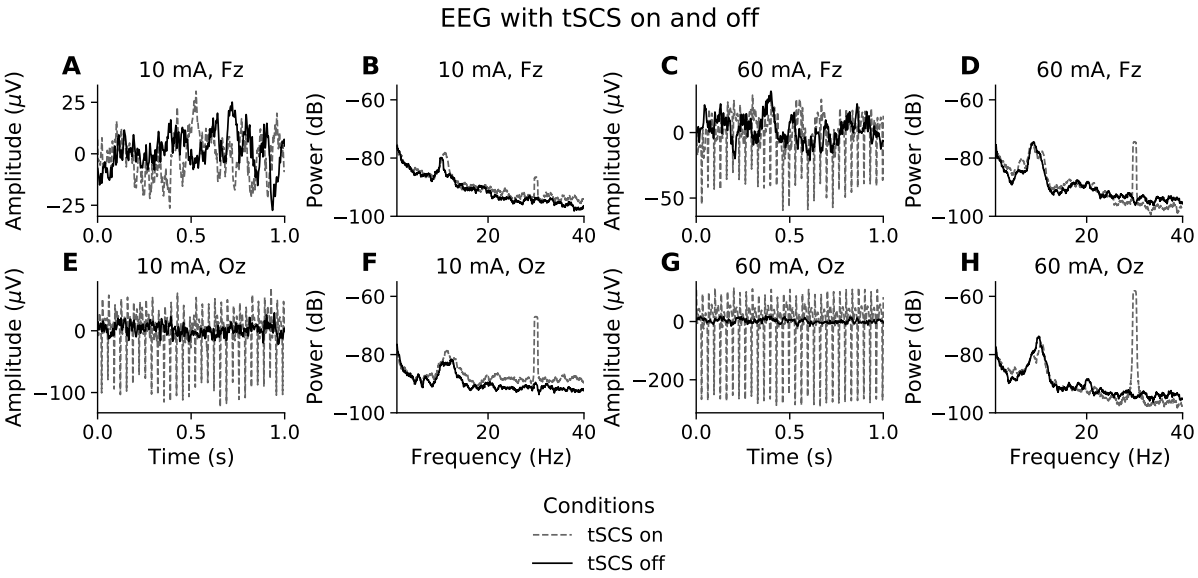

Fig. 3.1 Effect of tSCS on EEG in the time and frequency domain. Time domain (**A, C, E, G**): The first and third column show one second of resting state, eyes closed EEG for the participants with the lowest (10 mA) and highest (60 mA) tolerance to stimulation intensity, respectively. The EEG channel farthest from the stimulation site (Fz) is represented in the first row while the second row relates to the channel most proximal to the stimulation site (Oz). Frequency domain (**B, D, F, H**): The second and fourth column show the power spectral density of resting state, eyes closed EEG for the participants with the lowest (10 mA) and highest (60 mA) tolerance to stimulation intensity, respectively. EEG with stimulation on and stimulation off are presented with grey dashed and solid black lines, respectively.

3.4.2 Stimulation artifact in the frequency domain

Figure 3.1B,F show the power spectral density (PSD) of resting state EEG for a participant who received 10 mA of tSCS. Unlike in the time domain, where the presence of a stimulation artifact is unclear at channel Fz, Figure 3.1B displays a prominent peak at 30 Hz, and is even more pronounced at channel Oz, Figure 3.1F. This trend is mirrored in Figure 3.1D,H. The power is far greater in both channels, reflecting a much stronger current (60 mA). Outside of the 30 Hz frequency bin, the EEG spectra appear unaffected by tSCS compared to the PSD when tSCS is off.

3.4.3 Aliasing Effect

The tSCS artifact is not sufficiently captured by the EEG system, resulting in a constantly modulating artifact amplitude in the time domain (Figure 3.2A) and alternating power in the

frequency domain (Figure 3.2B). The aliasing effect has been reported for other non-oscillatory, periodic stimulation techniques, for instance deep brain stimulation [98].

3.4.4 Spatial distribution of tSCS contamination

To determine how tSCS artifacts manifested in multi-channel EEG with respect to distance from the stimulation site we showed the normalized spectral power at the stimulation frequency (30 Hz) across the midline electrodes (Figure 3.3C). The topographic distribution of 30 Hz power relative to tSCS-off is also given in Figure 3.3A. Further, we explored whether this artifactual component could be removed in the frequency domain to the extent that it was statistically indistinguishable from tSCS-off. A Shapiro–Wilk test found that the power values tended to follow a non-parametric distribution. The following pairwise comparisons, therefore, used the Wilcoxon signed-rank test to assess statistically significant differences between power distributions.

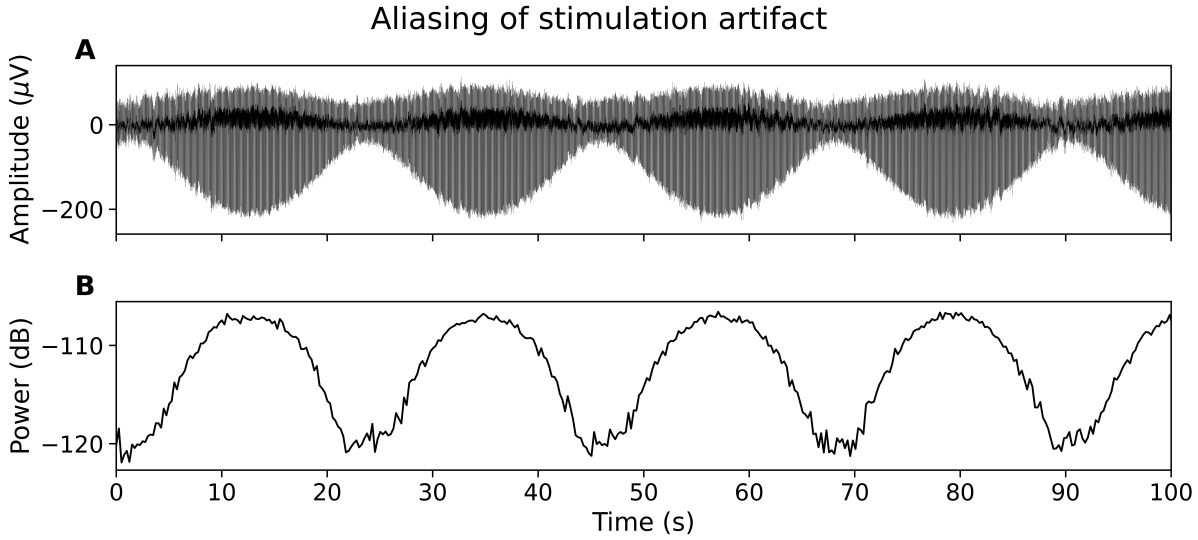

Fig. 3.2 The aliasing effect. **(A)**: EEG showing amplitude of tSCS peaks changing over time. **(B)**: Power spectral density at 30 Hz over time.

It is evident from Figure 3.3B that the power at 30 Hz is substantially increased by tSCS in all electrodes with a rising intensity as a function of distance to stimulation site. Figure 3.3A illustrates this power increase when tSCS is present across the entire head. Compared to when no stimulation is applied the power at 30 Hz is increased by 900% at the posterior channels, with a gradual reduction in power moving from the occipital region but never returning to tSCS-off levels.

Figure 3.3C shows the power at 30 Hz once artifact-reduction techniques were applied. The 30 Hz power in each of the filtered signals was significantly reduced and better resembled the power of the tSCS-off condition, represented by the blue line. The distribution of 30 Hz power when tSCS is off tended to decrease from channel Fz to Pz, before increasing from Pz to Oz. Two filters were able to reproduce this distribution: the SMA (green line) and adaptive filter (red line).

The SMA filter removed the spectral pattern seen before artifact suppression, leaving a more evenly distributed power topography. Power at 30 Hz is diminished in all channels with a maximum difference of -40%.

The adaptive filter (A) diminished the stimulation artifact significantly but was still elevated compared to tSCS-on alone, the power is greatly diminished at only 58% above the tSCS-off session. Interestingly, the adaptive filter performed better on the posterior electrodes, which trended towards 0% modulation compared with no stimulation and with no statistically significant difference in means ($p > 0.05$). This perhaps suggests the adaptive filter is more effective where the stimulation artifact has a stronger signal-to-noise ratio.

The median filter resulted in the greatest underestimation of 30 Hz power in all channels. The notch filter (N), on the other hand, performed the best among the filters, suppressing the 30 Hz artifact, with statistically similar power at all midline electrodes ($p > 0.05$), except for Poz ($p < 0.05$) and Oz ($p < 0.01$).

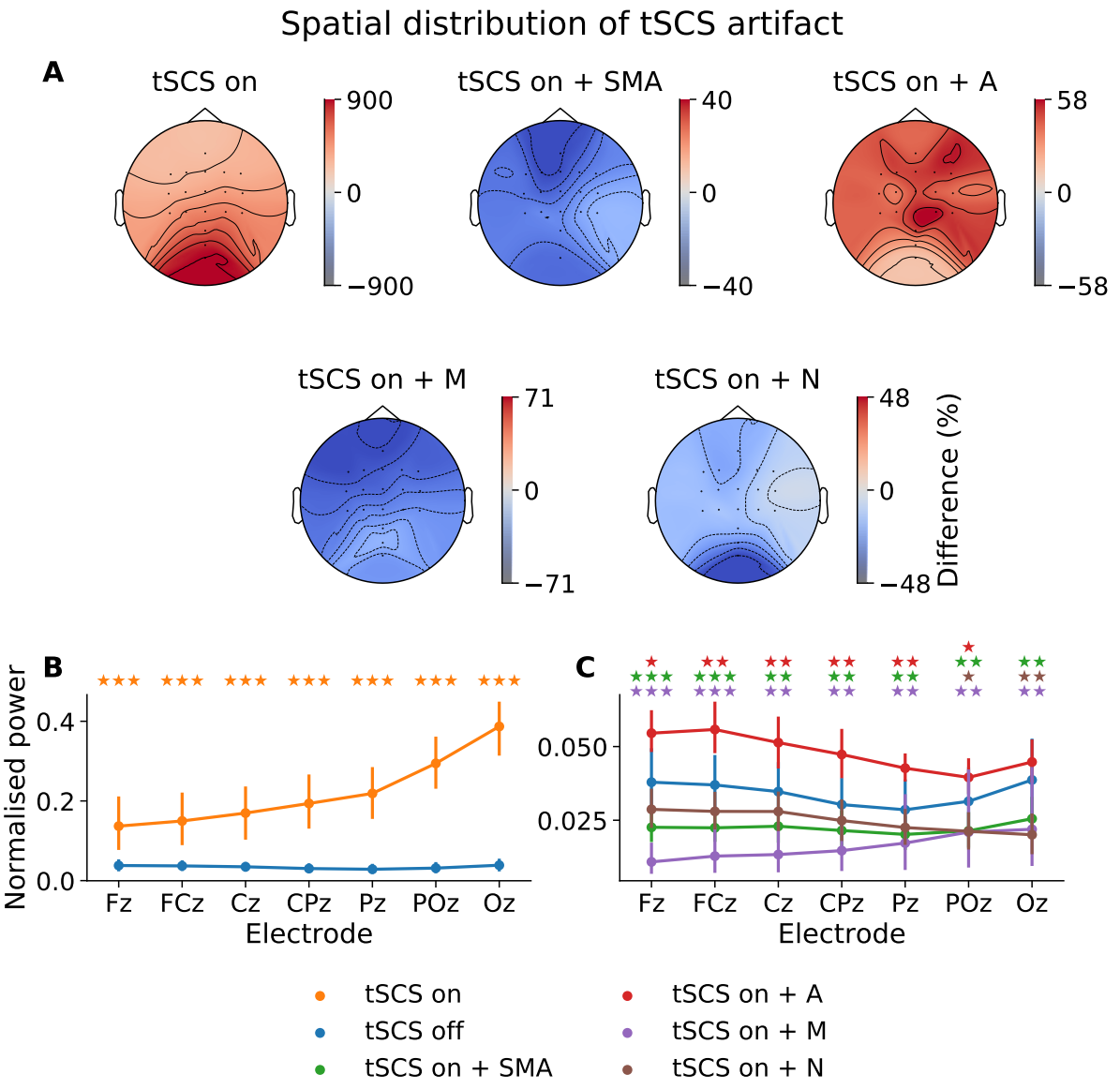

Fig. 3.3 Power distribution at 30 Hz (i.e., the stimulation frequency) across all participants. **(A)**: Topographic power differences of tSCS-on, and its filtered derivatives, relative to tSCS-off (%). SMA: superposition of moving averages filter; A: adaptive filter; M: Median filter; N: notch filter. **(B)**: Normalised spectral power at 30 Hz across midline electrodes during tSCS-on and tSCS-off. **(C)**: Normalised spectral power at 30 Hz across midline electrodes for tSCS-off and tSCS-on after artifact-suppression. The p-values from a Wilcoxon signed-rank test between tSCS-off and each tSCS-on condition are indicated with a colour-coded star for each electrode ($\star\, p < 0.05$, $\star\star\, p < 0.01$, $\star\star\star\, p < 0.001$).

3.4.5 Time domain: EEG descriptive statistics

To quantify the EEG signals in the time domain we used descriptive statistics, see Figure 3.4. The Levene test and Shapiro–Wilk test showed that each descriptive statistic failed to meet assumptions of homogeneity of variance ($p < 0.01$) and normality ($p < 0.01$), respectively. The Scheirer-Ray-Hare test (similar to a two-way ANOVA but for non-parametric data) was therefore used to determine statistically significant effects based on condition, electrode, and condition-electrode interaction.

All descriptive statistics showed statistically significant differences based on condition (Kurtosis: $p < 0.01$; RMS: $p < 0.01$; Higuchi fractal dimension: $p < 0.01$; Zero crossings: $p < 0.01$) and electrode (Kurtosis: $p < 0.01$; RMS: $p < 0.01$; Higuchi fractal dimension: $p < 0.01$; Zero crossings: $p < 0.01$) but no interaction between condition and electrode (Kurtosis: $p < 0.31$; RMS: $p < 0.90$; Higuchi fractal dimension: $p < 0.99$; Zero crossings: $p < 0.98$). The results from a Wilcoxon signed-rank test for electrodes Fz and Oz are presented in Table 3.1.

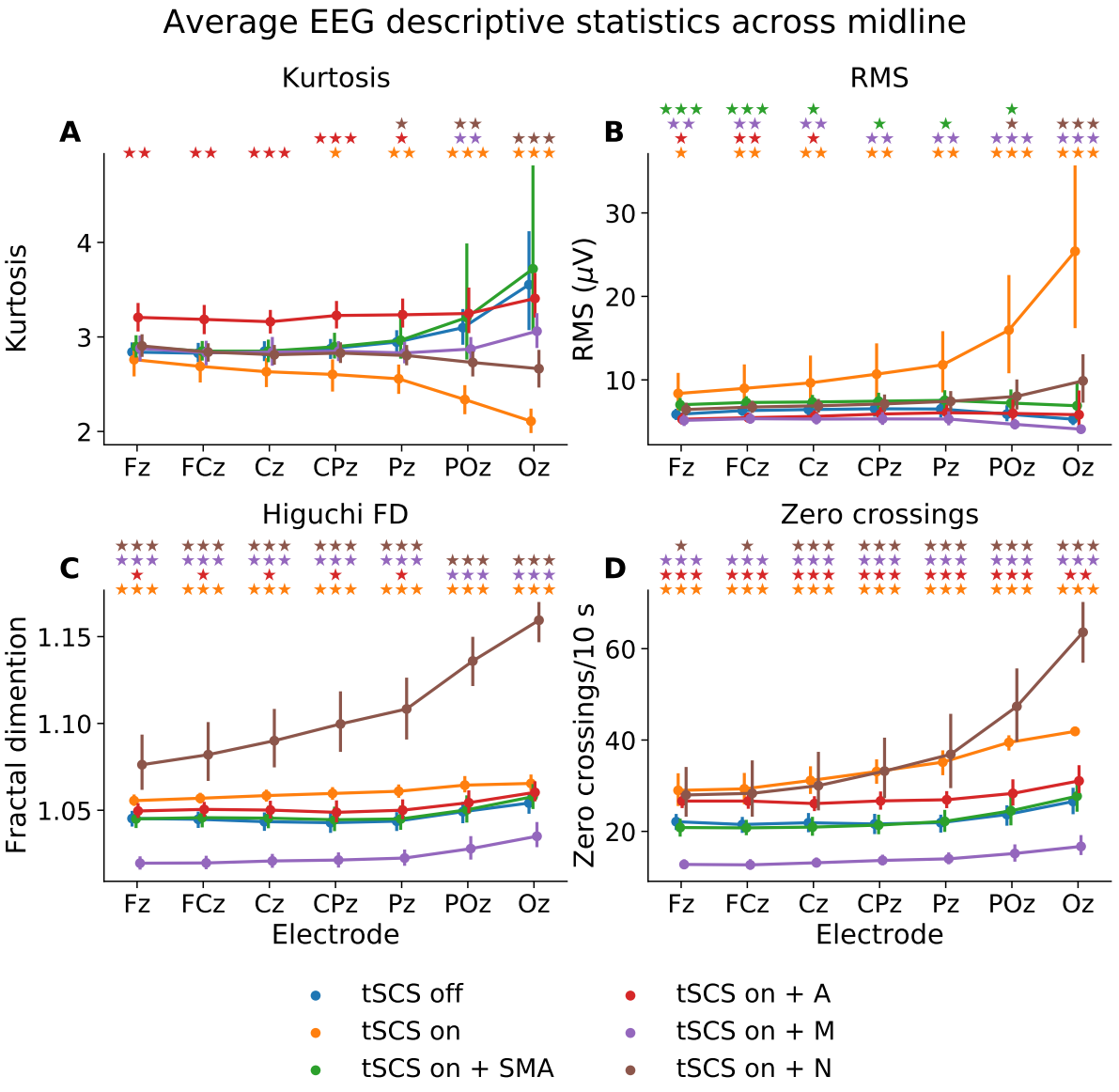

Fig. 3.4 Mean descriptive statistics—**(A)**: kurtosis, **(B)**: root mean square (RMS), **(C)**: Higuchi fractal dimension (FD), **(D)**: zero-crossings—of eyes closed, resting state EEG from midline electrodes, for tSCS-off, tSCS-on, and tSCS-on with filtering. SMA: superposition of moving average filter; A: adaptive filter; M: median filter; N: notch filter. The p-values from a Wilcoxon signed-rank test between tSCS-off and each tSCS-on condition are indicated with a colour-coded star for each electrode ($\star\ p < 0.05$, $\star\star\ p < 0.01$, $\star\star\star\ p < 0.001$).

A Wilcoxon signed-rank test showed that kurtosis was significantly different at CPz, Pz, POz, and Oz when tSCS was turned on. The SMA filter managed to transform the kurtosis at these channels to ranges statistically similar to that of EEG with tSCS turned off. The adaptive filter also performed well at POz and Oz but resulted in poorer signal reconstruction with

significantly different kurtosis values ($p < 0.01$) at Fz, FCz, Cz, and Pz, compared to tSCS-off, perhaps implying the adaptive filter performs better on signals with well-defined artifacts.

The RMS was significantly elevated in all channels but more so at the posterior electrodes: From 5.87 to 8.37 μV at Fz ($p < 0.01$) and from 5.29 to 25.40 μV at Oz ($p < 0.001$). There were no filters which managed to suppress the tSCS contribution at all electrodes. The notch filter, however, performed the best at returning the RMS to levels statistically similar to that of clean EEG in five out of the seven midline electrodes investigated.

Table 3.1 Participant-wise mean of EEG descriptive statistics of resting state EEG with eyes open. The difference between each tSCS-on condition with respect to tSCS-off is given in addition to the *p*-values associated with a Wilcoxon signed-rank test. The *p*-values were adjusted using the Benjamini/Hochberg false discovery rate correction method.

	Fz			**Oz**		
	Kurtosis (Unitless)					
	Mean	***p*-Value**	**Difference**	**Mean**	***p*-Value**	**Difference**
tSCS-off	2.84	-	-	3.55	-	-
tSCS-on	2.76	0.61	−0.08	2.11	<0.001	−1.44
tSCS-on + adaptive	3.21	<0.01	0.37	3.41	0.97	−0.15
tSCS-on + median	2.88	0.70	0.04	3.06	0.33	−0.50
tSCS-on + notch	2.90	0.47	0.07	2.66	<0.001	−0.89
tSCS-on + SMA	2.90	0.49	−0.06	3.72	0.69	0.17
	RMS (μV)					
	Mean	*p*-value	Difference	Mean	*p*-value	Difference
tSCS-off	5.87	-	-	5.29	-	-
tSCS-on	8.37	0.01	2.50	25.40	<0.001	20.11
tSCS-on + adaptive	5.28	0.05	−0.58	5.83	0.13	0.54
tSCS-on + median	5.15	<0.01	−0.72	4.09	<0.01	−1.20
tSCS-on + notch	6.45	0.16	0.58	9.88	<0.01	4.60
tSCS-on + SMA	7.02	<0.001	1.15	6.9	0.11	1.61
	Higuchi fractal dimension					
	Mean	*p*-value	Difference	Mean	*p*-value	Difference
tSCS-off	1.045	-	-	1.054	-	-
tSCS-on	1.056	<0.001	0.01	1.065	<0.01	0.01
tSCS-on + adaptive	1.050	<0.01	0.004	1.060	<0.01	0.006
tSCS-on + median	1.020	<0.001	−0.03	1.035	<0.001	−0.02
tSCS-on + notch	1.086	<0.001	0.03	1.159	<0.001	0.11
tSCS-on + SMA	1.045	0.93	−0.0002	1.058	0.30	0.004
	Zero crossings (Crossings/10 s)					
	Mean	*p*-value	Difference	Mean	*p*-value	Difference
tSCS-off	22.12	-	-	26.55	-	-
tSCS-on	29.0	<0.001	6.85	41.90	<0.001	15.34
tSCS-on + adaptive	26.64	<0.001	4.52	31.05	<0.01	4.50
tSCS-on + median	12.76	<0.001	−9.36	16.70	<0.001	−9.85
tSCS-on + notch	27.97	<0.01	5.85	63.60	<0.001	37.05
tSCS-on + SMA	20.84	0.077	−1.28	27.71	0.96	1.16

The Higuchi fractal dimension, a measure of signal complexity, was significantly altered at all channels once tSCS was applied ($p < 0.001$). The only filter able to suppress the tSCS-induced increase in complexity was the SMA filer which resulted in statistically similar values ($p > 0.05$) in all channels. The adaptive filter also performed well on POz and Oz. Interestingly, the notch filter increased the fractal dimension in all channels to an extent even greater than tSCS alone.

The number of zero crossings, a statistic that partly reflects signal frequency, was also significantly altered in all channels by tSCS. On average, the number of zero crossings per 10 s increased significantly from 22.12 to 29.0 ($p < 0.001$) at channel Fz and from 26.55 to 41.90 ($p < 0.001$) at channel Oz. Again, the SMA filter alleviated the effects of tSCS in all channels with 20.84 crossings per 10 seconds at Fz (a non-significant difference of -1.28, $p = 0.077$) and 23.60 at Oz (a non-significant difference of -1.16, $p = 0.96$). No other filter returned the average zero-crossings to levels statistically similar to that of tSCS-off EEG. The median filter significantly underestimated ($p < 0.001$), and the adaptive and notch filter significantly overestimated the number of zero crossings per 10 s ($p < 0.001$).

3.4.6 Frequency domain: individual alpha frequency

To assess how tSCS affected spectral features beyond the stimulation frequency we considered the individual alpha frequency for each participant at channel Fz and Oz, as illustrated in Figure 3.5. It is clear that the characteristic increase in peak alpha from the eyes open to eyes closed condition is displayed whether tSCS is applied or not. The normality and homogeneity were confirmed by the Shapiro–Wilk and Levene test, respectively. One-way ANOVAs were performed to compare the effect of EEG condition (tSCS-off, tSCS-on, tSCS-on with filters) on individual alpha peak frequency during different resting states and channels. The analysis revealed that there was no statistically significant difference in individual alpha at Fz or Oz with eyes open or closed, see Table 3.2. A pairwise *t*-test for multiple comparisons found that the mean individual alpha peak frequency was not significantly different between any condition ($p > 0.05$), however at channel Fz the adaptive filtered EEG during eyes open neared a significant difference ($p = 0.06$).

Figure 3.6 shows the effect of tSCS on individual alpha frequency at Oz. A Pearson's correlation coefficient was found to be 0.919 ($p<0.001$), implying a near linear relationship between frequencies. This result demonstrates that individual alpha frequency is not modulated by the application of tSCS.

Table 3.2 Subject-wise average of individual alpha peak frequencies. The result of a one-way ANOVA is given for the 'eyes open' and 'eyes closed' condition. A pairwise *t*-test for multiple comparisons determined if the mean of each condition was significantly different from the tSCS-off condition. The *p*-values were adjusted using the Benjamini/Hochberg false discovery rate method. The difference with the tSCS-off condition is given. Shapiro–Wilk's and Levene's tests were performed to confirm normality and homogeneity before each ANOVA ($p < 0.05$).

