BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-047670
Article Type:	Protocol
Date Submitted by the Author:	04-Dec-2020
Keywords:	REHABILITATION MEDICINE, Neurological injury < NEUROLOGY, Spine <

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	ORTHOPAEDIC & TRAUMA SURGERY, NEUROSURGERY, Clinical trials < THERAPEUTICS

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Deep brain stimulation for locomotion in incomplete human spinal cord injury (DBS-SCI) – protocol of a prospective one-armed multi-centre study

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Word count: 4374 words

ABSTRACT

Introduction: Spinal cord injury (SCI) is a devastating condition with an immediate impact on the individual's health and quality of life. Major functional recovery plateaus three to four months after injury despite intensive rehabilitative training. To enhance training efficacy and improve long-term outcomes, the combination of rehabilitation with electrical modulation of the spinal cord and brain has recently aroused scientific interest with encouraging results. The mesencephalic locomotor region (MLR), an evolutionarily conserved brainstem locomotor command and control centre, is considered a promising target for deep brain stimulation (DBS) in patients with SCI. Animal experiments showed that MLR-DBS can induce locomotion in rats with spinal white matter destructions of >85%.

Methods and analysis: In this prospective one-armed multi-centre study we investigate the safety, feasibility and therapeutic efficacy of MLR-DBS to enable and enhance locomotor training in severely affected, subchronic and chronic AIS C patients in order to ultimately improve functional recovery. Patients undergo an intensive training program with MLR-DBS while being regularly followed-up until 6 months post-implantation. The acquired data of each timepoint are compared to baseline while the primary endpoint is performance in the 6 Minute Walking Test (6MWT). The clinical trial protocol was written in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.

Ethics and dissemination: This first in-man study investigates the therapeutic potential of MLR-DBS in SCI patients. Thus far, one patient has been implanted with electrodes and underwent MLR stimulation during locomotion. Based on the preliminary results which promise safety and feasibility, recruitment of further patients is currently ongoing. Ethical approval has been obtained from the Ethical Committee of the Canton of Zurich (case number BASEC 2016-01104) and Swissmedic (10000316). Results will be published in peer-reviewed journals and presented at scientific conferences.

Trial registration: Registered on ClinicalTrials.gov (NCT03053791) on February 15, 2017 (https://www.clinicaltrials.gov).

Keywords: Spinal cord injury, deep brain stimulation, mesencephalic locomotor region, locomotion, training, rehabilitation

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This prospective one-armed multi-centre proof-of-concept study investigates the safety, feasibility and therapeutic potential of MLR-DBS to improve walking function after severe incomplete SCI.
- Patients with completed in-patient rehabilitation with highly limited ambulatory capacity are screened and considered for study enrolment.
- The study comprises a variety of clinical and electrophysiological assessments before, during, and after electrode implantation.
- Patients undergo intensive rehabilitative training with MLR-DBS and are followed-up on a regular basis until 6 months post-implantation.
- The primary endpoint is improvement of locomotion measured by the 6MWT 6 months after electrode implantation compared to baseline performance.

INTRODUCTION

In the event of spinal cord injury (SCI) a person's life turns upside down within a split second, and a multitude of body functions are either severely impaired or completely lost instantly. Reacquiring lost functions including locomotion is of high importance for affected patients.[1] However, it remains a largely unmet medical need due to the lack of treatment options to sufficiently rewire interrupted fibre tracts and enhance repair of the damaged human spinal cord. Despite decades of basic research, neuro-rehabilitative training currently remains the only treatment option that increases the chances of long-term improvement of sensory-motor functions.[2,3] Even though most SCIs spare some descending and ascending fibre tracts, leaving the sublesional spinal cord [4] only incompletely disconnected from the brain, functional recovery remains limited in most cases.[3,5,6] The number of spared, descending fibres is often insufficient to convey appropriate control signals to sublesional locomotor circuits, e.g. central pattern generators (CPGs), which are thus deprived of supraspinal input and modulation,[7] and fail to induce rhythmic motor patterns.[8,9] However, these local rhythm generators remain functional and can be reactivated, e.g. by direct electrical stimulation in combination with training.[10–12] To increase the efficiency and efficacy of neurorehabilitation, locomotor training has therefore been combined with electrical epidural and transcutaneous stimulation of the spinal cord in small cohorts of patients in recent years, yielding promising results.[3,13–15] Another encouraging approach to recruit inactive, yet intact, sublesional motor circuits involves the electrical activation of spared descending reticulospinal tract fibres (Figure 1).[16] The majority of reticulospinal fibres arise from the medial medullary reticular formation, which relays the output of its upstream target, the mesencephalic locomotor region (MLR),[17–19] to the spinal cord. The MLR is a phylogenetically conserved key locomotor control centre in the brainstem, and is comprised of two main nuclei, the pedunculopontine (PPN) and the cuneiform nucleus (CNF).[20–22] The PPN is associated with exploratory behaviour,[23] and deep brain stimulation (DBS) of the PPN in patients with Parkinson's disease can result in a reversal of freezing of gait.[24–27] On the other hand, the CNF is known to be a main control region for locomotion initiation, maintenance and speed regulation.[23,28,29] Recently, the CNF has gained scientific and clinical interest as therapeutic target for DBS to improve deficient gait after SCI [16] and stroke.[30] Electrical activation of the MLR during locomotion has been shown to acutely improve hindlimb function during walking and swimming in a rodent model of severe but incomplete SCI.[16] DBS in humans is considered safe, reversible and minimally-invasive, and is being routinely and successfully applied in the treatment of various movement disorders.[31–36]