	Fz					
	Eyes open			Eyes closed		
	$F(5,102) = 3.52$, $p = 0.069$, $\eta^2 = 0.15$			$F(5,102) = 0.50$, $p = 0.77$, $\eta^2 = 0.024$		
	Mean	*p*-value	Difference	Mean	*p*-value	Difference
tSCS-off	8.13	-	-	9.72	-	-
tSCS-on	8.38	0.54	0.25	9.80	0.91	0.08
tSCS-on + adaptive	9.34	0.06	1.21	10.01	0.85	0.29
tSCS-on + median	8.00	0.72	−0.13	9.61	0.94	−0.11
tSCS-on + notch	8.38	0.54	0.25	9.80	0.94	0.08
tSCS-on + SMA	8.78	0.10	0.67	9.61	0.94	−0.11
	Oz					
	Eyes open			Eyes closed		
	$F(5,102) = 3.52$, $p = 0.99$, $\eta^2 = 0.0050$			$F(5,102) = 0.031$, $p = 0.99$, $\eta^2 = 0.0015$		
	Mean	*p*-value	Difference	Mean	*p*-value	Difference
tSCS-off	9.42	-	-	10.21	-	-
tSCS-on	9.61	0.97	0.18	10.32	1.0	0.11
tSCS-on + adaptive	9.77	0.97	0.34	10.31	1.0	0.1
tSCS-on + median	9.53	0.97	0.11	10.30	1.0	0.08
tSCS-on + notch	9.61	0.97	0.18	10.32	1.0	0.11
tSCS-on + SMA	9.67	0.97	0.24	10.32	1.0	0.1

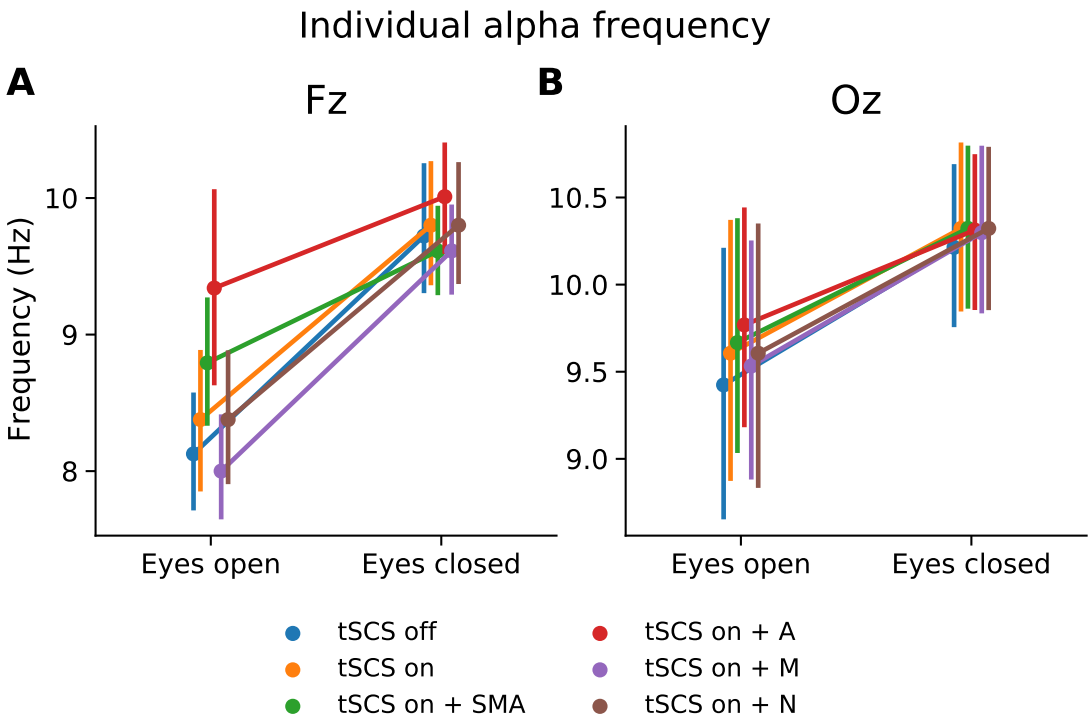

Fig. 3.5 Subject-wise peak frequency in alpha range (8–12 Hz) during resting state with eyes opened and eyes closed. **(A)**: Channel Fz, **(B)**: Channel Oz.

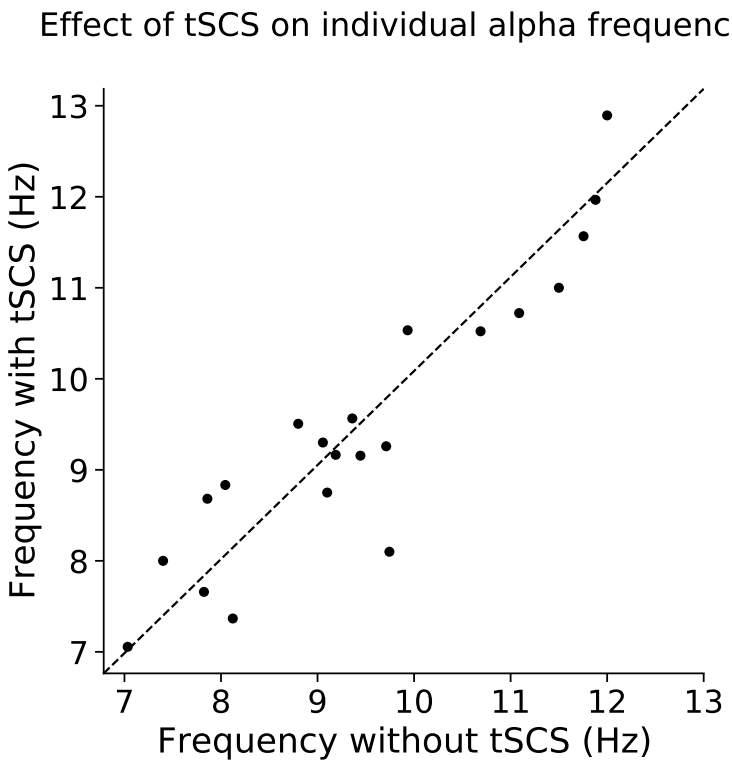

Fig. 3.6 Individual alpha peak frequency with and without tSCS. The Pearson's correlation coefficient was found to be 0.919 with a p value <0.001. Dashed line illustrates perfect linearity.

3.4.7 Classification of sensorimotor rhythms

To determine the feasibility of classifying sensorimotor rhythms during tSCS we used EEG from a movement execution task to form a two-class classification problem. The 10-fold cross-validation scores are given in Table 3.3. The CSP-LDA method was able to predict correctly right-hand and bimanual finger flexion on average 76.14 $\pm$ 12.42% of the time when stimulation was off, and 75.71 $\pm$ 10.62 when stimulation was on. Both scores lie above chance level for a two-class BCI with 30 trials per class (67%, p<0.05 [102]). A paired t-test reveled no statistically significant differences between these scores ($p > 0.05$). The p-values were adjusted using the Benjamini/Hochberg false discovery rate correction method.

Table 3.3 Mean 10-fold classification accuracies across all subjects. The significance level of a paired *t*-test is given with respect to the tSCS-off condition.

	Accuracy (%)	***p*-Value**
tSCS-off	76.14 ± 12.42	-
tSCS-on	75.71 ± 10.62	0.84
tSCS-on + SMA	76.79 ± 9.51	0.76
tSCS-on + adaptive	53.64 ± 12.24	0.00015
tSCS-on + notch	77.29 ± 11.17	0.6
tSCS-on + median	77.14 ± 10.22	0.55

Filtered EEG performed similarly well: SMA filter, 76.79 ± 9.51%; notch filter: 77.29 ± 11.17%; median filter: 77.14 ± 10.22%. Interestingly, these scores exceed the accuracies obtained using the tSCS-off and tSCS-on conditions, however not significantly so ($p > 0.05$). The adaptive filter performed poorly with 53.64 ± 12.24% accuracy, below chance level and therefore unsuitable for BCI applications.

Figure 3.7 shows the difference in ERD/ERS topographic distribution between movement conditions from the tSCS condition and with artefact-suppression techniques applied. A near identical pattern is observed after filtering with the median, SMA, and notch filters. The adaptive filter, on the other hand, contrasts with the other topographies. This could be a reflection of signal distortion by the adaptive filter and may have resulted in the poorer classification accuracy reported above.

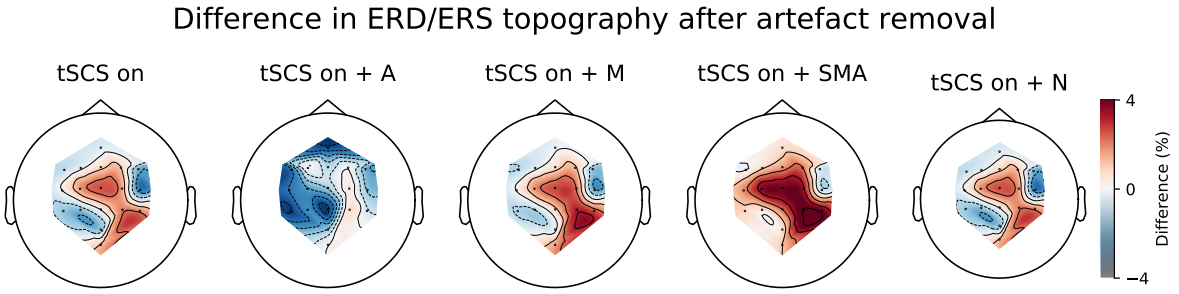

Fig. 3.7 Subject-wise average difference in ERD/ERS (%) topography between movement conditions during tSCS and with artefact suppression.

3.5 Discussion

This study, for the first time, characterised the artifacts associated with transcutaneous electrical spinal cord stimulation in electroencephalography recordings. We found that tSCS produced narrow, high-amplitude peaks in the time domain at a rate equal to the stimulation frequency at nearly an order of magnitude more powerful than normal EEG. Through volume conduction, all electrodes were affected by tSCS to a greater or lesser extent. The degree of contamination was highly dependent on stimulation intensity and electrode position. We also found, however, that it may be possible to utilise EEG during tSCS, after applying artifact-suppression techniques. This study supports the use of a superposition of moving averages (SMA) filter as it resulted in descriptive statistics most resembling that of normal EEG. Kohli et al. drew similar conclusions in their report of removing electrical artifacts from EEG, which used a similar filter-evaluation strategy [89]. Perfect EEG reconstruction was not achieved with the SMA filter, however. Even after filtering the power at the stimulation frequency was different to normal EEG. It is a matter of contention whether perfect reconstruction is necessary in order to conduct legitimate analyses. Further investigation is required to determine if tSCS exerts an instantaneous neuromodulatory effect on cortical oscillatory activity. This is necessary to fully quantify the performance of stimulation-artefact attenuation algorithms, as EEG may be endogenously modulated by tSCS.

Analyses that do not overlap with the stimulation frequency may not require artifact-suppression processing at all. For instance, we showed that individual alpha frequencies can be extracted accurately during tSCS from all EEG channels, even without filtering. If an analysis must overlap with the stimulation frequency then a notch filter may be sufficient to reduce tSCS contamination to levels statistically similar as normal EEG, at least in the frontal and central electrodes. At the occipital area we showed that the adaptive filter was most effective in attenuating tSCS artifacts. The notch filter, however, may be too much of a blunt tool as it was unable to reconstruct the spatial distribution of spectral power typically associated with EEG [103]. The adaptive method, however, performed better at reconstructing the higher spectral power associated with the posterior channels, perhaps as the stimulation artifact is better defined and was therefore easier for the algorithm to remove.

Interestingly, the results from our movement-classification analysis found that spinal stimulation posed no impediment to BCI performance. SMA, notch, and median filtering actually increased the classification performance, but not significantly so, perhaps suggesting a potential neuromodulatory effect of tSCS. Indeed, high-intensity functional electrical stimulation has been shown to result in stronger event-related desynchronisation in the beta band (14–30 Hz)

when applied to peripheral musculature, with an enhanced effect as a function of time [104, 80]. The movement execution task in this study, however, involved only 30 repetitions of each movement. Future work should investigate whether this increase in performance would trend towards significance if stimulation were applied for a longer duration. The adaptive filter, however, should not be implemented in future analyses given its poor performance in this study, consistently yielding scores below chance level for a two-class BCI. As shown in the descriptive statistics analysis outlined above the adaptive filter performed better where the stimulation artifact is particularly prominent; that is, on EEG from the posterior electrodes. Given that most discriminatory motor signals come from the central area and the effects of stimulation are less prominent among these channels, the adaptive filter is likely poorly approximating the stimulation artifact and is removing valuable sensorimotor information instead. Although this filter has demonstrated efficacy in other work, these studies involved the reconstruction of EMG signals [88, 87]. Therefore, it is likely not suitable for preserving the low-amplitude, low-frequency sensorimotor signals from EEG. Nevertheless, even without artifact-suppression, the tSCS-contaminated EEG proved classifiable with standard BCI techniques. This is a somewhat surprising result given the aliasing seen at the stimulation frequency. BCIs are often built around linear classifiers that require quasi-stationary band-power features to predict brain states. If the EEG power spectrum is exogenously modulated then band-power features likely carry less discriminatory power. Perhaps aliasing was not prominent enough given our 1200 Hz sampling rate to impact BCI performance. Future studies should bare this effect in mind, however, as a lower sampling rate would likely result in enhanced aliasing. Future studies should consider oversampling where practical [98].

Another practical consideration when performing an analysis on EEG recorded during tSCS is that it makes some conventional pre-processing steps challenging. For instance, many EEG pre-processing pipelines rely on rejection thresholds based on descriptive statistics—for example, channel amplitude, kurtosis, root-mean-square—to automatically remove bad spans of data [105, 106]. As we have demonstrated here, EEG descriptive statistics are substantially altered by tSCS, meaning thresholding techniques would eliminate spans of data that are otherwise good. This may be a reason in itself to apply artifact-suppression techniques as a primary step in a tSCS analysis pipeline, particularly when working on EEG from posterior locations.

A potential limitation of this study is that the average stimulation intensity applied to the healthy volunteers (10–60 mA) was likely lower than what would be delivered in clinical practice. Spinal-cord injured individuals tend to have impaired sensibility below their injury level and can likely tolerate higher currents on average (40–200 mA). The results from this

study therefore may not be representative of what is feasible in practice. Future analyses should replicate this study using a spinal-cord injured population to confirm if EEG monitoring is feasible at higher stimulation intensities.

A further potential limitation is that the method used to determine stimulation intensity lacks an objective basis, relying instead on the subjective feedback of participants. It is, therefore, unknown to what extent tSCS transsynaptically activated motor neurons relative to motor threshold. Indeed, participants who had poor tolerance to the stimulation may have received little-to-no dorsal root/column activation due to insufficient current transfer. Future investigations should determine stimulation intensity with reference to the motor threshold as determined by the posterior root-muscle reflex.

The results from this study should not be viewed as a definitive statement on the effects of tSCS on EEG. Due to the variation in stimulation parameters used across tSCS studies conclusions can only be inferred with regards to the parameters that we have used here. For instance, we chose a one-millisecond long pulse with a 10 kHz carrier frequency delivered at 30 Hz to the cervical region of the spine, reflecting recent studies of upper-limb motor rehabilitation [67, 65, 83, 82]. Other studies targeting lower limb rehabilitation or spasticity reduction have used different parameters: 20 or 50 Hz pulse trains, 5 kHz carrier frequencies, monophasic instead of biphasic pulses [64, 107, 108].

3.6 Conclusions

Owing to the relatively recent rise of tSCS there are many avenues of investigation currently unexplored. We note that investigations of cortical modulation have already begun and are likely to continue [72]. EEG offers invaluable access to brain dynamics, allowing source localisation and separation at excellent temporal resolutions [109]. This study provides an insight into the effects of cervical tSCS on EEG and our analyses showed that signal processing techniques such as the superposition of moving averages filter can reasonably suppress tSCS contamination. We conclude that simultaneous EEG monitoring is feasible and reliable, and encourage subsequent research to use EEG to better understand the activity of the sensorimotor cortex during tSCS-based rehabilitation of spinal-cord injury patients.

Author contributions

Conceptualization, C.M. and A.V.; methodology, C.M.; software, C.M.; validation, C.M., A.V.; formal analysis, C.M.; investigation, C.M.; resources, Y.Z.; data curation, C.M.; writing—

original draft preparation, C.M.; writing—review and editing, A.V. and M.A.; visualization, C.M.; project administration, M.A.; funding acquisition, M.A. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Human Subjects Ethics Sub-committee of the Hong Kong Polytechnic University (HSEARS20201105003, 26 Nov 2020).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data availability statement

Data will be made available upon reasonable request to the authors.

Acknowledgments

We sincerely thank the research participants for their patience and commitment to our study.

Conflicts of interest

The authors declare no conflict of interest.

Chapter 4

Effect of cervical transcutaneous spinal cord stimulation on sensorimotor cortical activity during upper-limb movements in healthy individuals

This chapter was written by Ciarán McGeady, with Monzurul Alam, Yong-Ping Zheng, and Aleksandra Vučković, and published in *Journal of Clinical Medicine* [92].

4.1 Abstract

Transcutaneous spinal cord stimulation (tSCS) can improve upper-limb motor function after spinal cord injury. A number of studies have attempted to deduce the corticospinal mechanisms which are modulated following tSCS, with many relying on transcranial magnetic stimulation to provide measures of corticospinal excitability. Other metrics, such as cortical oscillations, may provide an alternative and complementary perspective on the physiological effect of tSCS. Hence, the present study recorded EEG from 30 healthy volunteers to investigate if and how cortical oscillatory dynamics are altered by 10 min of continuous cervical tSCS. Participants performed repetitive upper-limb movements and resting-state tasks while tSCS was delivered to the posterior side of the neck as EEG was recorded simultaneously. The intensity of tSCS was tailored to each participant based on their maximum tolerance (mean: 50 $\pm$ 20 mA). A control session was conducted without tSCS. Changes to sensorimotor cortical activity during movement were quantified in terms of event-related (de)synchronisation

(ERD/ERS). Our analysis revealed that, on a group level, there was no consistency in terms of the direction of ERD modulation during tSCS, nor was there a dose-effect between tSCS and ERD/ERS. Resting-state oscillatory power was compared before and after tSCS but no statistically significant difference was found in terms of alpha peak frequency or alpha power. However, participants who received the highest stimulation intensities had significantly weakened ERD/ERS (10% ERS) compared to when tSCS was not applied (25% ERD; p = 0.016), suggestive of cortical inhibition. Overall, our results demonstrated that a single 10 min session of tSCS delivered to the cervical region of the spine was not sufficient to induce consistent changes in sensorimotor cortical activity among the entire cohort. However, under high intensities there may be an inhibitory effect at the cortical level. Future work should investigate, with a larger sample size, the effect of session duration and tSCS intensity on cortical oscillations.

4.2 Introduction

Transcutaneous spinal cord stimulation is a non-invasive neuromodulatory technique that has shown potential in reversing upper-limb paralysis in spinal cord injury (SCI) patients [83, 82]. The technique often involves placing one or more cathode electrodes at and around the spinal level of injury to deliver high-frequency currents at sub-threshold intensities. It has been postulated that electrical interaction with a combination of structures, such as dorsal column fibres, the dorsal horn and posterior/ventral roots, decreases the motor threshold, making voluntary motor control easier through residual descending pathways [110, 108, 111]. When combined with conventional rehabilitative therapies such as physical practice, tSCS has led to lasting functional improvements [83, 82, 66]. The extent to which tSCS modulates corticospinal pathways, however, is still a matter of contention.

Numerous studies have investigated tSCS modulation at both the cortical and spinal level [72, 112, 77, 71, 113, 94, 58]. Benavides et al., for example, investigated cortical modulation by comparing motor evoked potentials (MEPs) induced by transcranial magnetic stimulation (TMS) before and after 20 min of tSCS. They found that MEP amplitudes tended to increase following stimulation, implying facilitation of the corticospinal tract. Ambiguities still exist surrounding tSCS-based neuromodulation, however. In a similar study, Sasaki et al. reported a null effect of tSCS on MEP amplitude, albeit with sessions of a shorter duration [71]. Both studies, and indeed the majority of similar studies, used MEP amplitudes to provide a metric of cortical excitability. Other measures, such as cortical oscillations, offer an alternative perspective on the physiological effects of tSCS. Although MEP and oscillation amplitudes

have both been associated with motor cortical excitability, they are not strongly correlated, and likely reflect different neural processes [38, 79]. Where cortical oscillations tend to reflect the induced excitability of large populations of cortical neurons, MEPs are affected by the global excitability of corticospinal pathways [38, 36]. An understanding of how each measure is affected by tSCS will build a stronger foundation in which to guide future tSCS-based neurorehabilitation strategies. A further benefit of understanding the influence of tSCS on cortical oscillations concerns the use of brain–computer interfaces, which are increasingly being used in neurorehabilitation, often when combined with stimulation-based therapies [114, 115]. Such BCI paradigms rely on distinct and consistent modulation of sensorimotor oscillations during imagined or attempted movement. Facilitated expression of sensorimotor oscillations may improve the performance of such systems [104, 51].

As far as we are aware, no studies have yet considered tSCS-based neuromodulation in terms of sensorimotor cortical oscillations as measured from the electroencephalogram (EEG). Given reports of enhanced excitability of motoneuron and cortico-motoneuronal synapses through spinal stimulation, we would expect an expression of neuromodulation in terms of cortical oscillations, as is the case with stimulation-based modalities such as functional electrical stimulation (FES) [80], and transcutaneous electrical nerves stimulation (TENS) [116]. The variety of modulation is a matter of conjecture, however. On the one hand, we may expect sensorimotor cortical excitation, as sensory afferent volleys may be amplified resulting in stronger activation of the somatosensory cortex. On the other hand, we may expect cortical inhibition given that high-frequency spinal cord stimulation has been linked to serotonin release in the dorsal horn which may suppress nociceptive transmission [117, 118]. At the very least, we would expect a quantifiable difference in sensorimotor cortical activity with tSCS. Therefore, the aim of the present study was to investigate if sensorimotor cortical activity during upper-limb movement could be modulated by short-duration continuous tSCS.

To test this hypothesis, we had healthy volunteers perform upper-limb movements as continuous tSCS was delivered to the posterior region of the neck, using typical clinical stimulation parameters [82, 83]. EEG was recorded simultaneously and sensorimotor dynamics were extracted in an offline analysis. The alpha frequency is the most dominant EEG feature during the resting state, and its event-related (de)synchronisation (ERD/ERS) has been associated with cortical activation during sensorimotor tasks, reflecting asynchronous neural firing [119, 120, 36]. We performed a side-by-side comparison of ERD/ERS with and without tSCS. A further hypothesis was that sensorimotor neuromodulation by tSCS would be subject to a dose effect where the modulation would be facilitated or attenuated as a function of time. We tested this by considering the ERD/ERS of alpha and beta frequency bands across movement

repetitions. In addition to ERD during movement, we compared resting-state EEG before and after tSCS.

4.3 Materials and methods

4.3.1 Participants

Thirty able-bodied volunteers (9 females, 21 males; 26.7 $\pm$ 3.0 years old) participated in this study in line with previous studies and project timing constraints. Twenty-one participants were also included in the investigation described in Chapter 3. Exclusion criteria included musculoskeletal pathology of the upper limbs, metal or electronic implants, medications that influenced neural excitability (antiepileptic, antipsychotics, or antidepressants), allergy to the electrode material, epilepsy, and pregnancy.

Sessions were conducted at the same time of day to minimise baseline EEG variances and subjects were allowed to take breaks in between recording runs. Written informed consent was obtained from all participants. This study was approved by the Human Subjects Ethics Sub-committee of the Hong Kong Polytechnic University and conducted according to the principles and guidelines of the Declaration of Helsinki.

4.3.2 Experimental protocol

Based on a two-day crossover design, participants underwent two sessions on different days. Both sessions had participants perform a 10 min upper-limb movement task as EEG and EMG were recorded from the sensorimotor region of the scalp and forearms respectively (see Figure 4.1A for an illustration of the experimental setup). Continuous tSCS was applied concurrently to the cervical region of the neck during only one of these sessions (Figure 4.2A). The order in which participants received both sessions was pseudo-randomised.

There were two parts to a session: (1) resting-state EEG recording, and (2) a movement execution task. Part (1) was performed before and after the movement task to investigate potential modulation of physiological markers. While recording, participants were required to sit still in an upright position, minimising all body and eye movements. Resting-state EEG was recorded for 90 s with eyes closed. The movement execution task was performed in an upright, seated position and had participants perform rhythmic right-hand, left-hand and bimanual finger flexion, as cued by an interface on a computer screen (Figure 4.1A). A rightwards-pointing arrow cued right-hand movement, a leftwards-pointing arrow cued left-hand movement, and a double arrow pointing both left and right cued bimanual movements. We included a bimanual

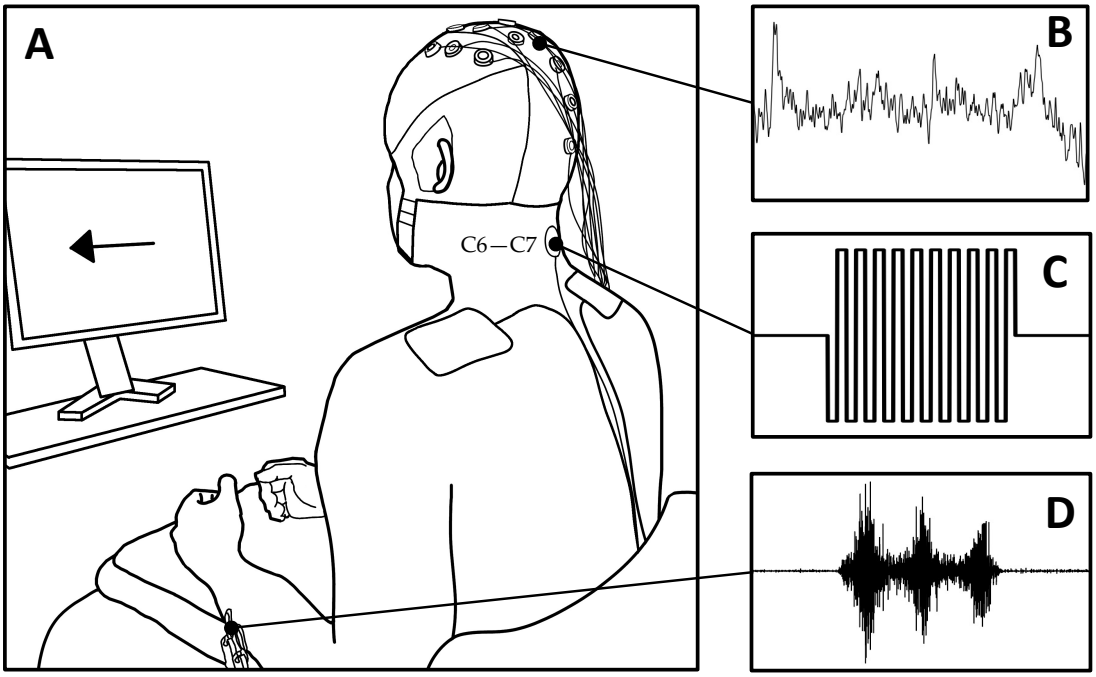

Fig. 4.1 Experimental setup showing recording and stimulation modalities. (**A**) Participant receives cues from a computer screen to perform upper-limb movements. (**B**) EEG is recorded from the central area of the scalp. (**C**) One millisecond long burst containing 10 biphasic pulses is delivered at 30 Hz to the posterior region of the neck during continuous tSCS. (**D**) EMG during left-hand rhythmic finger flexion/extension over the extensor carpi radialis. The same setup was used on the right side.

condition as SCI patients often use both hands during tSCS training, and most activities of daily living include coordination of both hands [121, 82, 122]. Each movement was performed and sustained for four seconds and repeated 30 times, with a randomised 1.5 to 2.5 s inter-trial interval. The timing scheme is illustrated in Figure 4.2B. EMG was recorded from the forearm muscles to measure movement onset.

4.3.3 Electroencephalography (EEG)

Two g.USBamp biosignal amplifiers (g.tec, Schiedlberg, Austria) recorded EEG at 1200 Hz from 19 passive electrodes: Fz, FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, C4, CP3, CP1, CPz, CP2, CP4, Pz, POz, and Oz, according to the international 10–20 system (See Figure 4.1A,B) [123]. Electrode AFz was used as ground and the reference electrode was placed on the right earlobe. EEG was filtered with a band-pass (0.01–100 Hz) and a notch filter (50 Hz). Electrode impedances were kept below 5 kΩ throughout the recording session, and participants

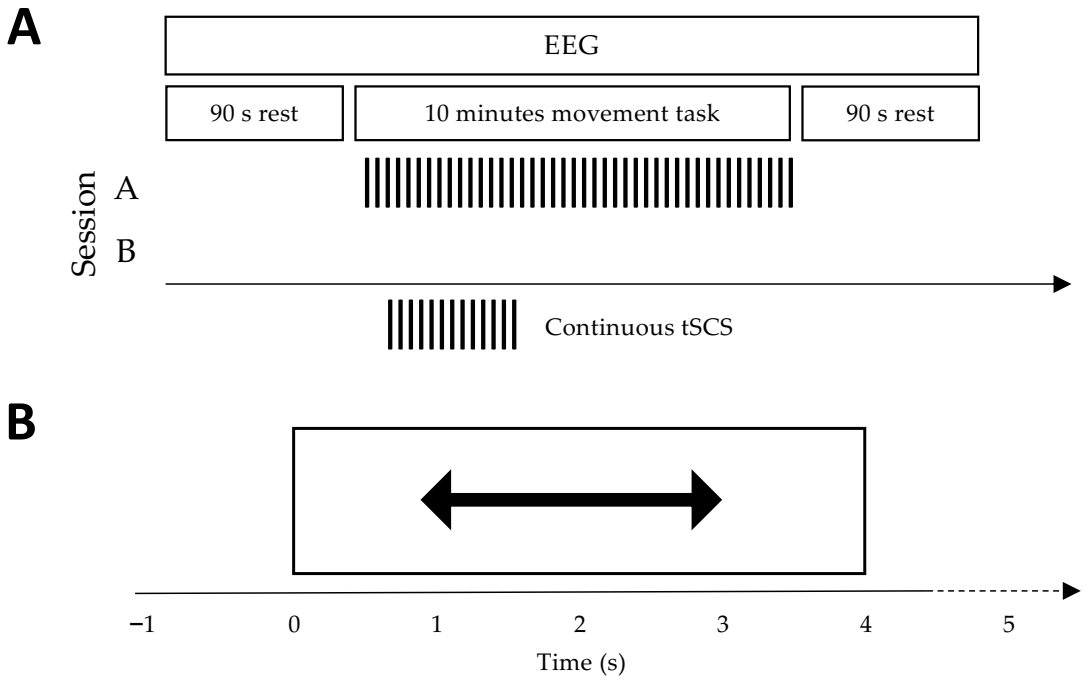

Fig. 4.2 Experimental session protocol and movement task timing scheme. (**A**) Outline of the experimental sessions, carried out on different days. Both sessions began and ended with the recording of resting-state EEG with eyes closed. An upper-limb movement task lasted 10 min while EEG was recorded simultaneously. Only during session A was continuous tSCS applied to the cervical region of the spine. (**B**) The timing scheme of a single trial from the movement task. At t = 0 s an arrow appeared onscreen prompting the participant to perform either left, right, or bimanual finger flexion. The movement was sustained for four seconds. This was followed by a randomised 1.5–2.5 s inter-trial interval. There were 30 repetitions of each movement, totalling 90 trials.

were instructed to minimise head and eye movements in order to ensure high fidelity recordings. Given the considerable artefacts produced by concurrent tSCS, conventional data-cleaning techniques were unsuitable [91]. For example, the high amplitude stimulation component meant that applying rejection thresholds on peak-to-peak amplitudes would eliminate segments of otherwise meaningful EEG. Hence, rejection thresholds were not used during pre-processing and instead strict adherence to the protocol outlined above was followed.

4.3.4 Electromyography (EMG)

To determine the onset of upper-limb movement, electromyography (EMG) was used to measure the activity of the extensor carpi radialis (ERC) muscles (See Figure 4.1D). Two electrodes (Ag/AgCl; F-301, Skintact, Innsbruck, Austria) were positioned on the dorsal side of each

forearm, above the belly of the ERC, with a 20 mm inter-electrode distance. Ground electrodes were attached to the lateral epicondyles. EMG was recorded with the same biosignal amplifier outlined above (band-pass filter: 5–1200 Hz; notch filter: 50 Hz) to ensure synchronisation with EEG. Movement onset was defined as the moment EMG activity exceeded the mean of the resting phase plus two times its standard deviation for at least 100 ms [124].

4.3.5 Transcutaneous spinal cord stimulation (tSCS)

Using a DS8R Biphasic Constant Current Stimulator (Digitimer, Hertfordshire, UK), spinal cord stimulation was delivered in bursts of ten 100 μs long biphasic rectangular pulses at a frequency of 30 Hz (see Figure 4.1B for an illustration of a single burst) [125]. A round 3.2 cm cathode electrode (Axelgaard Manufacturing Co., Fallbrook, CA, USA) was placed between the C5–C6 intervertebral space, placement reflective of upper-limb rehabilitation in clinical practice. Rectangular inter-connected anode electrodes (8.9 $\times$ 5.0 cm) were placed symmetrically on the shoulders, above the acromion (see Figure 4.1A for an illustration) [126]. We used feedback from the participant to determine the current intensity. Starting at 0 mA, the current was gradually increased in 2.5 mA increments until the participant verbally communicated their wish to stop increasing. Participants were asked before each incremental increase whether they would be able to tolerate the sensation for at least 30 s. If they were unable to tolerate the intensity, the current was reduced by one increment and was used for the remainder of the movement task. The area of discomfort varied across participants. Some participants reported that discomfort was focused under the cathode electrode; others found the contraction of back and neck muscles intolerable; some reported a combination of both. Across all participants, tSCS current intensity was on average 50 $\pm$ 20 mA, with a minimum and maximum current of 10 and 85 mA respectively.

4.3.6 Quantifying sensorimotor cortical activity during tSCS

EEG was pre-processed offline with a 3rd-order Butterworth band-pass filter (1–40 Hz) and notch filter (50 Hz). Next, continuous EEG was segmented into epochs from -2 to 6 s relative to movement onset. The power spectral density across time and frequency was found using the multitaper method (1–25 Hz) with a resolution of 0.5 Hz. This analysis was performed with channels C3, C4, and the mean of C3 and C4, for right, left, and bimanual movements respectively. Time-frequency power was normalised with respect to a pre-movement baseline, defined as -1.25 to -0.25 s before movement and the average time-frequency powers were averaged across all subjects for each movement type. Statistical masking was added to time-

frequency plots to display only power values which deviated significantly ($p < 0.05$) from baseline, as determined by a cluster-based permutation test.

We then separately considered the mean alpha (7–13 Hz) and beta (14–25 Hz) band ERD/ERS during two phases of movement: (1) movement initiation (0.5–1.5 s), and (2) sustained movement (1.5–3.0 s). We expected tSCS would strengthen ERD during the sustained movement phase, reflecting similar results observed using FES during motor imagery [104]. ERD values were averaged across movement phases and compared between stimulation conditions with a Wilcoxon signed-rank test, where $p < 0.05$ indicated a statistically significant difference in cortical activity. A further analysis was performed to investigate the effect of stimulation intensity on ERD/ERS by splitting participants into two groups based on the stimulation intensity they received: lowest and highest 25% of participants. This analysis considered broadband (de)synchronisation (7–25 Hz) with and without tSCS during 2.5 s of movement (0.5–3.0 s). A Pearson's correlation coefficient determined whether ERD/ERS was modulated with increasing stimulation intensity and contrasted to the tSCS-off condition. A subsequent analysis was performed to again consider alpha and beta band ERD/ERS during movement initiation and sustained movement for the two subgroups and statistical differences were assessed with a Wilcoxon signed-rank test.

A topographical analysis was performed by averaging the movement phases outlined above in the alpha and beta frequency bands for each recorded channel. The spatial distributions of cortical activation were used in a cluster-based permutation test to compare the ERD patterns while tSCS was on compared to when tSCS was off. A significance threshold of 0.05 was used to identify significant differences in topographical distributions between the two stimulation conditions.

Finally, in order to investigate a dose-effect of tSCS on cortical activity, we considered the correlation between ERD during each trial and sequence of trials by calculating Pearson's correlation coefficient. A Wilcoxon signed-rank test was used to determine if the participant-wise average correlation coefficients significantly differed between stimulation conditions.

4.3.7 Neuromodulation of resting-state EEG

We explored whether tSCS exerted a neuromodulatory effect on resting-state EEG by comparing individual alpha frequency before and after the movement task. We used resting state, eyes closed EEG and segmented it into one-second epochs with a 0.1 s overlap. Each epoch was windowed using a Hamming window and the periodograms (2^{15} point FFT) were averaged to estimate the power spectral density (PSD). The alpha peak frequency was defined as the

frequency with the maximum power in the 7–13 Hz range. The alpha peak frequency after the intervention was expressed as a percentage change from the alpha peak before the intervention. We also considered the power of the alpha peak and similarly normalised this with respect to pre-intervention power. A Wilcoxon signed-rank test was performed to determine if there was a significant difference in the change of alpha peak frequency and power between the tSCS-off and tSCS-on conditions.

4.4 Results

4.4.1 Event-related (de)synchronisation (ERD/ERS)

To investigate the effect of tSCS on sensorimotor activity during movement we calculated alpha and beta band power differences with respect to rest. Figure 4.3 shows time-frequency power values averaged across all participants for left, right, and bimanual finger flexion. The plots only display power values that significantly differed ($p < 0.05$) from baseline, as determined by a cluster-based permutation test. Each movement type showed significant broadband (8–25 Hz) ERD with particular power suppression in the alpha band (8–12 Hz). Right and bimanual movements tend to show similar patters of ERD regardless of whether tSCS had been applied or not. Left-hand movements appeared to have deeper and more sustained alpha desynchronisation when tSCS was applied.

To test for a significant difference of ERD between conditions we divided each movement into two phases: (1) movement initiation (0.5–1.5 s after movement onset), and (2) sustained movement (1.5–3.0 s after movement onset). Figure 4.4 shows the average ERD during movement initiation for each movement type and stimulation condition in the alpha and beta bands. There were no significant differences detected in the alpha band (Figure 4.4A: Left: $p = 0.15$; Right: $p = 0.14$; Bimanual: $p = 0.90$), nor in the beta band (Figure 4.4B: Left: $p = 0.77$; Right: $p = 0.60$; Bimanual: $p = 0.75$). Although ERD shows variability, the variance is inline with other studies reporting ERD within participants and across sessions [127]. On average, however, there was a lack of consistency in the direction of modulation with some participants having stronger ERD with stimulation, and some having suppressed ERD.

Similar results are seen in Figure 4.5 which presents ERD values during sustained movement (Alpha: Left: $p = 0.19$; Right: $p = 0.12$; Bimanual: $p = 0.40$; Beta: Left: $p = 0.4$; Right: $p = 0.90$; Bimanual: $p = 0.94$).

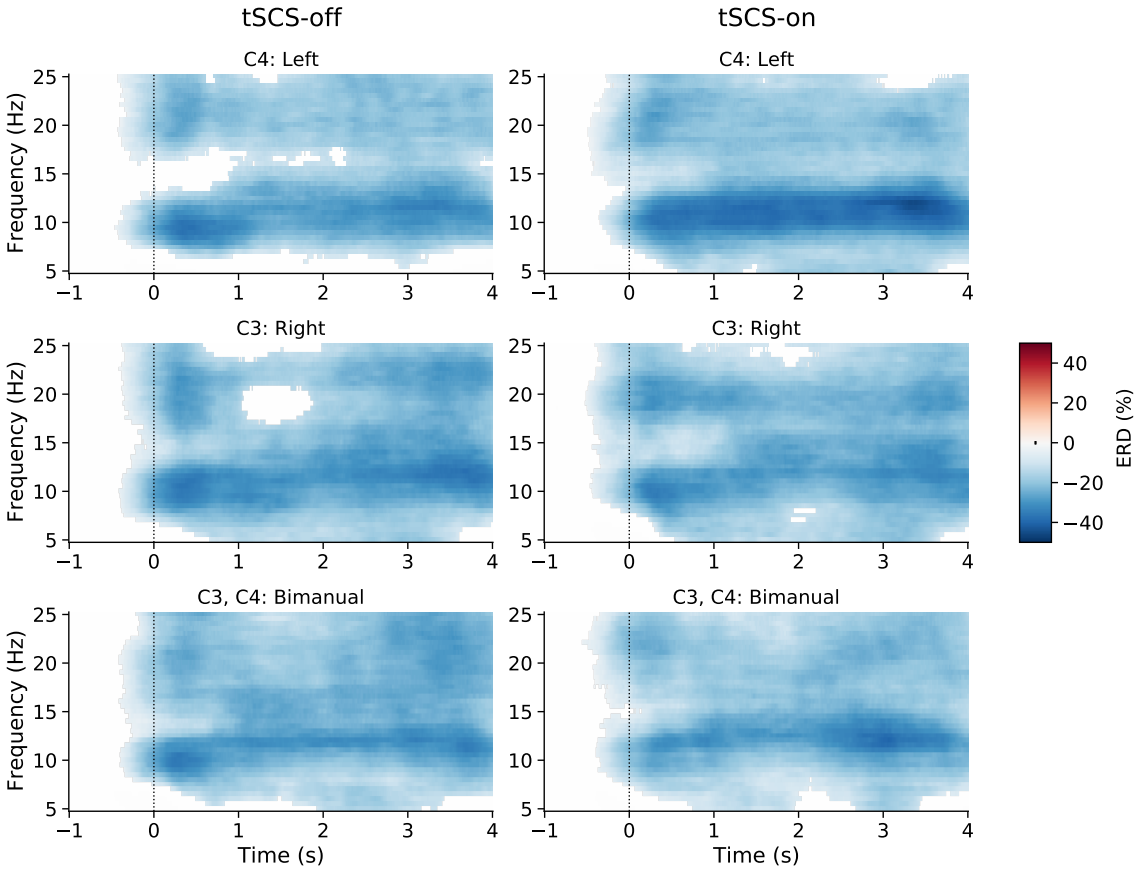

Fig. 4.3 Time-frequency plots of event-related desynchronisation (ERD) during repetitive left, right, and bimanual finger flexion with and without tSCS. Only values significantly different from 0% ERD ($p < 0.05$) are shown, as determined by a cluster-based permutation test.

4.4.2 Topographic Analysis of ERD

The ERD topographic patterns during movement initiation and sustained movement are illustrated in Figures 4.6 and 4.7 respectively. It can be seen that there is desynchronisation present at all the electrodes in the alpha and beta frequency bands in both stimulation conditions. Figure 4.7A shows bilateral alpha ERD when tSCS is off. When tSCS is on the pattern appears more contralaterally dominant over C4 electrodes (Figure 4.7C). However, a cluster-based permutation test showed that there were no regions of the topographical distributions that significantly differed between conditions. This was the case for the beta band and for sustained movement shown in Figure 4.6.

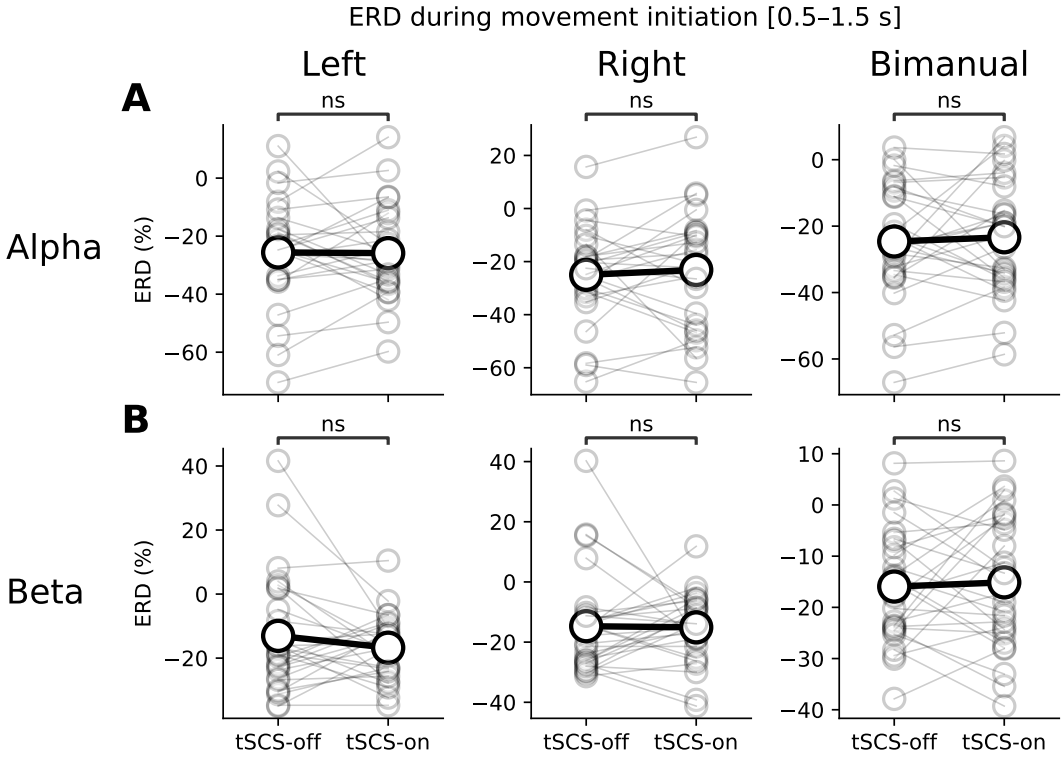

Fig. 4.4 Average ERD during movement initiation (0.5–1.5 s) for each type of upper-limb movement (left, right, and bimanual finger flexion). (**A**,**B**) show ERD in the alpha and beta bands respectively. Grey markers show ERD of individual participants and the black markers show the participant-wise average. A Wilcoxon signed-rank test explored statistically significance differences between the tSCS-off and tSCS-on conditions for each movement and frequency band ('ns' denotes no significant difference).

4.4.3 Dose effect of event-related desynchronisation

We found that on average there was no dose effect of tSCS on alpha or beta ERD (Figure 4.8). Taken as a group, the average correlation coefficients were close to zero with or without the presence of tSCS. A Wilcoxon signed-rank test corrected for multiple comparisons found no significant difference between conditions in either frequency band (Alpha: $p = 0.16$; Beta: $p = 0.75$).

4.4.4 Resting state modulation

We found that resting state individual alpha peak frequency was not significantly altered by tSCS ($p = 0.67$), showing an approximately 0% change from pre-intervention alpha for

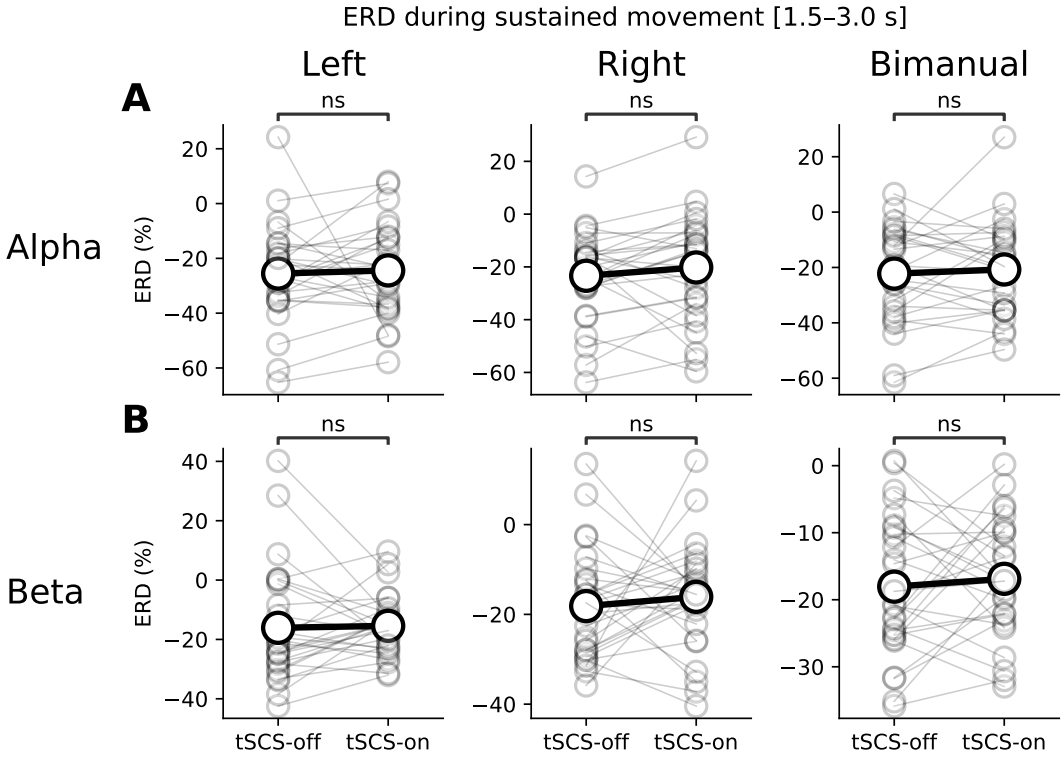

Fig. 4.5 Average ERD during sustained movement (1.5–3.0 s) for each type of upper-limb movement (left, right, and bimanual finger flexion). (**A**,**B**) show ERD in the alpha and beta bands respectively. Grey markers show ERD of individual participants and the black markers show the participant-wise average. A Wilcoxon signed-rank test explored statistically significance differences between the tSCS-off and tSCS-on conditions for each movement and frequency band ('ns' denotes no significant difference).

both stimulation conditions (Figure 4.9A). Furthermore, the change in alpha power was also unaffected by tSCS ($p = 0.20$), shown in Figure 4.9B.

4.4.5 Effect of tSCS intensity

Given the variability across sessions shown in Figures 4.4 and 4.5, we investigated whether the variance could partially be explained by stimulation current intensity, given intensity was tailored to the individual. Figure 4.10 shows that ERD/ERS appears similarly distributed between conditions at around 20% ERD for intensities between 10 and 60 mA. Intensities above around 65 mA, however, tended to result in suppressed ERD, or even ERS, relative to the tSCS-off condition. A linear regression found that ERD/ERS and tSCS intensity were indeed positively, and significantly, correlated ($r = 0.409$, $p = 0.025$).