Function and anatomy of the brainstem motor systems are highly conserved across mammalian species.[37] Due to their dispersed projection pattern throughout the spinal cord

white matter,[38,39] reticulospinal fibres are likely to be partially spared after incomplete SCI in humans,[40] and are crucial for functional recovery after SCI.[41,42]

Encouraging results from animal studies [16,30,43] have led to the initiation of a first in-man study that investigates MLR-DBS enabled intensive rehabilitative training and its potential to enhance locomotion in non-ambulatory, subchronic and chronic SCI patients. The study protocol is presented in this article.

We hypothesize that MLR-DBS can modulate the activity of spared reticulospinal fibres that bypass the site of injury and reintegrate quiescent sublesional circuits into a functional network that supports walking (Figure 2). We propose that enhancing excitability of sublesional spinal motor circuits increases training efficacy and promotes recovery of motor function in patients with incomplete, subchronic and chronic SCI.

METHODS AND ANALYSIS

Study design

This prospective one-armed phase I/II multi-centre study is being conducted as cooperation of the University of Zurich, the University Hospital Zurich and the Balgrist University Hospital Zurich. Patients are screened and selected by SCI specialists and physiotherapists at the Balgrist University Hospital. Incomplete SCI is confirmed based on clinical examinations, magnetic resonance imaging (MRI), and electrophysiological measurements. After patient inclusion and baseline examinations, a DBS lead is stereotactically unilaterally implanted into the cuneiform part of the MLR, followed by infraclavicular or abdominal implantation of an impulse generator (IPG, Figure 3). The side of lead placement is chosen based on the functional and anatomical lesion extent, with preference for the less severely affected side to transmit as much descending brainstem motor signal as possible beyond the lesion via the primarily uncrossed reticulospinal fibres. The patients are followed-up on a regular basis until 6 months post-implantation, and the acquired data of each timepoint are compared with baseline findings. The primary outcome measure for improvement of ambulation in this study is the difference in covered distance in the 6 Minute Walking Test (6MWT) at 6 months post-implantation compared to baseline level. The trial is considered successful if the patient's performance in the 6MWT 6 months after treatment start is at least 30% [44] higher compared to performance at baseline. For the design of the clinical trial protocol we followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.[45]

Study population

Female and male patients (18-75 years) with completed in-patient rehabilitation and at least 6 months of recovery after SCI are screened and considered for study enrolment. We aim at including 5 patients, who have to complete all preoperative and postoperative examinations until 6 months after electrode implantation, resulting in a total of 11 timepoints. In case of withdrawal of participation, dropouts and incomplete follow-up, we will include a maximum of 2 additional patients (replacement of dropouts/withdrawal). The study is open to national and international patients. Basic understanding of German or English is required. Patients who prematurely withdraw from the study will be offered complete removal of all implanted material, and will be followed-up according to clinical standards. The patients' study related data will remain in the study.

Inclusion and exclusion criteria

To be eligible for the study, a participant must fulfil all inclusion criteria and none of the exclusion criteria (Table 1).

Table 1 – Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Informed consent	Enrolment of the investigator, her/his family members, employees and other dependent persons
Participation in two assessment sessions before enrolment (screening and baseline)	Limitation of standing and walking function based on accompanying (CNS) disorders
Willingness and ability to comply with the protocol and to attend required study training and visits	Cardiovascular disorders restricting physical training or peripheral nerve disorders
Female or male subject	Implanted technical devices (pacemaker, defibrillator, others)
Age 18-75	History of significant autonomic dysreflexia
Motor incomplete SCI	Cognitive disorders/brain damage
Level of lesion at or above T10, based on AIS level, preservation of sacral function	Drug refractory epilepsy
Focal spinal cord disorder caused by either trauma or non-traumatic and non-progressive condition (like haemorrhage, benign tumour)	Severe joint contractures disabling or restricting lower limb movements
Minimum 6 months of recovery after SCI	Haematological disorders with increased risk of bleeding during surgical interventions
Completed in-patient rehabilitation program	Participation in another study with investigational drug within 30 days preceding and during the present study
WISCI II, level >2 (0-20 items): assistance of one or more persons. Ability to walk at least 10 meters	Congenital or acquired lower limb abnormalities (affection of joints and bone)
Stable medical and physical condition	Women who are pregnant or breast feeding or planning a pregnancy during the course of the study
Adequate care-giver support and access to appropriate medical care in patient's home community	Lack of safe contraception
	Inability of the participant to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc.
	Known or suspected non-compliance, drug or alcohol abuse
	Current or prior malignancy

CNS = central nervous system. SCI = spinal cord injury. AIS = ASIA (American Spinal Injury Association) Impairment Scale. WISCI = Walking Index for Spinal Cord Injury. PI = principal investigator.