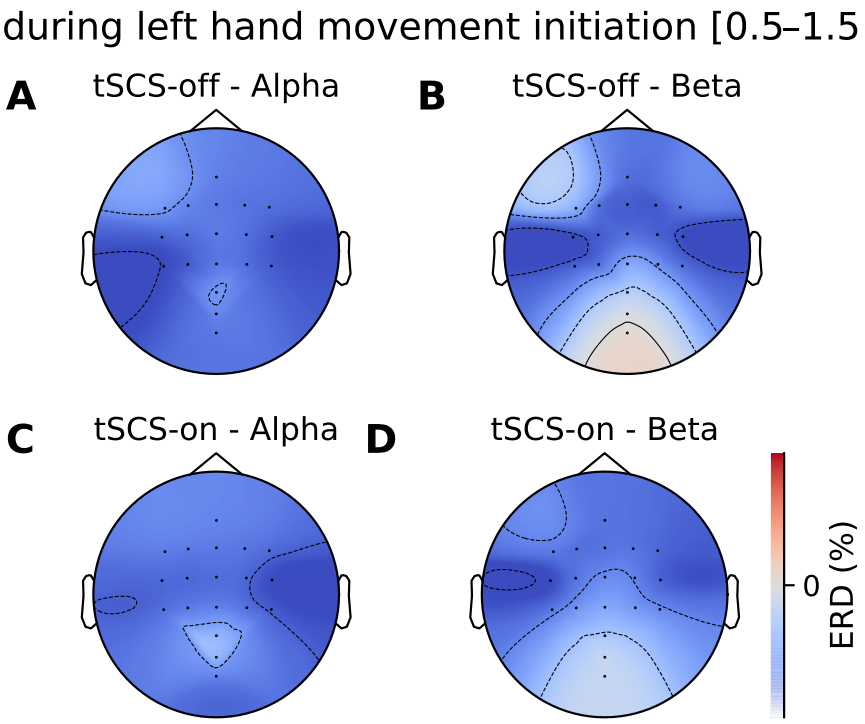

Fig. 4.6 Topographic ERD/ERS distribution during left handed movement initiation (0.5–1.5 s after movement onset). (**A**,**B**) show spatial distribution of ERD/ERS in the alpha and beta bands without tSCS. (**C**,**D**) show the spatial distribution in the alpha and beta bands during with tSCS.

The discomfort felt by participants tended to grow as a function of tSCS intensity. It may have been the case, therefore, that relative alpha power was being suppressed by the uncomfortable sensation, resulting in less desynchronisation during movement, a known consequence of pain on the alpha rhythm [128, 129]. Suppression would likely have been more prominent in participants who received the highest intensities. To test this, we found the correlation between intensity and pre-movement relative alpha power (-1.5 s to -0.5 s relative to movement onset): $r = -0.062$, $p = 0.75$. Although the correlation was not significant, the participants who received the highest intensities tended to have reduced alpha power during rest.

Interestingly, when two sub-groups were formed from participants from the lower and upper 25% of the intensity distribution, ERD/ERS become significantly altered by tSCS in the high-intensity group only. Figure 4.11 shows that in the early phase of movement, ERD/ERS is significantly elevated, ($p = 0.016$) from around -25% without tSCS to around 10% during tSCS, reflective of (event-related) synchronisation rather than desynchronisation. This is seen

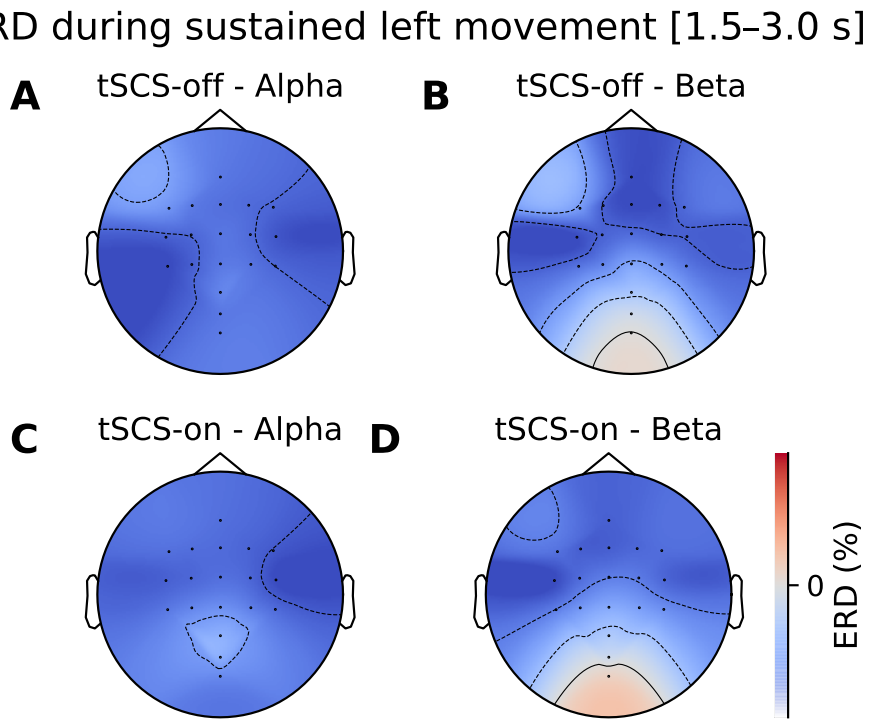

Fig. 4.7 Topographic ERD/ERS distribution during sustained left handed movement (1.5–3.0 s after movement onset). (**A**,**B**) show spatial distribution of ERD/ERS in the alpha and beta bands without tSCS. (**C**,**D**) show the spatial distribution in the alpha and beta bands during tSCS.

also in the beta band ($p = 0.015$) and the trend is seen during sustained movement but without significance ($p > 0.05$).

Resting-state alpha frequency and power were also reevaluated in terms of current intensity but no altered effect was found.

4.4.6 Stimulation adherence

Continuous tSCS was well tolerated by the majority of participants. In two cases, upon receiving tSCS at the beginning of the session, the sensation was considered overwhelming and the participants opted not to continue with the experiment. Both reported that, although not painful, stimulation was uncomfortable and made sitting still difficult.

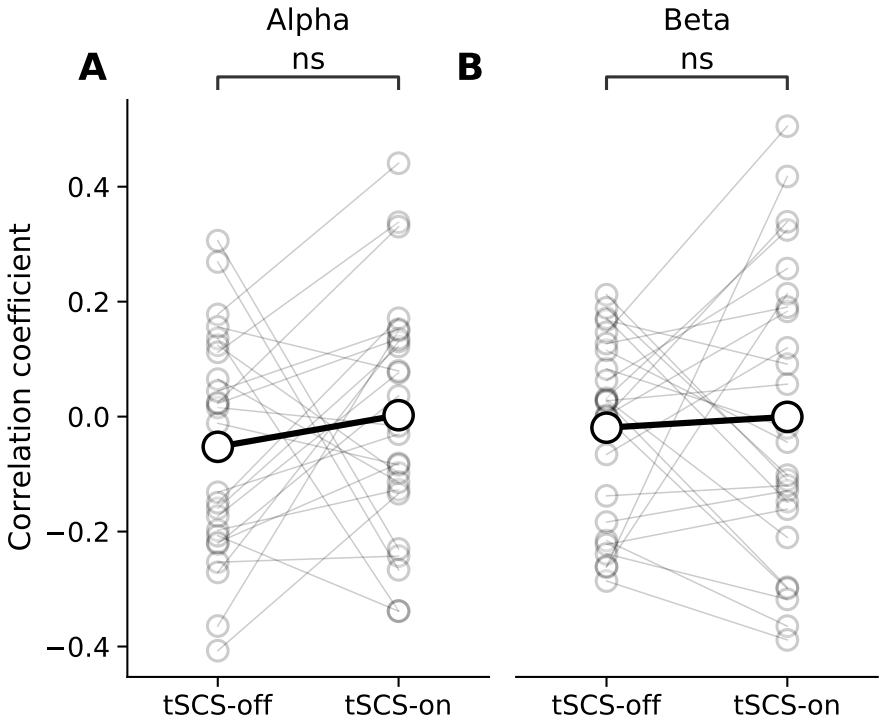

Fig. 4.8 Correlation coefficient between event-related desynchronisation (ERD) in the alpha (**A**) and beta (**B**) bands during repetitive bimanual finger flexion and the sequence of trials in with and without tSCS. The grey markers represent correlation coefficient values for individual participants and the black markers represent the across-participant session average. Significance levels from a Wilcoxon signed-rank test comparing conditions are indicated with an asterisk and 'ns' where there was no significant difference.

4.5 Discussion

The present study showed that a 10 min session of tSCS did not significantly modulate sensorimotor brain rhythms during repetitive upper-limb movements. Similarly, resting-state EEG, as characterised by alpha-band peak frequency and power, was unaffected by continuous tSCS. An investigation of tSCS intensity, however, revealed that cortical activity may have been suppressed among participants who received the highest stimulation intensities, given ERD/ERS was significantly altered for these participants. This work suggests that tSCS intensity may be an important factor to elicit consistent modulation at the cortical level. However, as this high-intensity group is a subset of the overall participant sample, the sample number is small and must be verified on a larger scale.

The inter-participant and inter-session variability in measures such as ERD and alpha power, tended to reflect the inherent variances associated with these measures, as they are

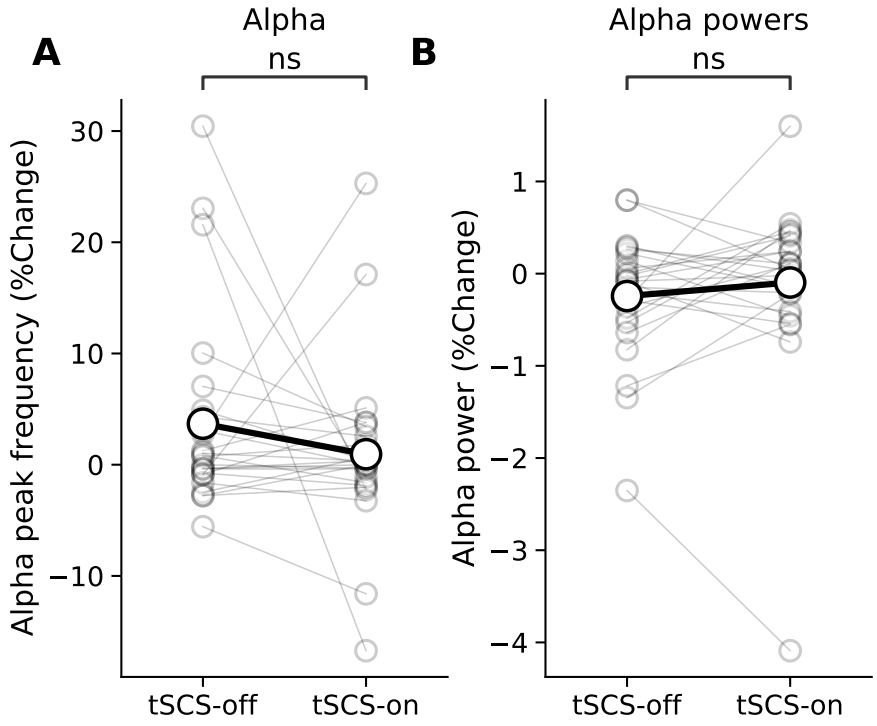

Fig. 4.9 Resting state EEG. (**A**) shows the change (%) in peak alpha frequencies from baseline during resting state with eyes closed with and without tSCS. (**B**) shows the change in power of the peak frequencies. The grey markers represent individual participants and the black markers represent the across-participant session averages. Non-significance, as determined by a Wilcoxon signed-rank test, is expressed as 'ns'.

in line with other research [127, 71]. However, the variance may partially be attributable to current intensity, which was individualised for each participant based on their maximum tolerance. This choice of protocol was based on typical clinical procedures for determining current intensity [82, 130, 67]. The alpha and beta ERD/ERS of participants who received the highest intensity stimulation tended to be weaker compared to when tSCS was not present. This may imply cortical inhibition following tSCS, which would echo similar claims made by Benavides et al. [72]. Conversely, this reduction in ERD/ERD may have been a consequence of the discomfort associated with high-intensity currents as reduced resting-state alpha power has been associated with exposure to painful sensations [129, 128], and lower alpha often correlates with weaker ERD during movement [131]. It is difficult to speculate on the role tSCS intensity played on the individual as each participant received only one level of tSCS intensity. Future analyses should have each participant receive multiple current intensities in order to discern if an intensity-dependent effect exists.

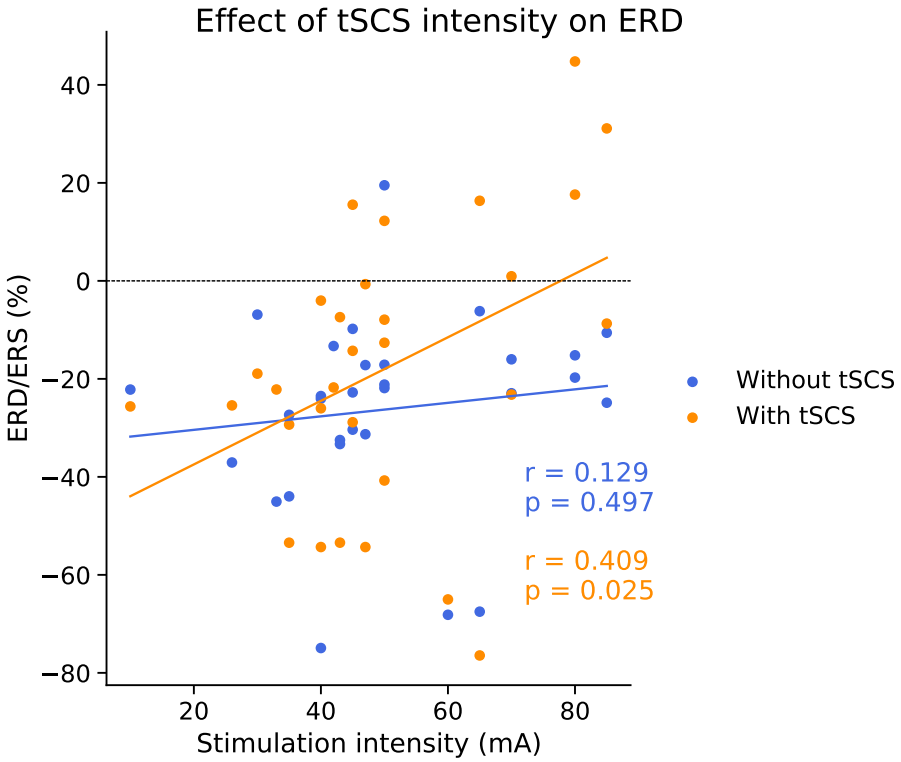

Fig. 4.10 Subject-wise ERD/ERS (%) against tSCS intensity. To aid comparison, ERD/ERS values from the tSCS-off condition are also shown. Stimulation intensity relates to the tSCS-on condition only. Statistical outcomes from a linear regression are given in terms of r and p values.

Transcutaneous spinal cord stimulation must penetrate deep into spinal structures, passing multiple layers of skin, fat, muscle, and vertebrae, in order to exert a neuromodulatory effect [56]. Stimulation intensity must, therefore, be strong enough to overcome the impedance of the medium between electrodes. High-intensity stimulation, however, can result in intense discomfort or pain following the contraction of neck and back muscles, and activation of cutaneous pain receptors [132]. In this study, stimulation was set to the participants' maximum tolerance. Maximum stimulation tolerance was shown by Manson et al. to constitute approximately 56% of the intensity required to induce a motor response [132]. This sub-threshold intensity is within the range that clinical studies have reported functional improvements following cervical tSCS [82, 130, 67]. It is possible, however, that participants with relatively poor stimulation tolerances did not receive activation of posterior-root afferents. This may explain the fact that neuromodulation of cortical oscillations was only observed in a subset of high-intensity participants. It may be the case, therefore, that tSCS, by its very nature, is unsuitable for a

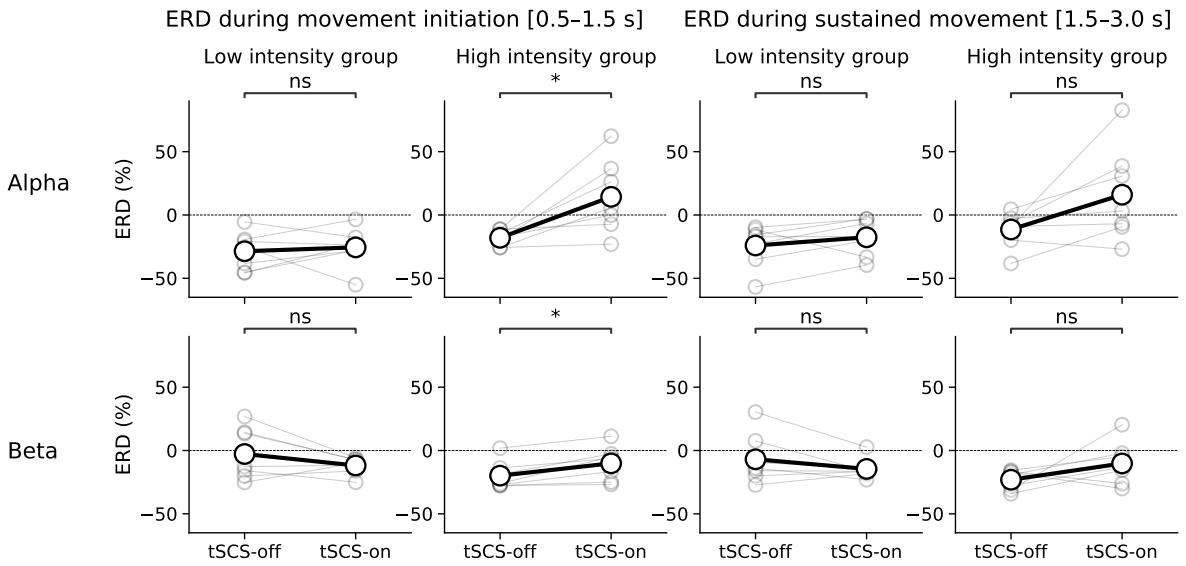

Fig. 4.11 Event-related desynchronisation during movement with participants divided into two groups depending stimulation intensity. Low-intensity participants received tSCS at currents between 10 and 40 mA. High-intensity participants received tSCS at currents between 60 and 85 mA. A Wilcoxon signed-rank rest was used to determine statistically significant differences in ERD between experimental sessions. * $p < 0.05$, ns denotes non-significance.

portion of a given sample. Future studies may need to consider exclusion criteria that eliminate participants who cannot tolerate stimulation intensities capable of spinal cord interaction. Further, stimulation intensity should be set relative to the resting-state motor threshold as determined by the posterior-root muscle reflex. This would provide assurance that tSCS is providing homogeneous spinal activation across participants.

Although this study is the first to investigate the effects of transcutaneous spinal cord stimulation on cortical oscillations, other studies have reported neuromodulation through electrical stimulation of peripheral musculature and nerves [80, 133, 134]. For instance, Insausti-Delgado et al. reported enhanced alpha and beta ERD during high intensity neuromuscular electrical stimulation of the wrist extensors [80]. They attributed this effect to the activation of muscle spindles and joint afferents which recruited proprioceptive fibres in the spinal cord, which in turn affected the motor cortex. Indeed, tSCS has been reported to also recruit large-to-medium proprioceptive fibres within posterior roots [56]. Yet the present study found that participants who underwent high-intensity tSCS displayed suppressed alpha and beta band ERD during movement, suggestive of inhibited cortical activity. It may be the case that high-frequency stimulation interfered with the conduction of sensory information to the somatosensory cortex, reducing cortical area activated during movement, which in turn

resulted in decreased expression of alpha and beta ERD. Benavides et al. also noted cortical inhibition following cervical tSCS with a 5 kHz carrier frequency, and the effect was even more pronounced in SCI patients [72]. They attributed this inhibition to the activation of inhibitory cortical circuits which influenced motor cortical activity. It is unclear whether this inhibition is related to the reduction of cortical activity in the present study. Further, it has been reported that exposure to tonic painful stimuli such as electrical stimulation can modulate alpha band characteristics, perhaps a result of heightened sensory processing [135]. It has also been shown that cortical synchronisation, a correlate of inhibition, is necessary for activating selective cortical patterns. It may be the case that the cortical processing of the painful stimuli among participants who received the highest stimulation intensities represented a task in itself and the addition of a second task–the movement task–may have required selective cortical activity resulting in alpha synchronisation compared to baseline [136]. Future work should investigate the relationship between tSCS-induced pain and ERS during movement. For instance, the application of anaesthetic gel around the stimulation site may allow for stimulation sensations to be decoupled from the activation of spinal structures.

Some EEG-based investigations featuring electrical stimulation are challenging or impossible without applying artefact-attenuation techniques [89]. However, stimulation artefact contamination was not considered a confounding factor here as previous work by our group showed that, so long as the spectral region of interest does not overlap with the stimulation frequency, resulting EEG bares statistically similar characteristics to that of normal EEG [91]. Therefore, any differences found in spectral power would be attributable to endogenous neuromodulation and not signal corruption.

The lack of sham condition in this study may constitute a limitation given that the placebo effect has been shown to impact EEG-based metrics [137]. However, implementing a sham control with tSCS is non-trivial as the intensity range at which tSCS exerts a non-therapeutic effect is currently unknown. Similarly, non-therapeutic duration is also unknown, hence, protocols that ramp down after a brief period of stimulation were considered unsuitable. Further, the intense, non-painful sensation associated with tSCS, even at low currents, makes the ambiguity required for establishing an effective sham control difficult. Indeed, as Turner et al. showed using transcranial direct current stimulation, participants were aware of whether they were or were not receiving active stimulation throughout the experimental procedure [138]. We expect that placebo effect contamination to be low, however, as the procedure and equipment were identical in both sessions, and the outcome measures (ERD/ERS during movement) were not known by participants. Effective sham-blinding protocols should be

verified in the future, perhaps by stimulating a spinal level that does not project to the motor pools under investigation.

A significant limitation of this study is that it lacks a clinical population. We note that studies that include a patient cohort in addition to healthy controls often reported more marked modulation in the SCI group [72]. It may be the case that, in healthy participants, a ceiling effect limits the recruitment of additional fibres as the cortical–spinal network is already being used to its fullest extent during movement. Additionally, an SCI cohort would allow for higher currents to be explored, owing to reduced sensitivity at and below the spinal level of injury. This would likely minimise the effect noted here whereby individuals receiving the highest intensities of tSCS exhibited reduced resting-state alpha power due to discomfort.

4.6 Conclusions

This study, for the first time, investigated cervical tSCS neuromodulation in terms of sensorimotor oscillations as measured by EEG. Our results showed that, on a group level, there was no consistent excitatory or inhibitory effect in terms of cortical activity during upper-limb movement. However, consistency appeared to emerge among participants who received the highest stimulation intensities. ERD, a measure of sensorimotor cortical activity, was diminished in these participants, potentially implying an inhibitory effect of tSCS at the cortical level. However, this sub-set of participants constitutes a small population size. Future work should, therefore, specifically investigate the effects of tSCS intensity on cortical oscillations. Additionally, future work should endeavour to determine the critical duration required for cervical tSCS to exert a measurable effect on sensorimotor cortical activity.

Author contributions

Conceptualisation, C.M. and A.V.; methodology, C.M.; software, C.M.; validation, C.M. and A.V.; formal analysis, C.M.; investigation, C.M.; resources, Y.-P.Z.; data curation, C.M.; writing—original draft preparation, C.M.; writing—review and editing, A.V., Y.-P.Z., and M.A.; visualisation, C.M.; project administration, M.A.; funding acquisition, M.A. All authors have read and agreed to the published version of the manuscript.

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Institutional review

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Human Subjects Ethics Sub-committee of the Hong Kong Polytechnic University (HSEARS20201105003, 26 November 2020).

Informed consent

Informed consent was obtained from all subjects involved in the study.

Data availability

Data will be made available upon reasonable request to the authors.

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We sincerely thank the research participants for their patience and commitment to our study.

Conflicts of interest

The authors declare no conflict of interest.

Chapter 5

Brain-computer interface priming for cervical transcutaneous spinal cord stimulation therapy: An exploratory case study

This chapter was written by Ciarán McGeady, with Aleksandra Vučković, Niraj Singh Tharu, Yong-Ping Zheng, and Monzurul Alam, and published in *Frontiers of Rehabilitation Sciences* [93].

5.1 Abstract

Loss of arm and hand function is one of the most devastating consequences of cervical spinal cord injury (SCI). Although some residual functional neurons often pass the site of injury, recovery after SCI is extremely limited. Recent efforts have aimed to augment traditional rehabilitation by combining exercise-based training with techniques such as transcutaneous spinal cord stimulation (tSCS), and movement priming. Such methods have been linked with elevated corticospinal excitability, and enhanced neuroplastic effects following activity-based therapy. In the present study, we investigated the potential for facilitating tSCS-based exercise-training with brain-computer interface (BCI) motor priming. An individual with chronic AIS A cervical SCI with both sensory and motor complete tetraplegia participated in a two-phase cross-over intervention whereby they engaged in 15 sessions of intensive tSCS-mediated hand training for 1 h, 3 times/week, followed by a two week washout period, and a further 15 sessions

of tSCS training with bimanual BCI motor priming preceding each session. We found using the Graded Redefined Assessment for Strength, Sensibility, and Prehension that the participant's arm and hand function improved considerably across each phase of the study: from 96/232 points at baseline, to 117/232 after tSCS training alone, and to 131/232 points after BCI priming with tSCS training, reflecting improved strength, sensation, and gross and fine motor skills. Improved motor scores and heightened perception to sharp sensations improved the neurological level of injury from C4 to C5 following training and improvements were generally maintained four weeks after the final training session. Although functional improvements were similar regardless of the presence of BCI priming, there was a moderate improvement of bilateral strength only when priming preceded tSCS training, perhaps suggesting a benefit of motor priming for tSCS training.

5.2 Introduction

One of the most devastating consequences of cervical spinal cord injury (SCI) is partial or complete loss of hand and arm function [139]. Loss of upper-extremity function has a drastic impact on a person's level of independence and quality of life, and as such is often their greatest priority in terms of rehabilitation [139, 14]. However, after an initial period of spontaneous recovery, a motor function plateau is reached and further meaningful recovery is rare [140]. Yet it has been shown that even in cases of severe SCI, there are often spared functional neurons that pass the level of injury which may be utilised to promote additional recovery [15]. Indeed, this fact underpins much of the current activity-based rehabilitation offered to people with SCI [14]. Despite the best efforts of clinicians, physiotherapists, and patients themselves, however, functional outcomes following rehabilitation are modest at best [13, 14]. Efforts must be taken to enhance the effects of rehabilitation.

Transcutaneous spinal cord stimulation (tSCS) has recently been proposed as a method for augmenting traditional exercise-based therapies [66]. This noninvasive technique involves delivering high frequency currents via surface electrodes at and around the spinal level of injury [113, 66]. It has been suggested that electrical interaction with various spinal structures, including dorsal column fibres, the dorsal horn and posterior/dorsal roots, decreases the motor threshold, making voluntary motor control easier through residual descending pathways [110, 56, 111]. Although few in number, studies investigating the effects of cervical tSCS on hand and arm function have reported promising results [67, 65, 84, 83, 82]. Inanici *et al.* showed that six individuals with chronic cervical SCI improved upper-extremity function following tSCS-facilitated intensive functional task training, with improvements remaining six months

after the end of training. Impressively, some participants were able to resume activities such as playing musical instruments [82].

A further strategy for facilitating exercise-based therapy concerns priming [17]. Movement-based priming involves repetitive or continuous volitional motor engagement with the purpose of enhancing the effects of a subsequent therapy [17]. Evidence suggests that mirror symmetric, bimanual motor priming can facilitate motor cortical excitability and increase the rate of motor learning in neurologically-intact and neurologically-impaired individuals [27, 30, 18]. Cortical excitability was reported to have been elevated above baseline for at least 30 minutes following movement priming [30]. Improved bimanual coordination and control may also increase the likelihood of functional improvements being maintained outside of the clinic, owing to bimanual movements being critical for performing activities of daily life [141, 142]. Owing to the multi-faceted nature of SCI pathology, it has been suggested that the future of SCI treatment will rely on combinational strategies [90]. Hence, where tSCS has been used to modulate spinal excitability, movement priming or motor imagery priming may be used to target supraspinal (cortical) networks [56, 23]. It has been shown that motor cortical activity is often diminished in individuals with chronic SCI, owing to damaged motor pathways and non-use of affected limbs [42, 43], yet cortical activation is a critical determinant of muscle strength [143]. Although there is no evidence to suggest that enhancing cortical activity alone would correlate with improved functional performance after SCI, it may offer a priming effect that could complement an efficacious rehabilitative intervention, such as tSCS-facilitated upper-extremity training.

In this article we present a brain-computer interface (BCI) priming strategy that translates sensorimotor rhythms recorded from the electroencephalogram (EEG), reflective of cortical activity during movement, into a control signal for an interactive priming paradigm [1]. Benefits of BCI-based motor priming include enhanced participant engagement, the ability to upregulate sensorimotor cortical activity, and lastly it provides insight to the SCI participant's neurophysiological state, which may provide markers that reflect functional recovery [115, 43]. We expected that a session of BCI motor priming before tSCS training could enhance the effects of tSCS training alone.

We tested this hypothesis by recruiting an individual with a complete cervical SCI, who acquired his injury 12 years prior to enrollment in this study, and was graded as American Spinal Injury Association Impairment Scale (AIS) category A. We first had the participant undertake a five-week program of intensive upper-limb training with multi-site tSCS delivered to the cervical region of the neck. After a two-week washout period, where no training was administered, the participant underwent a further five weeks of tSCS training with BCI motor priming preceding each session. We expected upper-limb motor function to improve across

both phases of the study, in line with previous literature. However, we expected enhanced rates of recovery during the priming phase.

5.3 Methods

5.3.1 Participant characteristics

A 40-year-old male with a chronic cervical SCI participated in this study. Prior to enrollment, his injury, which occurred 12 years before recruitment, was graded as ASI A, with a C4 neurological level of injury, according to the International Standards for Neurological Classification of SCI (ISNCSCI) [8].

This study was approved by the Human Subjects Ethics Sub-committee of the Hong Kong Polytechnic University (HSEARS20190121002; 9 Feb 2019) and the participant provided written informed consent.

5.3.2 Experimental protocol

This study implemented a two-phase crossover design. After a two-week baseline period, the first phase involved five weeks of tSCS training three times per week, and a second phase introduced BCI motor priming before tSCS training for a further five weeks (Figure 5.1A) [144, 67]. There was a two-week washout period between phases, and a follow-up assessment was conducted four weeks after the end of the second phase.

5.3.3 Hand and arm training

Hand and arm training consisted of repetitive uni- and bimanual exercises in conjunction with tSCS [122]. A typical session focused on a number of grasp types, including palmar grasping, pinching, pinching with rotation, and finger isolation. Tasks included flipping playing cards, moving ping pong balls between containers, scooping rice with a spoon, and stacking blocks, among others. Tasks were adjusted relative to functional improvements to maintain a degree of difficulty. For example, ping pong balls were replaced with marbles and then by small beads as the study progressed. Hand training was performed continuously over the 60-minute session with two brief pauses when the participant was given a break from tSCS.

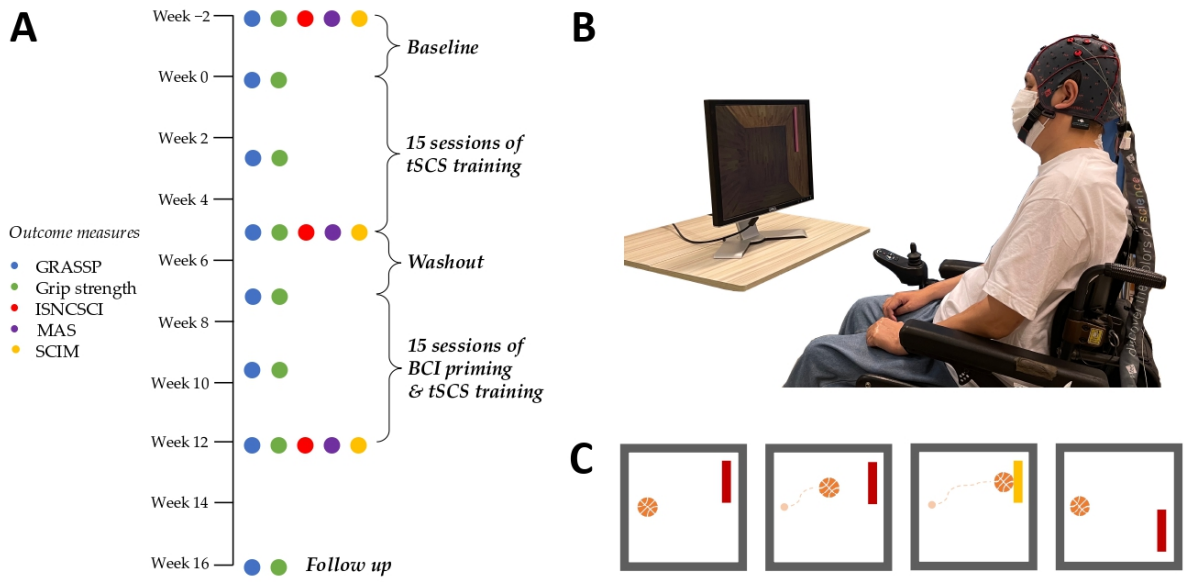

Fig. 5.1 Study protocol and BCI motor priming paradigm. (**A**) The 18 week study protocol showing primary and secondary outcome measures. (**B**) BCI priming setup. The participant wore an EEG cap and sat opposite a computer screen. The participant provided written consent that his photograph be used in any publications. (**C**) A simplified version of the BCI motor priming paradigm as displayed on a computer screen and observed by the participant. The participant's objective was to attempt repetitive bimanual finger flexion/extension to guide a photo-realistic basketball to a target. The ball moved horizontally at a constant rate. Vertical displacement was influenced by the participant's EEG and his ability to engage with the priming task.

5.3.4 Transcutaneous spinal cord stimulation (tSCS)

Two constant current stimulators (DS8R; Digitimer, Oxford, United Kingdom) delivered multi-site stimulation in bursts of ten 100 μs long biphasic rectangular pulses at a frequency of 30 Hz, reflecting recent clinical work [65, 82, 83, 68]. Two round cathode electrodes (3.2 cm; Axelgaard Manufacturing Co, Fallbrook, CA, USA) were positioned at and below the level of injury between i) C4 and C5, and ii) C5 and C6 spinous processes. Cathodes were fastened to the skin with hypoallergenic tape to ensure snug contact throughout the session. Two anode electrodes (8.9×5.0 cm; Axelgaard Manufacturing Co, Fallbrook, CA, USA) were inter-connected to both stimulators and placed symmetrically on the shoulders, above the acromion. In order to increase the likelihood of activating spinal structures, which lie below multiple layers of skin, fat, muscle, and vertebrae, stimulation intensity was set to highest tolerable degree (mean ± standard deviation; C4-C5: 49.0 ± 4.6 mA, C5-C6: 40.8 ± 5.1 mA) [56]. Current intensity was determined at the beginning of each session by gradually increasing

the current from zero mA in 2.5 mA increments. This continued until the participant verbally communicated that the stimulation was causing a painful sensation, as indicated by reference to the fifth increment (moderate–severe discomfort) of the Visual Analogue Scale for pain intensity [145]. The participant reported habituation after prolonged stimulation, therefore stimulation intensity was re-evaluated after 10 min.

Stimulation was applied for a total of 60 minutes during each session. To avoid heating and skin irritation from prolonged high-intensity stimulation, there was a 2-minute break every 20 minutes where the stimulator was switched off. Hemodynamic parameters (blood pressure and heart rate) were monitored during breaks to track any incidence of autonomic dysreflexia [146].

5.3.5 Brain-computer interface (BCI) motor priming

To motivate the participant to engage in motor priming, as well as record sensorimotor rhythms, we devised a game-like brain-computer interface priming paradigm based on the 'BCI2000' platform [147]. The participant positioned his wheelchair opposite a computer screen and was fitted with an EEG cap, as shown in Figure 5.1B. Conductive gel was injected into each electrode and signal quality was verified by visual inspection. Modulation of beta band power (14–25 Hz) from the participant's electroencephalogram (EEG) was used to guide a virtual basketball towards one of two targets. The participant underwent 300 repetitions of the priming task, divided into 10 runs, each separated by 10–60 s breaks to avoid fatigue. Each repetition, or 'trial', began with a photo-realistic basketball at the centre-left of the computer screen, and a target either at the top-right or bottom-right (see Figure 5.1C). The ball moved horizontally at a fixed rate from left to right. The participant attempted mirror symmetric bimanual finger flexion and extension to push the ball to the upper target and relaxed for the ball to fall downwards. The participant was encouraged to imagine the sensation of clutching a real basketball as they performed the movement, in line with kinesthetic motor imagery protocols [133]. Each trial lasted for four seconds and there was a 1.5–2.5 s inter-trial interval. Once priming was completed, the electrode gel was removed from the participant's hair, and the participant immediately proceeded to tSCS training.

In order to control the onscreen ball, EEG was recorded with a biosignal amplifier (g.USBamp; gtec, Schiedlberg, Austria) at a sampling rate of 256 Hz from ten active electrodes positioned at FC3, FC4, C1, C2, C3, C4, C5, C6, CP3, and CP4, according to the international 10-10 system [46]. Electrode AFz was used as ground and the reference electrode was placed on the right earlobe. Through the BCI2000 platform, incoming EEG were spatially filtered with a small Laplacian filter to enhance the spatial resolution at electrodes C3 and C4, approximating

the area above the sensorimotor cortices [148, 147]. The spatially filtered data was transformed into the frequency domain using an autoregressive spectral estimation [149]. The mid-beta frequency band (18-26 Hz) was found to be the most reactive band during movement and was used to influence the vertical trajectory of the ball. The sum of spectral power from electrode C3 and C4 was found every 50 ms from a 400 ms long window and vertical cursor control was determined by solving a linear equation. A detailed explanation of this procedure was described by Wolpaw and McFarland [147]. A 5-minute calibration session at the beginning of each session trained the program to classify between attempted movement and rest. The setup was identical to that of the above priming strategy. However, the ball only moved in the horizontal direction, with no vertical displacement.

The current setup required 30 minutes for BCI priming, including 10 minutes for setup and 5 minutes for equipment removal. The tSCS component required around 10 minutes to apply electrodes and establish stimulation parameters. Including breaks, a session of BCI priming with tSCS never exceeded 100 minutes.

5.3.6 Functional outcomes

The Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) and grip strength were the primary measure of functional outcome [9]. Grip strength was measured with the Vive Precision grip strength tester (Vive Health, Naples, FL, USA). GRASSP tested the strength of upper-limb muscles (Anterior deltoid, elbow flexors, elbow extensors, wrist extensors, extensor digitorum (DIII), opponens pollicis, flexor pollicis longus, finger flexors (DIII), finger abductors, first dorsal interossei), sensation on the dorsal and palmar sides of the hands, and fine and gross motor skills, quantified by scoring functional tasks (these included grasping and pouring water from a bottle, unscrewing the lids from jam jars, moving pegs between holes, inserting and rotating a key in a lock, inserting coins into a slot, screwing a nut onto a bolt).

Secondary outcome measures included the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) [8], and the Spinal Cord Independence Measure (SCIM) [11].

Further, the Modified Ashworth Scale (MAS) was used to quantify spasticity in the following upper-limb movements: shoulder abduction, elbow extension, elbow supination, wrist extension, and finger extension [10]. The assessment was performed with the participant in the supine position and a trained physiotherapist graded each movement depending on the level of rigidity during flexion and extension. The minimum and maximum score for each unilateral

movement was 0 (no spasticity) and 4 (velocity-dependent resistance to movement). A score of 1.5 was given when 1+ was selected (a detailed description of the MAS assessment was given by Charlambous *et al.* [10]). The sum of scores from the left and right side were found for each movement.

All outcome measures were performed at the beginning and end of each intervention phase. Primary outcome measures were also performed in the middle of each five-week phase, and again at a four-week follow-up session. Primary outcome measures were measured twice at baseline: once two weeks prior to the beginning of the first intervention phase, and once immediately before the first training session (refer to Figure 5.1A). Functional outcome measures were performed on different days from hand training sessions, and stimulation was not applied during any assessments.

5.3.7 Event-related (de)synchronisation (ERD/ERS)

An offline analysis of the participant's EEG during BCI motor priming was performed to determine if sensorimotor cortical activity was modulated during and/or across sessions. EEG was first band-pass filtered from 1 to 40 Hz with a 3rd order Butterworth filter. Next, we calculated the power spectrum density during each trial, that is, from one to three seconds relative to the appearance of the ball (t=0 s). The pre-trial period (-1.5 to -0.5 s) was also found relative to the appearance of the ball. The mean power across the beta band (18–26 Hz) was subtracted from and divided by the mean of the resting state beta power to give the percentage ERD/ERS relative to pre-trial power.

5.4 Results

5.4.1 Graded Redefined Assessment for Strength, Sensibility, and Prehension (GRASSP)

At both baseline assessments, the participant scored a total of 96 out of 232 points in the Graded Redefined Assessment for Strength, Sensibility, and Prehension (GRASSP), as shown in Figure 5.2A. After five weeks of tSCS training this score increased by 21 points to 117/232, demonstrating improved upper-limb function. A two-week washout phase, where no training was administered, showed that functional gains were maintained, with only a slight, four-point drop in performance. The participant improved by a further 18 points to 131/232 following five weeks of BCI priming and tSCS training. A follow-up session four weeks after the final

session showed that upper-limb functional improvements had generally been maintained, with a total GRASSP score of 121 points, a 26% increase in performance compared to baseline.

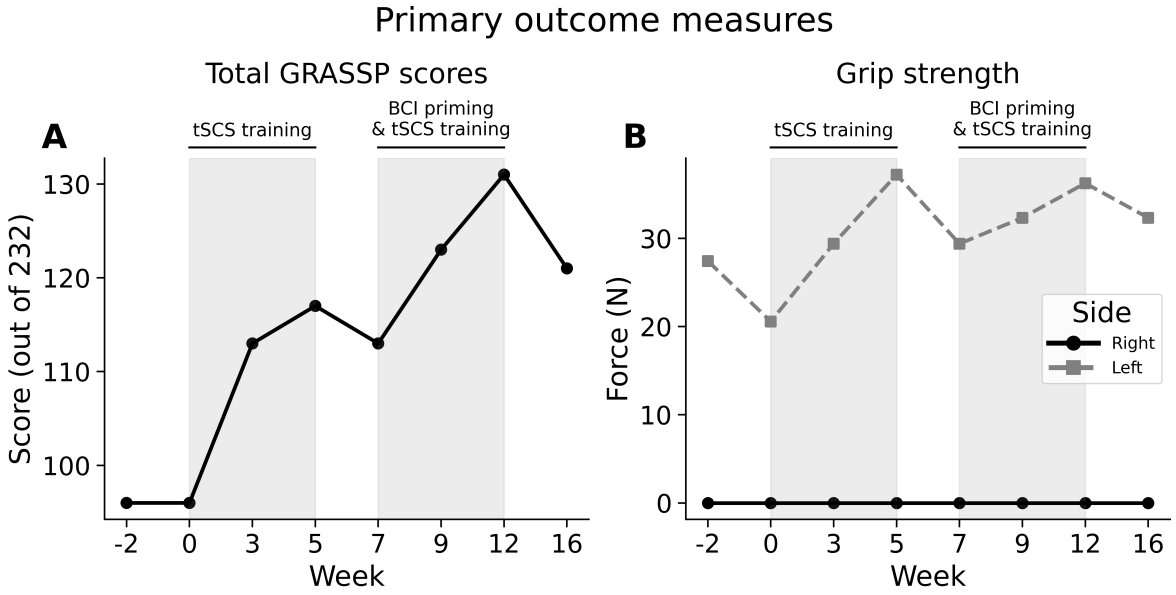

Fig. 5.2 Upper-extremity primary outcome measures. (**A**) Score totals from the Graded Redefined Assessment for Strength, Sensibility, and Prehension (GRASSP) across the study. Shaded areas indicate the two therapeutic phases: 'tSCS training' and 'BCI priming & tSCS training'. (**B**) The participant's hand grip strength across study. The left and right hand is indicated with a gray dashed and solid black line, respectively.

The right side was found to be more impaired that the left side at baseline in terms of strength, sensation of the hand, and ability to perform functional tasks. Improvements made during the first phase were generally attributable to the right side only, with strength, sensibility and prehension reaching to or exceeding the threshold for minimally detectable difference (MDD), Figure 5.3B. The MDD is the minimum amount of change in a participant's score that signifies that the change is not the result of measurement error (with 95% certainty) [150].

Strength in the left hand only improved when BCI priming preceded tSCS training, increasing by 6 points (28/50 to 34/50), above the MDD for unilateral strength (5 points). This strength gain was maintained four weeks after the final session. Improved score was attributable to contraction of the flexor pollicis longus, finger abductor, and first dorsal interossei, which had demonstrated no palpable contraction at the beginning of the second phase.

Sensibility, a measure of fingertip sensation, did not exceed MDD (more than 4 points) during either phase; I: +3.5 and II: +1, for dorsal sensibility, and -0.5 and +3 for palmar sensibility. There was, however, a 4.5-point increase in sensibility taking both phases into account, half a point above the MDD threshold.

The prehension subtest consisted of two domains: 'ability', a qualitative assessment of the participant's ability to position their hands in different grasping patterns—cylindrical grasp, lateral key pinch, and tip-to-tip pinch; and 'performance', measured by timing and scoring the participant as he performed functional tasks—such as entering a key into a lock, unscrewing lids from jam jars, and placing a nut on a bolt. Prehension ability improved by 4 points in the right hand and 2 points in the left hand following the first phase, meeting or exceeding the minimum detectable difference (2 points), see Figure 5.3A and B. The second phase did not improve this score beyond the MDD in either hand, and there was a drop beyond the MDD at the one-month follow-up. Performance of the right hand showed great improvement after the first phase of tSCS training alone, increasing by 6 points (3 points beyond the MDD). This score improved by a further two points after the second phase of priming and tSCS training, one point short of the MDD. Interestingly, performance of the right had was maintained at the one-month follow-up despite a drop in prehension ability. Performance of the left hand did not demonstrate the same improvements as the right hand, with only a one point increase after the first phase, and a one point decrease after the second phase, which was maintained by the four-week follow-up.

5.4.2 Grip strength

At baseline, the participant could produce 24.03 N of force with his left hand (Figure 5.2B). This increased to 37.27 N after the first phase of tSCS training, but decreased by 7.85 N when training was removed during the washout phase. His strength increased again following the second phase of tSCS training with BCI priming to 36.28 N. His left hand grip strength remained improved compared to baseline four weeks after the final training session at 32.36 N. The participant was unable to exert a detectable force on the grip strength meter with his right hand at any stage of the study.

5.4.3 International standards for neurological classification of spinal cord injury (ISNCSCI)

At baseline, upper-extremity motor scores measured during the ISNCSCI test showed greater impairment of the right side (13 points) compared to the left side (18 points; see Table 5.1), mirroring the GRASSP 'strength' subtest. After 15 sessions of tSCS training, the right elbow extensors improved by one point, showing active movement against some resistance. After a further 15 sessions of tSCS with BCI priming, right finger flexors showed signs of contraction, contrasting with total paralysis at baseline and after tSCS training alone. Improvements in

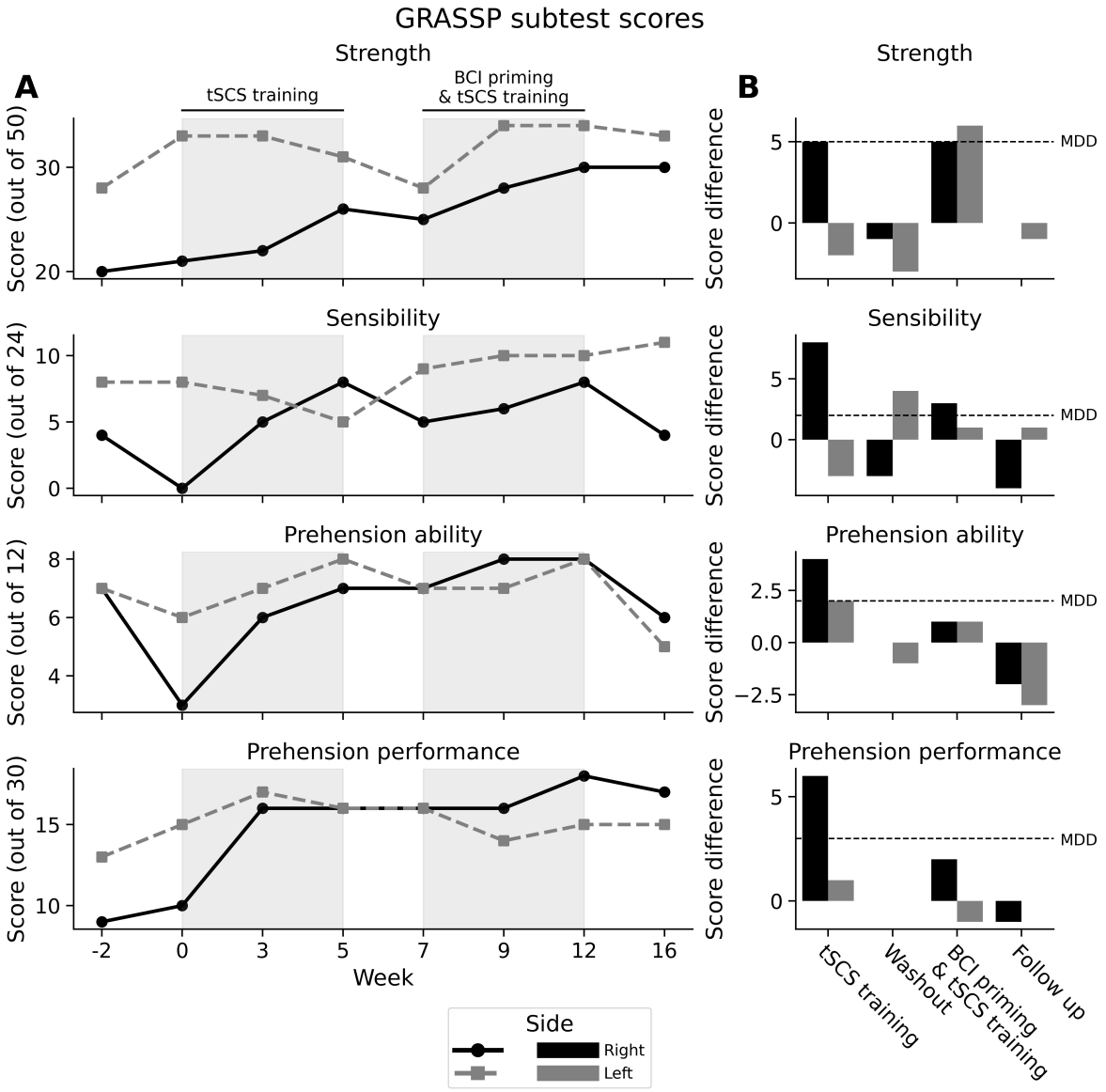

Fig. 5.3 GRASSP subtest scores. (**A**) Subtest scores from the Graded Redefined Assessment for Strength, Sensibility, and Prehension (GRASSP) Strength across the study. Shaded areas indicate the two therapeutic phases: 'tSCS training' and 'BCI priming & tSCS training'. (**B**) Unilateral differences across each phase. Left and right side is indicated with grey and black, respectively. The minimally detectable difference (MDD) is the minimum score change required such that the difference cannot be attributed to measurement error (with 95% certainty). MDD is illustrated with a horizontal dashed line.

the left upper-extremity were not as consistent. Elbow extensors increased by a single point following tSCS training alone, which was maintained at the final assessment. However, wrist extensors dropped a single point following tSCS training with BCI priming. In summary,

upper-extremity strength tended to increase on the more impaired side, during both phases of the intervention. The left side saw inconsistent changes of the upper-extremity motor score.

The participant's perception of a pin prick generally improved following each session of the study, with more prominent changes on the more impaired side, that is, the right side. After a modest two-point increase after tSCS training (9 to 11 points), right-side pin prick perception increased by four points after tSCS training with BCI priming (11 to 15 points). On the left side, pin prick sensation improved from 12 to 14 points after the first phase of tSCS training and was maintained by the end of the second phase of BCI priming and tSCS training.

The participant's ability to perceive a light touch was again enhanced more on the right side during the therapy. After a single-point decrease in light touch sensation after tSCS training alone (from 10 to 9 points), the right side improved by 6 points (from 9 to 15 points) after BCI priming and tSCS training. The left side saw reduced levels of light touch sensation following both arms of the study, with a one point decrease after tSCS training (12 to 11 points), and a two point decrease following tSCS training with motor priming (11 to 9 points).

Taking both light touch and pin prick sensation together, the most caudal dermatome with intact sensation was C4 at baseline and C4 after tSCS training alone. After BCI priming and tSCS training, however, intact sensation was detected at C5. Taking both sensory and motor function into account, the participant's neurological level of injury shifted by one spinal level, from C4 to C5. Additionally, the most caudal myotome capable of active movement against gravity was C7 on both sides at baseline. After tSCS training, the motor score on the left side improved to C8. This was maintained for the rest of the study.

Table 5.1 ISNCSCI scores during baseline, after five weeks of 'tSCS training', and after five weeks of 'priming & tSCS training'. Measures include, upper-extremity motor scores (UEMS), light touch (LT) and pin prick (PP) sensory scores, neurological level of injury (NLI), American Spinal Injury Association Impairment Scale (AIS) category, and motor level. Scores from right and left side are indicated with R and L, respectively. Bold denotes an increase from baseline.

	UEMS		LT		PP		NLI	ASI	Motor level	
	R	L	R	L	R	L			R	L
Baseline	13	18	10	12	9	12	C4	A	C7	C7
tSCS training	**14**	**19**	9	11	**11**	**14**	C4	A	C7	**C8**
Priming + tSCS training	**15**	18	**15**	9	**15**	**14**	**C5**	A	C7	**C8**

5.4.4 Modified Ashworth scale (MAS)

Spasticity was generally reduced across the study, with improvements following both phases. Table 5.2 shows that shoulder abduction stayed at grade zero throughout the research period, indicating no spasticity, whereas wrist extension remained at grade 1, indicating minimal resistance to passive extension. During elbow supination, spasticity decreased by 0.5 points after tSCS training alone (3 to 2.5 points) and by 2.5 points after priming with tSCS training (2.5 to 0), a considerable improvement. Spasticity was recorded as zero during elbow extension following tSCS training alone, a 2.5 point reduction in spasticity from baseline, but was again detected following the priming phase. Compared to baseline, spasticity was elevated during finger extension following both phases: by 1.5 points following tSCS training alone, and by 0.5 points after a further phase of BCI priming and tSCS training. In sum, spasticity decreased equally following each phase of the study.

Table 5.2 Modified Ashworth Scale. Scores are given in terms of right and left side, indicated by R and L respectively. Bold text indicates an improvement from baseline.

	shoulder abduction		Elbow extension		Elbow supination		Wrist extension		Finger extension		Total	
	R	L	R	L	R	L	R	L	R	L	R	L
Baseline	0	0	1	1.5	1.5	1.5	0	1	1	1	3.5	5
tSCS training	0	0	**0**	**0**	**1**	1.5	0	1	1.5	2	**2.5**	**4.5**
Priming + tSCS training	0	0	1	**1**	**0**	**0**	0	1	1	1.5	**2**	**3.5**

5.4.5 Spinal cord independence measure (SCIM)

According to the SCIM questionnaire (Table 5.3), the participant reported the same level of independence in self-care, respiration and sphincter management, and mobility at each phase of the study, suggesting that the functional improvements detected by the GRASSP did not translate to activities of daily life. An improvement in ability to move in bed was reported after the second phase of the study.

Table 5.3 Spinal cord independence measure (SCIM). Bold text indicates an improvement from baseline.

	Self care (20)	Respiration and sphincter management (40)	Mobility (40)	Total (100)
Baseline	6	15	6	27
tSCS training	6	15	6	27
Priming + tSCS training	6	15	**8**	**29**

5.4.6 BCI motor priming

The accuracy of the BCI motor priming paradigm was defined as the percentage of successful target hits compared to the total number of trials. Figure 5.4 illustrates that the participant was able to modulate his sensorimotor rhythms efficiently across all priming sessions, with accuracies well above chance level (56%) [102]. He successfully guided the ball to the correct target in 78% of trials during the first session and increased his accuracy to around 95% during the final sessions.

The improvements in classification accuracy were likely due to the participant becoming more adept at modulating his brain rhythms. Figure 5.5A and B show average beta band power during the two priming conditions—attempted movement and rest respectively—across the priming arm of the study. As expected, power during attempted movement is consistently lower than during rest. The difference in average power between conditions is shown in Figure 5.5C. Here it can be seen that the power difference widens over the first six sessions, before plateauing, indicating a learning process in the early sessions where the participant became increasingly able to induce distinct neural states. His ability to induce beta band event-related desynchonisation (ERD) during attempted movement was consistent across the study at around -55%, as shown in Figure 5.5D. This suggests, therefore, that improved classification accuracies were likely associated with better control of the resting state.

5.4.7 Participant compliance and stimulation intensity

Stimulation intensity was determined at the beginning of each session by slowly increasing the current until the participant's maximum tolerance was reached. After 10 minutes of continuous stimulation, the participant was asked if he could tolerate a stronger intensity. As Figure 5.6 illustrates, the participant's maximum tolerance increased by around 10 mA in the vast majority of sessions, in both the rostral (C4–C5) and caudal (C5–C6) electrode. It can also be noted that the maximum tolerable intensity was consistently higher in the rostral electrode.

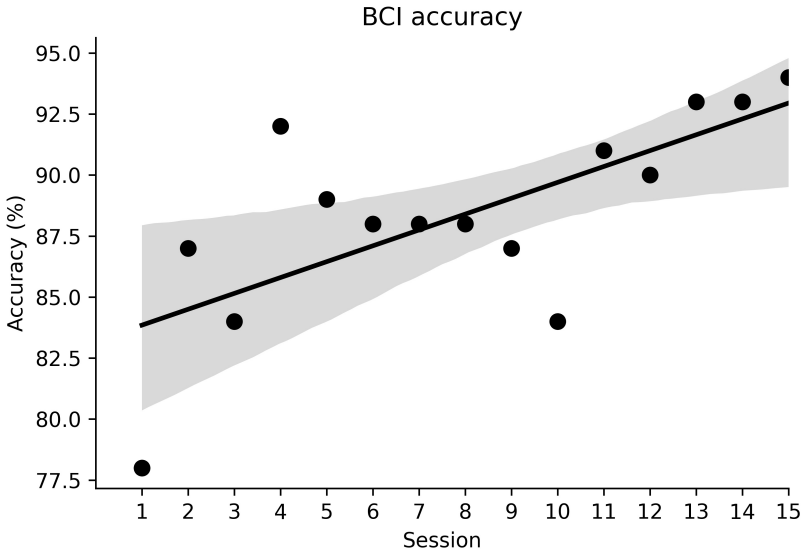

Fig. 5.4 BCI classification accuracy across sessions. The shaded area represents the 95% confidence interval.

His maximum tolerable intensity at both stimulation sites was consistent across both arms of the study, at around 47 mA and 40 mA for the rostral and caudal electrode. It is of interest to note that these stimulation intensities were within the range previously demonstrated with able-bodied individuals using their maximum tolerance [91, 92].

The participant was well able to tolerate the stimulation and it did not impede his ability to engage with the activity or in conversation. His heart rate and blood pressure were stable throughout and across sessions.

The participant often attributed the discomfort of high intensity stimulation to excessive contraction of neck and back muscles. Occasionally, the participant reported a tingling in the hip region, a sensation he commented he had not experienced since before his injury.

5.5 Discussion

In this case study we investigated whether brain-computer interface motor priming could enhance upper-extremity function following intensive transcutaneous spinal cord stimulation training. After 15 sessions of tSCS training alone, the participant showed improved unilateral strength, sensation, and gross and fine motor control. After a further phase of combined BCI priming and tSCS training the participant made strength improvements bilaterally. This result may support the notion that the presence of a priming component in rehabilitative therapy

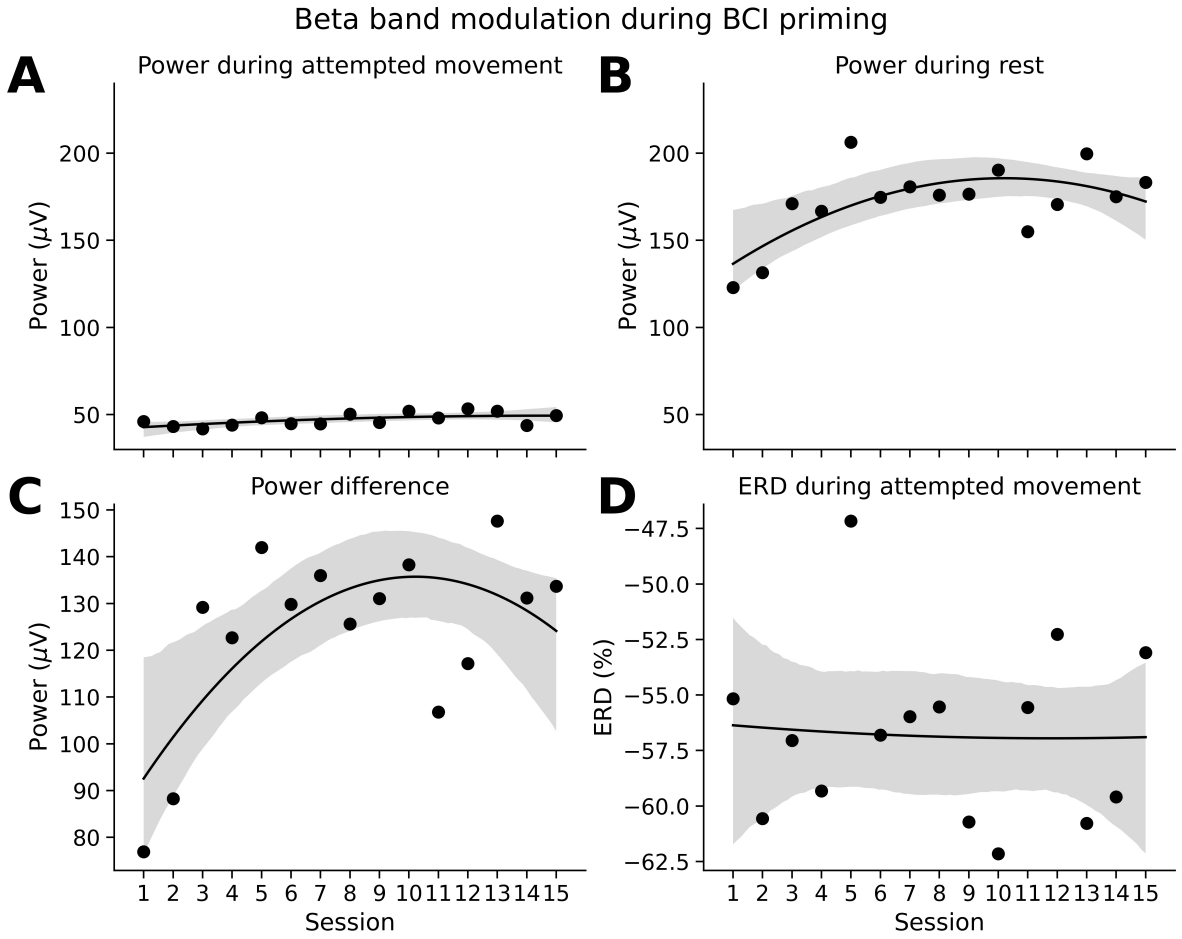

Fig. 5.5 EEG characteristics during BCI motor priming. (**A, B**) Average beta band power during BCI priming conditions—attempted movement and rest respectively—across sessions. (**C**) Difference in beta band power between priming conditions. (**D**) Beta band event-related desynchronisation (ERD) during movement with respect to pre-trial interval. The shaded areas represent the 95% confidence interval from a second order linear regression.

could enhance the effect of a subsequent intervention. However, inconsistency across outcome measures tempers this notion. It may be that improved scores in the second phase were a continuation of the progress made in the first phase through tSCS alone. Future work is required to draw firm conclusions on the potential of priming for tSCS training.

The BCI component of the study relied on the modulation of the participant's EEG to control a computer game through attempted bimanual movement. Despite individuals with chronic SCI tending to display diminished sensorimotor cortical activity due to de-efferenation following injury [42], the participant was able to consistently modulate their sensorimotor rhythms, resulting in accurate control of the BCI priming paradigm, with improved performance

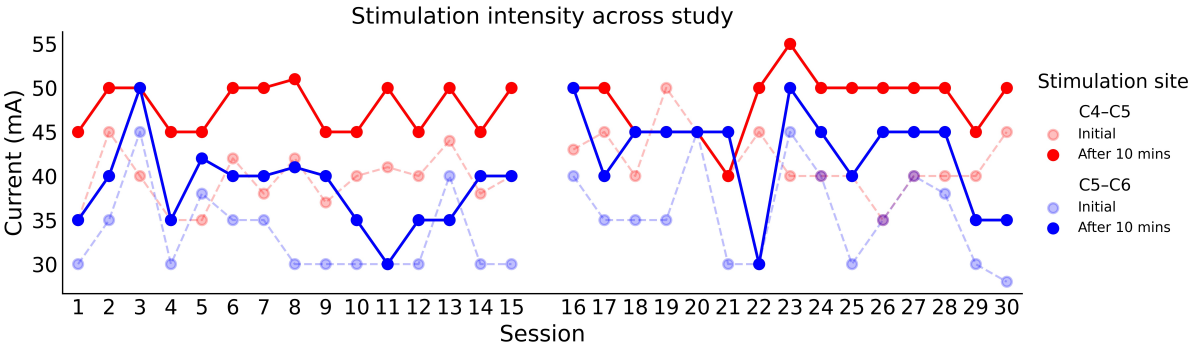

Fig. 5.6 Stimulation intensity used in each training session across the study. The rostral (C4–C5) and caudal (C5–C6) electrodes are represented with red and blue respectively. The faded traces indicate the initial current intensity before habitation.

over the course of the study. Good BCI performance indicated good compliance to the priming modality.

This work joins the growing literature supporting the use of tSCS for promoting functional recovery following SCI. There are strong parallels with a case study by Zhang *et al.* which reported that an individual with chronic SCI improved their total GRASSP score beyond the threshold for minimal detectable difference, with improvements being most prominent in the strength and prehension category. Moreover, improvements were maintained above baseline at a one-month follow-up assessment [83]. On the other hand, the current results contrast with the work by Zhang *et al.* in terms of hand grip strength, which showed only mild improvement in the left hand and no improvement whatsoever in the right hand. Further, Zhang *et al.* reported immediate functional improvements in grip strength and motor control following tSCS onset. The current study reported no such instantaneous improvement. Only after multiple sessions of tSCS training did the participant begin to show improvements in strength and finger dexterity. This is somewhat surprising given that the participant in the current study had better upper-limb function at baseline compared to the individual described by Zhang *et al.*, implying a greater volume of intact descending neurons.

Another notable study concerning upper-extremity tSCS training was conducted by Inanici *et al* [82]. Here, GRASSP was used to track the functional evolution of six chronic cervical SCI participants as they engaged in intensive tSCS-based physical practice. The impairment category tended to be less severe compared to the current study, with participants varying from AIS category B to D. Functional improvements were similar to the current study in the more severely injured participants, implying that tSCS training may be less suitable for those classified as AIS A. In addition to steady functional improvements over the course of multiple training sessions, Inanici *et al.* also reported improvements immediately following tSCS onset.

It may be the case that electrode configuration played a role. In the two aforementioned studies, inter-connected anode electrodes were positioned symmetrically over the illiac crest. Whereas, in the current study, the anode was placed symmetrically over the shoulders. Electrode position has been shown to have a significant impact on the extent to which spinal structures are recruited by single-pulse stimulation [110]. However, its importance on sub-threshold therapeutic stimulation is unclear. It may also be the case that a lack of instantaneous response to tSCS is a product of SCI pathology and not an instrumentation problem. An investigation of the mechanisms behind instantaneous versus delayed performance enhancement would greatly benefit the field.

Surprisingly, the participant reported greater tolerance to stimulation at the rostral electrode, at odds with what one may expect given that sensory impairment tends to increase caudally from the injury level. However, this appears to be in line with ISNCSCI sensory scores. The participant's ability to detect a pin prick was intact until the fourth cervical dermatome, followed by altered sensation at C5, followed by intact sensation again from the sixth to seventh cervical dermatome, displaying a non-linear reduction in sensation. The greater tolerance to stimulation at the rostral electrode may be due to its location over this area of altered sensation.

In addition to GRASSP, we included grip strength as a primary outcome measure. This was measured with a digital grip dynamometer. The left hand showed increased strength after both phases. However, improvement was less pronounced during the second phase, potentially implying that priming did not provide an enhanced effect, or perhaps had a detrimental effect on tSCS training outcomes. Of the two baseline assessments performed, this interpretation relies on the measurement taken immediately preceding the first phase. The initial baseline measurement, however, showed greater left hand strength, demonstrating inter-session variability. This may be due to a variety of participant-related factors, such as fatigue and mood. If both baseline grip strength measurements are considered, the strength improvements during each phase become similar, implying that priming neither enhanced nor inhibited tSCS training. Moreover, despite GRASSP showing improved right hand strength, the right hand displayed zero grip strength at the beginning and throughout the study. We expect, however, that this was partially attributable to insufficient instrument sensitivity, and that right hand grip strength did improve to an extent, as indicated by the participant's increasing ability to perform grasping tasks across the study. A more complete view of the participant's grip strength would have been possible with a more sensitive measure of grip strength, targeting both cylindrical and pinch grasping.

Spinal cord stimulation has been shown to be a viable option for attenuating spasticity following SCI [151, 108, 82]. The current study supports this notion in that MAS sum scores improved after each intervention phase. On individual muscles, however, there were

inhomogeneous changes in spasticity. For example, elbow extension improved after the first phase but returned to baseline levels after the second phase. Aside from this perhaps being an issue of inter-rater reliability, it may be that agonist/antagonist groups were being activated in an inverse pattern due to multiple muscles being innervated by the C6/C7 myotome, lending a degree of variability to measures of spasticity. In the future, other measures should complement MAS, such as EMG-based evaluation of tonic stretch reflexes.

Safety is of prime concern during research with SCI participants, especially studies which administer noxious stimuli such as electrical stimulation. This is due to the potential for triggering autonomic dysreflexia, a life-threatening condition prevalent among people with cervical SCI [146]. In the current study, we monitored the participant for signs of autonomic dysreflexia by tracking hemodynamic parameters, looking for signs of sudden facial flushing, or headaches, and by taking short breaks from tSCS. We found no adverse effects to stimulation. Occasionally, when the electrodes were removed at the end of a session, mild redness of the skin was observed. The skin in this area was not painful to the touch, and would fade within minutes–hours, in line with previous reports [73]. Overall, the participant tolerated the multi-site stimulation well and did not report pain or annoyance. Paraesthesia in the arms and fingers was often reported by the participant. This was not unpleasant for the participant and was taken as a welcome marker of spinal cord stimulation [56].

In addition to safety, we were also concerned by the practical considerations involved in performing BCI and stimulation experiments in series, as both techniques required time to setup equipment while the participant was idle. This could fatigue the SCI participant and affect his willingness to engage with the intervention. The participant in the current study managed the setup time well and did not appear fatigued by the time required to setup equipment. Moving forwards, however, setup time can and should be optimised, for instance by reducing the number of EEG electrodes used for BCI priming. Moreover, we found that despite the setup time, the participant provided consistent effort for the duration of the priming sessions. This may be because the game-like nature encouraged him to actively participate, and the novelty of a BCI was interesting to him. This was desirable given that effort is a partial predictor of outcome in rehabilitation.

The use of priming for neurorehabilitation has gained momentum in recent years [17]. Methods for priming the central nervous system have varied across studies, with strategies employing techniques such as motor imagery, action observation, and peripheral nerve stimulation [17, 18]. In the present study, mirror symmetric movement priming was used to ready the upper-extremities for subsequent tSCS training. It has been previously demonstrated that 20 min of active-passive wrist flexion-extension can enhance corticospinal excitability in healthy

participants [30]. Here, it was hypothesised that a similar protocol could also elevate corticospinal network reactivity. However, quantifiable methods of excitability were not recorded. Future work should consider measuring corticospinal excitability–using techniques such as transcranial magnetic stimulation, or posterior root muscle reflexes–before and after BCI priming to verify a priming effect. Furthermore, efforts should be taken to understand the number of mirror symmetric repetitions required to ensure engagement of priming mechanisms.

Studies have shown that individuals with chronic SCI display reduced sensorimotor cortical activity during attempted movement of their impaired limbs [42, 44, 43]. The participant in the current study had minimal motor and sensory ability of the distal upper-extremities. However, from the first session, the beta band showed strong levels of event-related desynchronisation (ERD) during attempted bimanual finger flexion, implying strong activation of the sensorimotor representational areas responsible for eliciting finger flexion [119, 36]. Indeed, it was expected that beta-band ERD would be relatively weaker at the beginning of the priming phase and show gradual strengthening over the course of the study. This would mirror similar work by Lopez-Larraz *et al*. which showed that ERD was significantly enhanced in a chronic C4 AIS A tetraplegic individual following four sessions of upper-alpha band neurofeedback training [43]. Instead ERD was strong throughout the study and comparable to the activity of able-bodied individuals [127, 92]. Perhaps this disparity is attributable to the participant in the current study having some residual control over his fingers, whereas the participant in the study by Lopez-Larazz *et al*. had no control below the elbow. Our rationale for priming with a brain-computer interface was to guide and quantify motor cortical activity during movement, such that enhanced activity would facilitate subsequent tSCS training. However, given that the individual in this current study exhibited maximal values of cortical activation at the beginning and throughout the study, it may be that supraspinal excitability was already at its greatest extent, making priming a superfluous addition. Potentially, priming of the nature described herein would benefit only those with impaired cortical activity, such as the variety described by Lopez-Larazz *et al*. and others [44, 43, 42].

Although improvements were relatively minor, demonstrated in part by minor changes noted in the Spinal Cord Independence Measure, the participant demonstrated improved control of his fingers, making some of the most demanding tasks, such as screwing a nut onto a bolt, possible. Improved total GRASSP scores were noted after every stretch of training. It is reasonable to assume that function would continue to improve given more sessions. Future work should consider training over a greater number of sessions to characterise the recovery of motor function. It would be valuable to determine whether BCI priming before tSCS training

could reach a motor function plateau faster than tSCS training alone, or enhance the magnitude of recovery before plateau onset.

This current work sought to establish whether BCI motor priming could enhance the benefits of tSCS for SCI rehabilitation. To this end, our investigation assumed the efficacy of tSCS training *a priori*, given recent clinical studies [82, 66]. For instance, Inanici *et al.* used a two-arm, cross-over study with two cross-over phases to demonstrate that tSCS-facilitated functional task training exceeded the therapeutic effects of functional task training alone. The current study did not follow such an approach, which may be considered a limitation, as it may be the case that similar functional improvements could have been achieved through hand training alone [14]. To better understand how the combination of interventions may impact recovery a pilot study may be performed with multiple participants case matched into three groups: 1) training only, 2) tSCS training, and 3) BCI priming and tSCS training.

5.6 Conclusions

The aim of this work was to investigate whether BCI motor priming could improve the effect of transcutaneous spinal cord stimulation therapy in an individual with a cervical spinal cord injury. Following 15 sessions of intensive tSCS-facilitated hand training, the participant's upper-limb function improved in terms of strength, sensation, and ability to perform functional tasks. This was followed by a further 15 sessions of tSCS training, with the addition of BCI motor priming preceding each session. Improvements of a similar magnitude were recorded. However, no measure exceeded that which was achieved with tSCS training alone, with the exception of bilateral strength as measured with GRASSP. The power of this finding is diluted, however, given that strength, as measured during the ISNCSCI assessment, did not show the same pattern. It is likely that the GRASSP strength improvements in the second phase were a continuation from the first phase and would have occurred regardless of priming. The results of the current study do not eliminate the possibility that motor priming could impart meaningful efficacy upon tSCS training. Only through future work using a greater number of sessions, multiple cross-over phases, multiple case-matched participants, with comprehensive measures of corticospinal excitability, would allow for such a conclusion to be drawn. We hope that the current work is a meaningful step towards this robust study.

Author Contributions

Conceptualization, C.M., A.V. and M.A.; methodology, C.M. and M.A.; software, C.M.; validation, C.M., A.V. and M.A.; formal analysis, C.M.; investigation, C.M. and N.S.T.; resources, Y.Z.; data curation, C.M.; writing—original draft preparation, C.M.; writing—review and editing, A.V., N.S.T., Y.Z. and M.A.; visualization, C.M.; project administration, M.A.; funding acquisition, C.M. and M.A. All authors have read and agreed to the published version of the manuscript.

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Chapter 6

Discussion and conclusions

6.1 Novel contributions

The research undertaken in this thesis has brought together two technologies that have promising potential in the area of spinal cord injury rehabilitation: transcutaneous spinal cord stimulation and electroencephalography/brain-computer interfaces. The investigation was approached from three perspectives. The first perspective, technical feasibility, revealed the extent of tSCS-artefact contamination in EEG and characterised its temporal and spatial contributions. This insight will be valuable for informing future research concerning brain activity during tSCS. Indeed, the results from this work prompted the second perspective: neuromodulation. This thesis provides evidence that tSCS may provide an inhibitory cortical effect among individuals who have a high tolerance to stimulation intensity. In addition, it was revealed that resting state alpha activity was unaffected by prolonged (10 min) exposure to tSCS. Finally, the third perspective, which concerned end-user interaction, recruited a chronic cervical SCI individual to target upper limb function restoration. Here, a novel motor priming paradigm was devised to ready the participant for tSCS hand and arm training.
The main findings of this thesis are summarised below:

1. Robust characterisation of the temporal and spatial impact of tSCS-induced noise in simultaneously recorded EEG.

2. Demonstration that typical physiological features–individual alpha-band peak frequency, for instance—can be accurately extracted during tSCS.

3. Established that cortical oscillations can be classified during tSCS, leading the way for real-time online brain-computer interfaces operating tSCS.

4. Provided evidence for cortical neuromodulation during tSCS.
5. Showed that resting state individual alpha frequency is unaffected by prolonged exposure to tSCS.
6. Proposed a novel method of motor priming using a brain-computer interface.
7. Showed evidence that tSCS-facilitated hand and arm training can lead to functional improvements in chronic cervical SCI.

6.2 Discussion

The aim of this thesis was to provide an evidence base for exploring the effects of tSCS on brain activity as measured by EEG. An important first step was to demonstrate the technical feasibility of such an approach. To this end, an investigation, described in Chapter 3, was conducted to characterise tSCS contamination in EEG recordings. This research was motivated by other work using electrical stimulation modalities, for instance, transcranial alternating current stimulation (tACS). It was found that, in line with previous reports using tACS, tSCS presented in EEG to a similar extent, albeit with differences in artefact prominence and spatial distribution [89]. Additionally, it was found that previously proposed methods for suppressing electrical artifacts were effective at reducing the contribution of tSCS and returning contaminated signals to levels statistically similar to that of EEG [87, 89, 88]. The potential of tSCS for neuromodulation of cortical activity was the focus of the study outlined in Chapter 4. This study provided evidence that tSCS during upper limb movement inhibited cortical activity—although, on the whole, the sample did not exhibit a significant difference compared to without tSCS. In agreement, Benavides et al. used short interval intracortical inhibition (SICI) to assess intracortical mechanisms within the primary motor cortex, reporting increased SICI after 20 min of tSCS [72]. This may reflect a similar mechanism as that contributing to modulated ERD expression. It should be noted that a study by Kumru et al. found tSCS had no impact on intracortical inhibition, which may be attributable to a disparity in methodological differences, such as duration of stimulation and stimulation frequency parameters [77]. Future work should consider measuring SICI and EEG-based cortical oscillations in the same experimental protocol to determine if they are reflective of the same inhibitory motor circuits. Finally, the third study, detailed in Chapter 5, took a more direct clinical approach by targeting upper limb recovery in an individual with chronic AIS A cervical SCI. This work lends greater credibility to cervical tSCS hand and arm training as a method for improving upper limb function after SCI, joining a

relatively small number of published work [65, 67, 83, 82]. The benefits of preceding training with BCI motor priming remain less clear. The study showed that, despite motor function improving throughout the priming phase, improvements were of a similar magnitude to the tSCS-only phase. The benefits of priming may not be eliminated as a possibility, however. The study remains limited in its scope of upper limb recovery following tSCS training and leaves unanswered questions. The first relates to the number of sessions. The second phase (priming and tSCS training) began when motor function was still improving during the first phase (tSCS only). It may be more suitable to continue tSCS-only training until a motor function plateau is reached, after which priming can be introduced to determine if this plateau can be broken. A second question concerns the rate of recovery. It is possible that having BCI priming and training in the first phase could have resulted in speedier gains in function. Only through future studies with a larger number of SCI individuals and multiple pseudo-randomised cross-over phases could this be verified. On the other hand, the feasibility of our approach to priming, that is, using EEG to allow the participant to interface with a computer game, was confirmed. The participant interacted well with the paradigm and learned to improve his ability to control the system over the course of the study.

Moving forward, the results presented here can help inform future research directions. Although there is a growing body of evidence supporting tSCS for facilitating upper-limb recovery following SCI, the neural mechanisms underpinning this observation are far from understood. By exploring cortical oscillations, the work undertaken here provides a fresh perspective on tSCS-induced neuromodulation. Owing to the inhibitory effect to alpha and beta band amplitude reported in Chapter 4, combined with the technical evidential base established in Chapter 3, the field should adopt EEG measures as part of its effort to understand the effects spinal stimulation. The research undertaken here investigated modulation by measuring alpha band frequency and power before and after tSCS, and ERD during upper limb movements. Giving that the latter appeared to demonstrate modulation in a narrow subset of participants, it would be interesting to devise a future study rigorously targeting this effect. The research presented showed that there may be a neuromodulatory effect when stimulation intensity is sufficiently high. A future study should use an appropriate sample size and implement a more quantitative method of establishing tSCS intensity, in contrast to the current work, which relied on the subjective reporting of highest tolerable intensity. Owing to this subjectivity it is difficult to predict the extent to which motor neurons are pushed to the their firing threshold. Future studies should measure the motor threshold directly by recording the posterior root-muscle reflex and setting stimulation intensities relative to this metric. This, however, may result in stimulation intensities exceeding acceptable levels of discomfort. Hence, a strict participant

inclusion criteria should be applied to ensure participants are appropriate for the study, excluding sensitive participants, otherwise sufficient spinal stimulation cannot be guaranteed.

Despite this thesis being the first body of work to investigate the impact of tSCS on cortical oscillations from EEG, previous work explored cortical modulation using motor evoked potentials elicited by TMS [71, 112]. Results have been disparate, however, and there is no consensus yet on how tSCS impacts the cortical level. The disparity across studies may be attributable to the method of stimulation delivery. The studies in this thesis delivered cathodal stimulation between cervical vertebra, with inter-connected anodes placed over the acromions. However, there is great variance in anode electrode placement across studies, with some using the illiac crest or the anterior aspect of the neck, among others. In order to optimise the potential of tSCS for SCI rehabilitation there needs to be a concerted effort among researchers to establish firm evidential foundations for what are critical experimental parameters [152].

An assumption underlying our Chapter 5 case study was that the effects of BCI priming, specifically, up-regulated sensorimotor cortical activity, would complement subsequent tSCS-assisted physical practice. As Chapter 4 indicated, however, tSCS may exert an inhibitory effect at the cortical level, which may reflect a mechanistic role of the restorative effects in neurologically-impaired individuals reported by other studies [82, 153]. Therefore, the lack of clear benefit of BCI priming for tSCS therapy may be that it targeted excitation instead of inhibition. Neurofeedback protocols have been devised to allow BCI users to both up and down-regulate neural oscillations [154, 155]. Bracklein et al. showed in two groups that participants could both increase and decrease beta rhythm amplitude during a movement task [154]. If indeed inhibited cortical activity is conducive to motor learning, as has been suggested [156], down-regulation of sensorimotor cortical rhythms prior to tSCS physical practice may provide more fruitful outcomes. This could be tested in a SCI clinical study with two groups receiving up-regulated and down-regulated BCI training, respectively, and a sham group receiving random neurofeedback. Furthermore, outcomes may be improved by considering only participants who display impaired cortical activity at baseline. Part of the lack of clear benefit over tSCS-training alone, may be that the SCI participant had somewhat normal expression of movement-related ERD to begin with, contrasting with the typical pattern of impaired ERD among individuals with chronic SCI [43]. Future work would benefit from patient screening which recruited individuals with limited ERD/ERS during attempted upper limb movement. However, if inhibition is indeed a prerequisite for motor learning it may be impractical to further inhibit already weakened cortical activity.

The work undertaken here explored cortical oscillatory activity from EEG within the typical sensorimotor spectrum of between 8 and 30 Hz. However, the work also implies that accurate

reconstruction of EEG with artefact-suppression algorithms may allow study of other EEG components of interest. The movement-related cortical potential (MRCP), a low frequency potential at around 0–5Hz, characterised by a negative shift immediately prior to movement followed by a motor potential at movement execution, could also be used as a meaningful metric in which to explore tSCS modulation [157]. The cortical generators of MRCPs have been suggested to be the premotor cortices, supplementary motor areas, and cingulate cortices, with subcortical structures, particularly the basal ganglia, also thought to play a part [158]. Transcutaneous spinal cord stimulation may convey inputs to the brainstem and thalamic nuclei, potentially reaching corticothalamic circuits and manipulating the characteristics of the MRCP. Altered expression of MRCP would provide further insight into tSCS as a means for augmenting movement preparation, execution and control, and give a complementary metric to a more rigorous investigation of oscillatory modulation.

In addition to using BCI to exert a priming effect for a subsequent tSCS-assisted therapy, there may be scope to applying tSCS during BCI training. Despite electrical interference being considered a major detriment to accurate classification of EEG, Chapter 3 showed that movement-related cortical states can be accurately predicted. To date, BCIs that demonstrate the most prominent functional outcomes for neurorehabilitation combine accurate volitional control with rich afferent feedback, for instance, by using functional electrical stimulation (FES) [49, 159]. Detection of movement intention from the sensorimotor cortex is recorded, processed, and classified, sending a command to an electrical stimulator that elicits a functional muscular contraction. This closes the so called visuo-motor loop, between intention and action sensation, despite being artificial. Combining this protocol with tSCS may lead to improved outcomes since the elevation of the transmembrane potential of afferent and efferent fibres could facilitate the neuroplastic mechanisms underpinning this already efficacious rehabilitation protocol. Although applied in series in the case study described above, the application of both BCI and tSCS was well tolerated by the participant. In addition to improvements in outcome, providing both interventions in parallel would reduce session time, making it more feasible in clinical session, where there are often strict time constraints. Although the patient reported in the above case study tolerated well both the EEG and tSCS equipment for up to 90 minutes, the actual feasibility of such a setup which would require closer study with a far larger clinical cohort. Such a protocol would involve a complex assemblage of equipment, simultaneously: EEG electrodes on the scalp, FES stimulating electrodes on target musculature, and tSCS on the posterior side of the neck and elsewhere on the body. However, complexity for SCI rehabilitation should not necessarily be avoided. Indeed, it is being recognised that due to the

multi-faceted nature of SCI pathology there may never be no single solution and that complex interventions should be embraced for effective recovery [160].

In addition to SCI rehabilitation, recent opinion is forming around the effectiveness of tSCS for improving stroke-related paresis [161]. It has been conjectured that tSCS may have an even stronger impact on stroke recovery because post-stroke spinal circuits are fully intact. Given that the vast majority of BCI research concerning neurological disease concerns stroke, it would be a natural next step to apply tSCS and EEG-based BCIs in parallel. The work presented in this thesis will be highly relevant in providing an evidence base for the feasibility of such an approach.

6.3 Conclusions

The work presented in this thesis builds on a growing body of research supporting the use of transcutaneous spinal cord stimulation for spinal cord injury rehabilitation. By offering previously unexplored perspectives, the three studies undertaken move the field of rehabilitation engineering forward in a number of key ways. Beginning with investigations with able-bodied participants, it was shown that cortical activity can be effectively extracted from EEG when recorded simultaneously with tSCS, and that movement-related brain states can be classified accurately. Further, a measurable effect of tSCS on alpha and beta oscillations during movement was found, implying neuromodulation at the cortical level. The implications of these results are vast and may serve as a foundation for a new area of study. The neural mechanisms underpinning functional recovery following tSCS-based therapy are not well understood. Implementing studies which measure corticospinal activity from a variety of perspectives, spinal reflexes, motor-evoked potentials, and now, cortical oscillations, would better place the research community to resolve the uncertainty. Moreover, these results complement our case study findings as they suggest that cortical oscillations are inhibited by tSCS, which may correlate with motor relearning. This should motivate further research of BCI priming during tSCS therapy in order to optimise coriticospinal activity for restorative therapies.

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Appendix A

Clinical assessments

A.1 ASIA worksheet

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY (ISNCSCI)

ASIA American Spinal Injury Association — ISCOS International Spinal Cord Society

Patient Name _____ Date/Time of Exam _____

Examiner Name _____ Signature _____

RIGHT

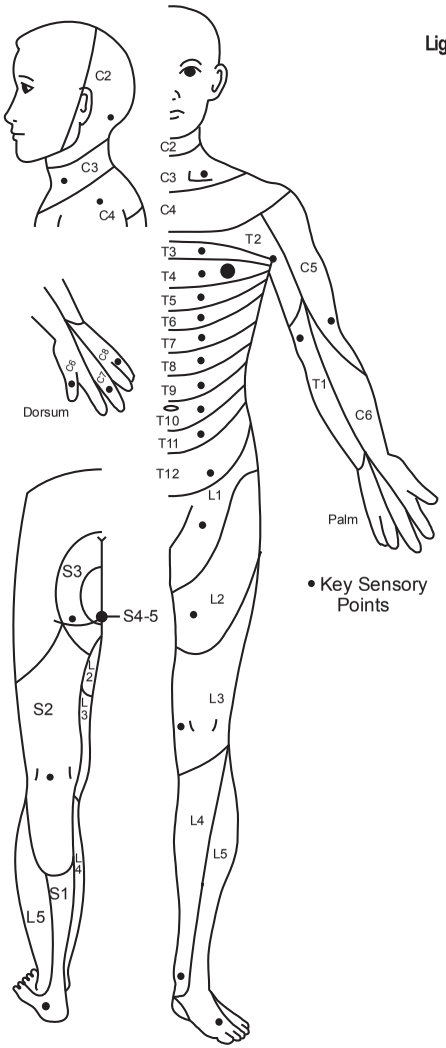
		MOTOR KEY MUSCLES	SENSORY KEY SENSORY POINTS Light Touch (LTR)	Pin Prick (PPR)
	C2			
	C3			
	C4			
Elbow flexors	C5			
Wrist extensors	C6			
Elbow extensors	C7			
Finger flexors	C8			
Finger abductors (little finger)	T1			
	T2			
	T3			
	T4			
	T5			
	T6			
	T7			
	T8			
	T9			
	T10			
	T11			
	T12			
	L1			
Hip flexors	L2			
Knee extensors	L3			
Ankle dorsiflexors	L4			
Long toe extensors	L5			
Ankle plantar flexors	S1			
	S2			
	S3			
	S4-5			
RIGHT TOTALS (MAXIMUM)				
		(50)	(56)	(56)

UER (Upper Extremity Right)

LER (Lower Extremity Right)

Comments *(Non-key Muscle? Reason for NT? Pain? Non-SCI condition?):*

(VAC) Voluntary Anal Contraction (Yes/No) ☐



LEFT

		SENSORY KEY SENSORY POINTS Light Touch (LTL)	Pin Prick (PPL)	MOTOR KEY MUSCLES	
	C2				
	C3				
	C4				
C5	Elbow flexors				
C6	Wrist extensors				
C7	Elbow extensors				
C8	Finger flexors				
T1	Finger abductors (little finger)				
	T2				
	T3				
	T4				
	T5				
	T6				
	T7				
	T8				
	T9				
	T10				
	T11				
	T12				
	L1				
L2	Hip flexors				
L3	Knee extensors				
L4	Ankle dorsiflexors				
L5	Long toe extensors				
S1	Ankle plantar flexors				
	S2				
	S3				
	S4-5				
	LEFT TOTALS (MAXIMUM)				
		(56)	(56)	(50)	

UEL (Upper Extremity Left)

LEL (Lower Extremity Left)

MOTOR (SCORING ON REVERSE SIDE)

0 = Total paralysis
1 = Palpable or visible contraction
2 = Active movement, gravity eliminated
3 = Active movement, against gravity
4 = Active movement, against some resistance
5 = Active movement, against full resistance
NT = Not testable
0, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present*

SENSORY (SCORING ON REVERSE SIDE)

0 = Absent — *NT = Not testable*
1 = Altered — *0*, 1*, NT* = Non-SCI condition present*
2 = Normal

(DAP) Deep Anal Pressure (Yes/No) ☐

MOTOR SUBSCORES

UER ☐ +UEL ☐ = *UEMS TOTAL* ☐ — MAX (25) (25) (50)

LER ☐ + LEL ☐ = *LEMS TOTAL* ☐ — MAX (25) (25) (50)

SENSORY SUBSCORES

LTR ☐ + LTL ☐ = *LT TOTAL* ☐ — MAX (56) (56) (112)

PPR ☐ + PPL ☐ = *PP TOTAL* ☐ — MAX (56) (56) (112)

NEUROLOGICAL LEVELS
Steps 1- 6 for classification as on reverse

	R	L
1. SENSORY	☐	☐
2. MOTOR	☐	☐

3. NEUROLOGICAL LEVEL OF INJURY (NLI) ☐

4. COMPLETE OR INCOMPLETE? ☐
Incomplete = Any sensory or motor function in S4-5

5. ASIA IMPAIRMENT SCALE (AIS) ☐

(In injuries with absent motor OR sensory function in S4-5 only)

6. ZONE OF PARTIAL PRESERVATION
Most caudal levels with any innervation

	R	L
SENSORY	☐	☐
MOTOR	☐	☐

REV 04/19

Muscle Function Grading

0 = Total paralysis

1 = Palpable or visible contraction

2 = Active movement, full range of motion (ROM) with gravity eliminated

3 = Active movement, full ROM against gravity

4 = Active movement, full ROM against gravity and moderate resistance in a muscle specific position

5 = (Normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person

NT = Not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)

0*, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present [a]

Sensory Grading

0 = Absent **1** = Altered, either decreased/impaired sensation or hypersensitivity

2 = Normal **NT** = Not testable

0*, 1*, NT* = Non-SCI condition present [a]

[a] Note: Abnormal motor and sensory scores should be tagged with a '*' to indicate an impairment due to a non-SCI condition. The non-SCI condition should be explained in the comments box together with information about how the score is rated for classification purposes (at least normal / not normal for classification).

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Movement	Root level
Shoulder: Flexion, extension, adbuction, adduction, internal and external rotation **Elbow:** Supination	**C5**
Elbow: Pronation **Wrist:** Flexion	**C6**
Finger: Flexion at proximal joint, extension **Thumb:** Flexion, extension and abduction in plane of thumb	**C7**
Finger: Flexion at MCP joint **Thumb:** Opposition, adduction and abduction perpendicular to palm	**C8**
Finger: Abduction of the index finger	**T1**
Hip: Adduction	**L2**
Hip: External rotation	**L3**
Hip: Extension, abduction, internal rotation **Knee:** Flexion **Ankle:** Inversion and eversion **Toe:** MP and IP extension	**L4**
Hallux and Toe: DIP and PIP flexion and abduction	**L5**
Hallux: Adduction	**S1**

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments S4-5 by LT, PP or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body. (This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥ 3.

D = Motor Incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3.

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.

ASIA
AMERICAN SPINAL INJURY ASSOCIATION

INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

ISCOS
INTERNATIONAL SPINAL CORD SOCIETY

Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.
Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI).
This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.
(i.e. absence or presence of sacral sparing)
*If voluntary anal contraction = **No** AND all S4-5 sensory scores = **0***
*AND deep anal pressure = **No**, then injury is **Complete.***
*Otherwise, injury is **Incomplete**.*

5. Determine ASIA Impairment Scale (AIS) Grade.
Is injury Complete? If YES, AIS=A

NO ↓

Is injury Motor Complete? If YES, AIS=B

NO ↓ (No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?

NO ↓ AIS=C **YES ↓ AIS=D**

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact and the ASIA Impairment Scale does not apply.

6. Determine the zone of partial preservation (ZPP).
The ZPP is used only in injuries with absent motor (no VAC) OR sensory function (no DAP, no LT and no PP sensation) in the lowest sacral segments S4-5, and refers to those dermatomes and myotomes caudal to the sensory and motor levels that remain partially innervated. With sacral sparing of sensory function, the sensory ZPP is not applicable and therefore "NA" is recorded in the block of the worksheet. Accordingly, if VAC is present, the motor ZPP is not applicable and is noted as "NA".

A.2 Graded Redefined Assessment for Strength, Sensibility, and Prehension

B: GRASSP Version 1.0

GRADED and REDEFINED ASSESSMENT Of STRENGTH, SENSIBILITY and PREHENSION Version 1.0 *(GRASSP Version 1.0)*

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Supporting Organizations: North American Clinical Trials Network, European Clinical Trials Network, ICORD, Krembil Neurosciences Centre

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INTRODUCTION

Initiated by the North American Clinical Trials Network (NACTN) and the European Clinical Trials Network (EUCTN), a meeting was held on May 12 and 13, 2006 in Chicago (local organizer Drs. Zev Rymer and Lisa-Ann Wuermser, financially supported by the Christopher and Dana Reeve Foundation) to discuss the measurement of hand impairment and function in patients suffering from cervical spinal cord injury (cSCI). Members of the networks and independent clinical specialists in hand measurement and therapy, as well as researchers with expertise in engineering and computer technology discussed the development of a comprehensive protocol to assess upper limb impairment and recovery post cSCI. The result of the meeting was a task force to further develop a clinical assessment protocol of hand function by modifying existing tools and introducing new measures that would allow for the quantification of change in hand function for individuals with cSCI. The GRASSP is a combined effort by six clinicians/researchers who have contributed their work (results of tool development through previous research, in some instances graduate studies), skills, and time. The GRASSP is a mosaic of the Link Hand Function Test (Link, 2004) and The Tetraplegia Hand Measure (Kalsi-Ryan et al. 2004).

PURPOSE OF THE MEASURE

The overall objective for the assembly of the GRASSP was to develop a clinical research tool that could capture information on hand impairment from the cervical (C0-T1) spinal cord injury (SCI) population, obtain integrated sensory and motor impairment data, and discriminate the population according to the level of lesion. The purpose of this project was to design a hand impairment tool: 1) that was highly responsive (sensitive) to change over time; 2) that could assess the extent of spontaneous (natural) recovery; and 3) be applicable for use in clinical trials to evaluate the effect of novel interventions (pharmacological and surgical). The GRASSP is recommended for use in the very early acute phases out to approximately one year post injury. Use of the GRASSP is recommended when a change in neurological status is being assessed.

DESIGN AND DEVELOPMENT OF THE GRASSP

The GRASSP is a framework that assembles different clinical tools to measure the various aspects of complex sensori-motor hand function. The GRASSP is embedded with currently existing measures of upper limb function.

For the development of the GRASSP each of the three modules was assigned to one of the measurement developers (Strength – Susan Duff, Sensibility- Sukhvinder Kalsi-Ryan, and Prehension – Claudia Link-Rudhe) under the direction of Armin Curt and Molly Verrier. Although, individuals were responsible for separate modules all members of the task force made significant contributions to all components of the GRASSP.

MODULES

The GRASSP is comprised of three separate modules, Strength, Sensibility, and Prehension. Multiple modules allow for a comprehensive assessment at multiple time points in the post-injury continuum. Each module can be tested according to the scheduled timeline provided by a trial protocol.

INSTRUCTIONS FOR IMPLEMENTATION OF THE GRASSP:

Consent: Always obtain informed consent from the subject (patient) and collect the necessary demographic data based on interview with the patient/family and chart review.

Positioning the Patient: In the acute period the patient is lying supine with both arms exposed to the shoulders and should be tested in this position. During other test sessions the subject should be seated in his/her own seating system with his/her appropriate supports. During all testing, the entire upper extremity

should be exposed (up to the shoulder). An adjustable table which can move in and out of wheelchair space will be required to perform the assessment. The subject's hands should be positioned on the table, with approximately 30 degrees of shoulder flexion, 65 degrees of elbow flexion and the hands and distal half of the forearms supported on the table. This position can be modified slightly to ensure comfort for the individual being tested. The room where the testing will be done should be well lit.
Length of the Testing: The time required to complete all of the tests in one session is approximately 30 - 45 minutes (depending on patient ability). It is not recommended to break the testing up into two sessions over two days as an individual's response can vary and recovery can potentially affect the results. For the best outcome it is recommended to complete the testing in one session, however, between sub-tests the individual and the examiner can break and stretch. In the early phases of injury (0-21 days) it is recommended to only perform the partial GRASSP which consists of the sensory, strength and qualitative prehension portions (15-20 minutes) of the test. After the early phase the full GRASSP is recommended.

STRENGTH
Muscles specific to the upper limb and hand were added to the ASIA (Marino et al. 2004) repertoire of testing to establish greater sensitivity to potential change post-injury. Strength will be assessed with Manual Muscle Testing (MMT) (Daniels & Worthington, 1995). An isotonic muscle contraction will be required by the subject to grade muscle strength. Specifically, resistance should be given at the distal end of the moving bone while the subject moves the limb through the specific range (Daniels and Worthingham, 1995). The following table defines the scaling for the muscle testing and the instructions for testing each muscle.

Muscle Testing
Prior to beginning muscle testing the subject should be oriented to the test by demonstration on an active body part. If the testing will be done in supine the examiner should stand comfortably at the bedside. If the subject is seated, the examiner may choose to stand next to the wheelchair or sit next to/across from them. During assessment of the distal arm musculature the subjects' forearm should rest on an adjustable table. Begin by testing the muscle for a grade three (range against gravity), ensuring the joints are isolated. If the individual is able to move through full range of motion (ROM) against gravity then the same movement should be tested with resistance for a grade 4 or 5 through full ROM. The examiner will grade the individual according to the scoring key. Resistance is given at the distal end of the moving bone during an isotonic contraction. Table 1 defines the muscles to be tested, the starting position, the stabilization and resistance required for testing these muscles and the scoring key to be used. Remember that for finger muscles gravity does not have an effect, which defines grade 2 as: movement of the corresponding body part but not through the full range of motion and grade 3 as: movement through full ROM. All MMT scoring should be recorded in the scoring sheets section.

Note: 1) Full range of motion for anterior deltoid should be established and then measured based on available range (available should be considered full range). 2) For elbow extension if the starting position (full elevation) is not feasible then elbow extension can be tested in 90 degrees of shoulder elevation.

Table1: Strength Testing and Instructions

Muscle	Action	Stabilization	Starting position	Resistance
Anterior/Mid Deltoid C5-6	Shoulder abduction 90°/ flexion in supine	Trunk	0^0 shoulder abduction/ flexion	Anterior, distal humerus
Elbow flexors (Biceps) C5-6	Flex elbow	Humerus	Full Elbow extension, shoulder adduction, forearm in supination	Distal, volar forearm
Elbow extensors (Triceps) C6-C8	Extend elbow	Humerus	Elbow flexion, shoulder abduction (hand behind the head, or 90° abd and full inward rotation of the humerus	Distal forearm
Wrist extensors C6-C8	Extend wrist	Forearm	Wrist in flexion, forearm in pronation	Distal, dorsal 3rd metacarpal
Extensor Digitorum C6-C8	Extend MP's digits 2-5	2-5 Metacarpals	Flexion IP's / MP's digits 2-5, forearm in pronation (fingers hanging over edge of table)	Dorsal Proximal phalanges digits 2-5
Opponens Pollicis C6-C7	Rotate 1st metacarpal toward 5^{th} digit pad	wrist/ 2-5 metacarpals	Thumb in a resting posture next to 2nd metacarpal, slightly abducted, forearm in supination	Volar proximal phalanx with derotating pressure
Flexor Pollicis Longus C6-C8	Flex thumb IP joint	Thumb Proximal phalanx/ metacarpal	0^0 thumb IP extension, MP supported in 0^0 extension	Volar thumb pad
Finger flexors (3rd FDP) C7-T1	Flex DIP joint of 3rd digit	MP, PIP joint 3rd digit	3rd digit DIP extension, 3^{rd} PIP/MP supported in 0^0 extension on table	3rd volar finger pad
Finger abductors (5th) C8-T1	Abduct 5th digit	5th metacarpal	5th digit adducted, MP's extended, forearm in pronation. (Position hand on sheet of paper to reduce friction)	Ulnar side of inter-phalangeal joint of 5th digit
First Dorsal Interossei C8-T1	Abduct index	2nd metacarpal	Index adducted next to long finger, MP's extended, forearm in pronation (Position hand on sheet of paper to reduce friction on the table)	Radial side of inter-phalangeal joint of 2nd phalanx

ASIA Muscles in Italics (Daniels and Worthingham, 1995; Kendall, McCleary and Provance, 1993)

Table 2: Scoring for Manual Muscle Testing

0	Absent – No palpable muscle contraction
1	Trace – Palpable Muscle Contraction
2	Poor – Moves full ROM with gravity eliminated
3	Fair – Moves full ROM against gravity without added resistance
4	Good – Moves through full ROM against gravity against moderate resistance
5	Normal – Moves through full ROM against gravity against maximal resistance

SENSIBILITY

Sensory testing should always be conducted in a room that is at a comfortable temperature (as close to room temperature as possible). When applying the stimulus to the hands the examiner must ensure that he/she does not touch the hand as this can alter the individual's ability to sensate accurately. Prior to beginning the testing the subject should be oriented to the test by demonstration on an area of intact sensation such as the face. The examiner will be standing beside the bed or seated across from the subject. The test is performed with the subjects eyes closed or occluded. The forearm and hand should be supported in supination or pronation with a towel or a pillow (not with the examiners hands). A circumferential 2 inch Velcro strap may be used to secure the hand to the pillow allowing for access to the palm and finger tips during the testing.

Semmes Weinstein Monofilament Testing (SWM) The monofilaments should be applied to all 6 points (test points 1 to 6 in Figure 1). The filament should be applied until it bends: applying for 1.5 seconds, holding for 1.5 seconds, and removing for 1.5 seconds. Filament 3.61 is to be applied three times at all test locations, 2/3 positive responses indicates intact sensibility of that force. The assessor should determine if the participant has sensation by asking "do you feel a touch?" and following by "where do you feel the touch?" It the patient is not able to adequately localize the stimulus then he/she is not feeling the applied stimulus. The remaining three filaments are applied once. The test is started on the dorsal side of the hand. The first filament (3.61) is applied three times; all dorsal test locations (points 1-3) can be tested before moving to the palmar test locations (4-6). Delayed responses of more than three seconds are abnormal. If the patient feels the first filament in all areas the examination is complete. It will not be necessary to use the other filaments. If the patient does not respond to the 3.61 filament the next heavier filament is used. Only test locations which do not respond to the previous filament need to be tested with the next filament. The exam continues until the patient recognizes a force in all test locations or until it is established that he/she does not feel even the heaviest filament. When the response is positive for a particular filament a check can be put in the associated box. When all the test locations have been tested the filament force should be scored appropriately into the final box score. Table 3 defines the score associated to the log label of the monofilament (Mackin et al. 2002).

Figure 1: Diagram for Sensibility Test Locations

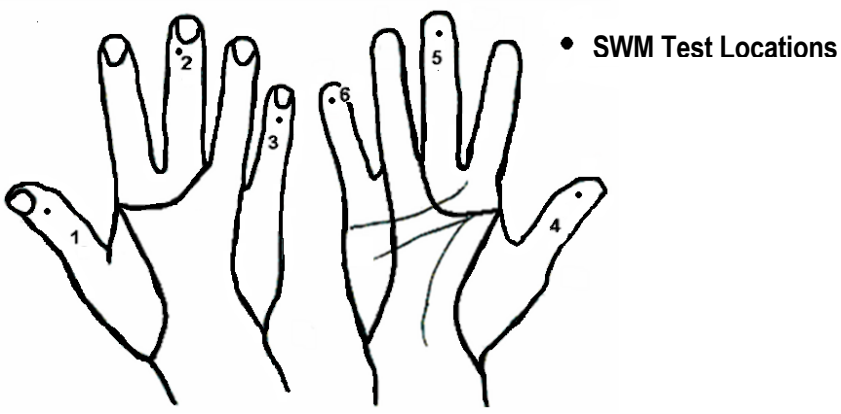


Table 3: Scoring of Pressure Sensibility with Semmes Weinstein Monofilaments

Filament Label	3.61	4.31	4.56	6.65	No Response
Filament Force in g/F	0.217	2.35	4.19	279.4	No Response
Score	4	3	2	1	0

PREHENSION

Prehension is assessed both qualitatively and quantitatively.

A. Qualitative Prehension Testing The aim of this sub-section is to ensure that the early movement is captured before an individual may be ready for a seated assessment. No specific positioning of the patient is required, but appropriate positioning of the hand for movement should be ensured. The patient is asked to form three prehension patterns with each hand separately. The requested movement and grasp patterns can be demonstrated by the examiner. The purpose of this testing is to establish which components of the finger-hand-forearm can be actively or passively positioned and directed to allow a grasp function and if the movement is wrist dominant. The intent is to establish whether the participant can perform a limited movement that does or does not include the components to develop an active grasp. The assessor should be looking to isolate, wrist, fingers and

thumb. The basic pattern for grasping might be visible although the patient yet can not quite grasp. In the very early stages a patient will require the assessor to support the hand so that the patient can see it. This may require providing the neutral position of the wrist as well. Table 4 defines the three grips to be tested and the associated scoring.

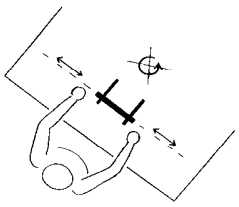
Table 4: A. Qualitative Prehension, Instructions and Scoring

Qualitative Prehension	**Task**
Cylindrical Grasp	Neutral wrist position and finger movements performed with gravity eliminated
Lateral Key Pinch	Neutral wrist position and finger movements performed with gravity eliminated
Tip to Tip Pinch (thumb and index finger)	Neutral wrist position and finger movements performed with gravity eliminated

Scoring
0 - Subject is not able to position the wrist or fingers in any specific pattern for the requested grasp.
1 - Subject is able to move the wrist actively and fingers passively assume the requested prehension pattern (able to begin a grasp using the wrist and no finger movement)
2 - Subject is able to partially or completely move the fingers actively into the requested prehension pattern (combination of wrist movement and intrinsic hand muscle activation) but fails to generate force because the grasp is acquired through passive positioning from the activating the wrist.
3 - Subject is able to actively position the fingers and/or thumb into the requested prehension pattern with normal wrist movement for a grasp, touching the opposite finger(s) or the palm with some noticeable active force.
4 - Subject is able to perform the grasp with normal strength (in a normal shaking hand).

B. Quantitative Prehension Testing The patient is positioned in a sitting position symmetrically in front of a table. Additional support for trunk stability is allowed. This includes for example the use of a belt but also sitting in bed supported by the back rest or using the bed side table to set up the test.

· A change in position, concerning the person's angle to the table, is not allowed during the standardised test administration.
· The test is conducted twice, once for the right hand and then once for the left hand.
· The stabilisation of the objects/test board, if necessary, is done by the examiner.
· The test board is placed parallel to the edge of the table, in front of the patient. Moving the board in a parallel line to the table's edge is permitted. Turning or rotating of the board is not permitted (see picture).
· All other items are placed on the table in front of the patient.



Procedure
The required material for the different tasks is placed on the table in front of the patient just prior to the performance of each task. Prior to the first test administration, the patient is allowed to perform each task once as a rehearsal, without being scored. This will allow familiarization with the task and reduce the learning effect. The rehearsal time is limited to 1 minute for each task. The precise administration procedure for each task can be found in the table below. The examiner times each task. The timing starts at a clear signal "start" by the examiner and ends when the task is fully completed. The material can only be touched or grasped after the "start" signal by the examiner. Table 5 defines the instructions to the examiner and the patient. The initiation of each task is defined by clear activity, such as moving pegs, lifting up coins, manipulating the bottle of water in the hand. To score a 1 at least one part of the task must be done (i.e. lifting up a coin, grasping and/or moving a coin, holding/lifting the bottle). Moving the hand alone is not regarded as "done part of the activity"; neither is placing the hand on the test equipment. The examiner observes task performance focussing on the form of the grasp. The time required for task performance is recorded on the score sheet and the task is scored according to the scoring key in Table 6. Quantitative prehension performance leads to a score with an associated time that is recorded separately. The maximum score for each task is 5 points with a maximal total score of 30 points per hand. To judge the quality of the performance, the examiner must refer to the description of the "expected performance". This description defines the typical form of grasp used and performance with an unaffected hand (see Table 5). One minute and 15 seconds is allowed for the completion of each task, if the individual is unable to complete the task within 1 minute

and 15 seconds score accordingly and move on to the next task (Sollerman and Ejeskar, 1995). There is no specific order to the tasks and they appear in order of simplicity (least difficult to more difficult).
Dropping of objects: If a patient drops an object and it falls onto the table, still reachable for the patient to retrieve, the task is continued without stopping the clock the drops are counted and the number is entered in the # of drops column. If the object falls onto the floor or the lap of the patient and cannot be reached by the patient, the clock is stopped. The examiner can pick the object up and the task may be repeated. If the drop lands on the floor or lap of the patient again, during the repeated execution, the task is judged as “not conducted" (0 points) and comments are noted.

Table 5: Quantitative Prehension, Instructions and Scoring

Task and Instructions to Examiner	
Expected Prehension Pattern for Task	**Task Instructions for Subject**
1. The filled, already opened bottle (0.5L) and the cup are placed onto the table in front of the patient. The task is completed if the water is poured in the cup and cup and bottle are put back down onto the table. The cup is stabilized by the examiner. 50% of task 1 is when the participant has begun to pour the water.	
Cylindrical grasp	1. Take the bottle and pour the water into the cup, approx. ¾ full.
2. The two jam jars are placed onto the table in front of the patient. The lids should sit tightly on the jar but should not require much strength to be opened (check before task administration). The task is completed when both lids and jars lay on the table. The jars are stabilized by the examiner. 50% of task 2 is when the participant has removed one lid.	
Spherical grasp	2. Unscrew the lids of the 2 jars and place them on the table.
3. The peg board is placed on the table in front of the patient. It does not matter if the pegs are moved from right to left or left to right; the patient can choose his preference. The task is completed when all 9 pegs are placed in the opposite board. The board is stabilized by the examiner or use of dycem. 50% of task 3 is when the participant has inserted 4 pegs.	
Tip to Tip pinch (thumb and index finger) / Tripod pinch	3. Pull the 9 pegs, **one by one**, out of the block and place them back into the markings on the opposite side.
4. The test board is placed on the table, parallel to the table’s edge, in front of the patient. The distance from the table’s edge to the test board is not important. The key is put on the table in front of the patient. The turning direction of the key is of no importance. The task is completed when the key was rotated 90°. The board is stabilized by the examiner or use of dycem. 50% of task 4 is when the participant is able to get the key to insertion point.	
Lateral Key pinch	4. Take the key from the table, insert it in the lock and turn it 90°.
5. The position of the test board is as described for task no. 4. The coins are placed in a row on the table in front of the patient. The task is completed when all coins are dropped into the slot. The board is stabilized by the examiner or use of dycem. 50% of task 5 is when the participant is able to insert 2 coins	
Tip to Tip Pinch (thumb and index finger)	5. Pick up the 4 coins, **one by one**, from the table and drop them through the slot.

6. The position of the test board remains the same as described for task no.4 and 5. The 4 nuts are placed in a row onto the table in front of the patient. The task is completed when all nuts are screwed onto the matching screws, the screw's-end aligned with the nuts. Rotating the test board is not permitted in this task either. The board is stabilized by the examiner or by dycem. 50% of task 6 is when the participant is able to screw two nuts on	
Tip to Tip pinch (thumb and index finger) and/or Tripod pinch	**6.** Pick up the 4 nuts, **one by one**, from the table and screw them onto the matching screws.

Table 6: Scoring for the Quantitative Prehension

Scoring (a maximum of 1 minute and 15 seconds is allowed for each task)
0 - the task can not be conducted at all
1 - the task can not be completed, (less than 50% of the task)
2 - the task is not completed, (50% or more of the task)
3 - the task is conducted (completed) using tenodesis or an alternative grasp other than the expected grasp
4 - the task is conducted using the expected grasp with difficulty (lack of smooth movement or difficult slow movement)
5 - the task is conducted without difficulties using the expected grasping pattern and unaffected hand function.

SCORING SHEETS

1 - Demographics

Patient Name	
Examiner	
Assessment Number	1 2 3 4 5 6
Date of Assessment	
DOB	
Gender	
Hand Dominance	
Pre-injury	
Post-injury	
Injury Date	
Injury Type Brief Description	
Surgery/Intervention and Date	
Comments	

2 - Strength - score 0 to 5 as per instructions in each box, then sum for each side

Right	Muscles Tested for MMT	Left
	Anterior Deltoid	
	Elbow Flexors	
	Elbow Extensors	
	Wrist Extensors	
	Extensor Digitorum (DIII)	
	Opponens Pollicis	
	Flexor Pollicis Longus	
	Finger Flexors (DIII)	
	Finger Abductors	
	First Dorsal Interossei	
/50	**Total out of 50 for each side**	**/50**

3 – Sensibility

SWM Threshold Scores																
Right Hand									Left Hand							
3.61 (4)	3.61 (4)	3.61 (4)	4.31 (3)	4.56 (2)	6.65 (1)	NR (0)	Score	**Area**	3.61 (4)	3.61 (4)	3.61 (4)	4.31 (3)	4.56 (2)	6.65 (1)	NR (0)	Score
								1								
								2								
								3								
Dorsal Total							**/12**		**Dorsal Total**							**/12**
								4								
								5								
								6								
Palmar Total							**/12**		**Palmar Total**							**/12**
Dorsal Total+Palmar Total=Total SWM							**/24**		**Dorsal Total+Palmar Total=Total SWM**							**/24**

4 - Prehension

A - Qualitative Prehension

Right	Qualitative Grasps	Left
	Cylindrical Grasp	
	Lateral Key Pinch	
	Tip to Tip Pinch	
/12	**Total out of 12**	**/12**

B - Quantitative Prehension

Right			Task/ Instruction Expected Prehension	Left		
Time	**Score**	**Drops**		**Time**	**Score**	**Drops**
			1. Take the bottle and pour the water into the cup, approx. ¾ full. Cylindrical grasp			
			2. Unscrew the 2 lids of the jam jars and put them onto the table. Spherical grasp			
			3. Pull the 9 pegs, one by one, out of the foam and stick them back into the markings on the opposite side. Tip to Tip pinch			
			4. Take the key from the table, insert it in the lock and turn it 90°. Lateral Key pinch			
			5. Pick up the 4 coins, one by one, from the table and put them through the slot. Tip to Tip Pinch			
			6. Pick up the 4 nuts, one by one, from the table and screw them on the matching screws. Tip to Tip pinch and/or Tripod pinch			
			Total Score /30			

5 – Summary and Total Scores

Right		Left
	STRENGTH-Upper limb (50/50)	
	SWM –DORSAL (12/12)	
	SWM-PALMAR (12/12)	
	PREHENSION – Qualitative (12/12)	
	PREHENSION – Quantitative (30/30)	
	TOTALS /116	

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A.3 Modified Ashworth scale

Modified Ashworth Scale Instructions

General Information (derived Bohannon and Smith, 1987):

- Place the patient in a supine position
- If testing a muscle that primarily flexes a joint, place the joint in a maximally flexed position and move to a position of maximal extension over one second (count "one thousand one")
- If testing a muscle that primarily extends a joint, place the joint in a maximally extended position and move to a position of maximal flexion over one second (count "one thousand one")
- Score based on the classification below

Scoring (taken from Bohannon and Smith, 1987):

0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

Patient Instructions:

The patient should be instructed to relax.

Modified Ashworth Scale Testing Form

Name:_____ Date:_____

Muscle Tested	Score
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Reference for test instructions:

Bohannon, R. and Smith, M. (1987). "Interrater reliability of a modified Ashworth scale of muscle spasticity." Physical Therapy 67(2): 206.

A.4 Spinal Cord Independence Measure

שירותי בריאות
כ ל ל י ת

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Department IV, Medical Director: Dr. Amiram Catz **Tel: 972-9-7709090 Fax: 972-9-7709986** e-mail: amiramc@clalit.org.il

Patient Name: _____ **ID:**_____ **Examiner Name:** _____

(Enter the score for each function in the adjacent square, below the date. The form may be used for up to 6 examinations.)

SCIM-SPINAL CORD INDEPENDENCE MEASURE

Version III, Sept 14, 2002

EXam 1 2 3 4 5 6

Self-Care

DATE \ \ \ \ \ \

1. Feeding (cutting, opening containers, pouring, bringing food to mouth, holding cup with fluid)

0. Needs parenteral, gastrostomy, or fully assisted oral feeding
1. Needs partial assistance for eating and/or drinking, or for wearing adaptive devices
2. Eats independently; needs adaptive devices or assistance only for cutting food and/or pouring and/or opening containers
3. Eats and drinks independently; does not require assistance or adaptive devices

2. Bathing (soaping, washing, drying body and head, manipulating water tap). **A-upper body; B-lower body**

A. 0. Requires total assistance
1. Requires partial assistance
2. Washes independently with adaptive devices or in a specific setting (e.g., bars, chair)
3. Washes independently; does not require **a**daptive **d**evices or **s**pecific **s**etting (not customary for healthy people) (adss)

B. 0. Requires total assistance
1. Requires partial assistance
2. Washes independently with **a**daptive **d**evices or in a **s**pecific **s**etting (adss)
3. Washes independently; does not require **a**daptive **d**evices (adss) or **s**pecific **s**etting

3. Dressing (clothes, shoes, permanent orthoses: dressing, wearing, undressing). **A-upper body; B-lower body**

A. 0. Requires total assistance
1. Requires partial assistance with **c**lothes **w**ith**o**ut **b**uttons, **z**ippers or **l**aces (cwobzl)
2. Independent with cwobzl; requires **a**daptive **d**evices and/or **s**pecific **s**ettings (adss)
3. Independent with cwobzl; does not require adss; needs assistance or adss only for bzl
4. Dresses (any cloth) independently; does not require adaptive devices or specific setting

B. 0. Requires total assistance
1. Requires partial assistancewith **c**lothes **w**ith**o**ut **b**uttons, **z**ipps or **l**aces (cwobzl)
2. Independent with cwobzl; requires adaptive devices and/or specific settings (adss)
3. Independent with cwobzl without adss; needs assistance or adss only for bzl
4. Dresses (any cloth) independently; does not require adaptive devices or specific setting

4. Grooming (washing hands and face, brushing teeth, combing hair, shaving, applying makeup)

0. Requires total assistance
1. Requires partial assistance
2. Grooms independently with adaptive devices
3. Grooms independently without adaptive devices

SUBTOTAL (0-20)

Respiration and Sphincter Management

5. **Respiration**

0. Requires tracheal tube (TT) and permanent or intermittent assisted ventilation (IAV)
2. Breathes independently with TT; requires oxygen, much assistance in coughing or TT management
4. Breathes independently with TT; requires little assistance in coughing or TT management
6. Breathes independently without TT; requires oxygen, much assistance in coughing, a mask (e.g., peep) or IAV (bipap)
8. Breathes independently without TT; requires little assistance or stimulation for coughing
10. Breathes independently without assistance or device

6. Sphincter Management - Bladder

0. Indwelling catheter
3. Residual urine volume (RUV) > 100cc; no regular catheterization or assisted intermittent catheterization
6. RUV < 100cc or intermittent self-catheterization; needs assistance for applying drainage instrument
9. Intermittent self-catheterization; uses external drainage instrument; does not need assistance for applying
11. Intermittent self-catheterization; continent between catheterizations; does not use external drainage instrument
13. RUV <100cc; needs only external urine drainage; no assistance is required for drainage
15. RUV <100cc; continent; does not use external drainage instrument

7. Sphincter Management - Bowel

0. Irregular timing or very low frequency (less than once in 3 days) of bowel movements
5. Regular timing, but requires assistance (e.g., for applying suppository); rare accidents (less than twice a month)
8. Regular bowel movements, without assistance; rare accidents (less than twice a month)
10. Regular bowel movements, without assistance; no accidents

8. Use of Toilet (perineal hygiene, adjustment of clothes before/after, use of napkins or diapers).

0. Requires total assistance
1. Requires partial assistance; does not clean self
2. Requires partial assistance; cleans self independently
4. Uses toilet independently in all tasks but needs adaptive devices or special setting (e.g., bars)
5. Uses toilet independently; does not require adaptive devices or special setting**)**

SUBTOTAL (0-40)

Mobility (room and toilet)

DATE \ \ \ \ \ \ \

9. Mobility in Bed and Action to Prevent Pressure Sores

0. Needs assistance in all activities: turning upper body in bed, turning lower body in bed, sitting up in bed, doing push-ups in wheelchair, with or without adaptive devices, but not with electric aids
2. Performs one of the activities without assistance
4. Performs two or three of the activities without assistance
6. Performs all the bed mobility and pressure release activities independently

10. Transfers: bed-wheelchair (locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet).

0. Requires total assistance
1. Needs partial assistance and/or supervision, and/or adaptive devices (e.g., sliding board)
2. Independent (or does not require wheelchair)

11. Transfers: wheelchair-toilet-tub (if uses toilet wheelchair: transfers to and from; if uses regular wheelchair: locking wheelchair, lifting footrests, removing and adjusting armrests, transferring, lifting feet)

0. Requires total assistance
1. Needs partial assistance and/or supervision, and/or adaptive devices (e.g., grab-bars)
2. Independent (or does not require wheelchair)

Mobility (indoors and outdoors, on even surface)

12. Mobility Indoors

0. Requires total assistance
1. Needs electric wheelchair or partial assistance to operate manual wheelchair
2. Moves independently in manual wheelchair
3. Requires supervision while walking (with or without devices)
4. Walks with a walking frame or crutches (swing)
5. Walks with crutches or two canes (reciprocal walking)
6. Walks with one cane
7. Needs leg orthosis only
8. Walks without walking aids

13. Mobility for Moderate Distances (10-100 meters)

0. Requires total assistance
1. Needs electric wheelchair or partial assistance to operate manual wheelchair
2. Moves independently in manual wheelchair
3. Requires supervision while walking (with or without devices)
4. Walks with a walking frame or crutches (swing)
5. Walks with crutches or two canes (reciprocal walking)
6. Walks with one cane
7. Needs leg orthosis only
8. Walks without walking aids

14. Mobility Outdoors (more than 100 meters)

0. Requires total assistance
1. Needs electric wheelchair or partial assistance to operate manual wheelchair
2. Moves independently in manual wheelchair
3. Requires supervision while walking (with or without devices)
4. Walks with a walking frame or crutches (swing)
5. Walks with crutches or two canes (reciprocal waking)
6. Walks with one cane
7. Needs leg orthosis only
8. Walks without walking aids

15. Stair Management

0. Unable to ascend or descend stairs
1. Ascends and descends at least 3 steps with support or supervision of another person
2. Ascends and descends at least 3 steps with support of handrail and/or crutch or cane
3. Ascends and descends at least 3 steps without any support or supervision

16. Transfers: wheelchair-car (approaching car, locking wheelchair, removing arm- and footrests, transferring to and from car, bringing wheelchair into and out of car)

0. Requires total assistance
1. Needs partial assistance and/or supervision and/or adaptive devices
2. Transfers independent; does not require adaptive devices (or does not require wheelchair)

17. Transfers: ground-wheelchair

0. Requires assistance
1. Transfers independent with or without adaptive devices (or does not require wheelchair)

SUBTOTAL (0-40)

TOTAL SCIM SCORE (0-100)