Target area definition

While the rodent CNF and its microstructure are nowadays well characterized,[23,28,29] the human CNF is poorly described, and presented only in a very limited number of stereotactic atlases. However, due to the high phylogenetic conservation,[37] the CNF can be defined by surrounding landmarks and coordinates available from lead implantation into the PPN and rodent stereotactic atlases (Figure 4).

Surgery

All individuals included in the study undergo unilateral frame-based (Riechert-Mundinger frame; Inomed, Emmendingen, Germany) stereotactic implantation of an intracranial lead (model 3389-28; Medtronic, Minneapolis, MN, USA) via a unilateral burrhole under local anaesthesia. The distal end of the DBS lead features narrow (0.5 mm) spacing between each of the four stimulation contacts of 1.5 mm length each. After mounting of the stereotactic frame, high resolution cranial computed tomography (CT) scans are performed and fused with the individual's MRI scan to retrieve stereotactic coordinates based on the pre-planned trajectory. Depending on the patient's preferences and the surgeon's decision, patients either receive a full implant consisting of a DBS lead, an extension and an IPG within one surgical session, or receive a lead only, which is externalized for maximal 10 days for evaluation of side effects and responsiveness to stimulation. In the latter scenario, the patient undergoes a second surgery with either removal of the lead (dropout of the study participant) or completion of the DBS system. For completion, the lead is connected to a Medtronic Activa SC model 37603 IPG using a Medtronic model 37086-60 or 37086-95 extension cable. The IPG is implanted subcutaneously in the pectoral or abdominal region, respectively, depending on the patient's physiognomy and preference.

Intraoperatively, mapping of the CNF, behavioural and neurophysiological testing is performed, and different stimulation parameters (frequency, pulse width, stimulation intensity and voltages) are tested. Microelectrodes can be precisely inserted along a predefined trajectory aiming towards the CNF with the Neuro Omega neuromodulation system and manual drive (Alpha Omega Engineering, Nazareth, Israel) attached to the Riechert-Mundinger frame. During electrode insertion (0.5 mm steps), microelectrode recordings (30 s at each position) of single and multi-unit activity (local field potentials, LFPs) are performed during resting state, imagination of walking, passive and active lower limb movement within 10 mm prior and maximum 5 mm after the projected target point. Signals are band pass filtered (1-500 Hz). In case of a presumed elevated risk of haemorrhage, the surgeon can decide to exclusively use macroelectrodes instead of microelectrodes. In parallel, constant-frequency stimulation is performed while the patient performs a selection of motor tasks with the lower limbs hanging off the surgery table, accompanied by simultaneous electromyographic (EMG) recordings. Stimulation amplitude is slowly increased, and changes in range of motion with and without stimulation are measured by goniometers attached to knee and ankle while the patient

performs rhythmic knee and ankle flexion/extension movements. Furthermore, speech and cognition are tested with and without stimulation, and the appearance of side effects, in particular pain sensations and paraesthesia, is closely monitored and documented. Additional electrophysiological measurements, including motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs), are performed, and event related potentials (ERPs) are analysed. Ultimately, the coordinates resulting in best motor performance (e.g. greatest range of motion of knee joint, highest frequency of rhythmic knee flexions/extensions) at the lowest stimulation parameters without provoking side effects are chosen, and the quadripolar DBS lead is implanted, fixed to the skull, and either temporarily externalized or connected to an extension and IPG. All subjects subsequently receive a postoperative cranial CT scan to verify correct lead position and exclude surgery-associated complications (e.g. haemorrhages). Each patient recovers from surgery in the intermediate care unit overnight.

Clinical assessments

6 Minute Walking Test (6MWT)

During the 6MWT,[44] the patient is asked to cover a maximal distance within 6 minutes on even ground without any obstacles. The patient is accompanied by an experienced investigator (i.e. physiotherapist) to prevent falling, and may rest at his own discretion and use a walking aid (consistent across all timepoints). The distance covered (m), time and number of rests (min, count) is documented. Each assessment is video recorded.

10 Meter Walking Test (10MWT)

The 10MWT [46] is a widely used assessment tool to measure maximal walking speed (m/s). The patient is instructed to walk 10 m as quickly as possible, but safely, and is given 5 m for acceleration and deceleration. Patients may use assistive devices (consistent across all timepoints).

Timed-Up and Go Test (TUG)

The TUG is a basic evaluation tool of functional mobility. It measures the time (s) needed to rise from a chair, walk 3 m, turn around and return to a seated position. Participants are asked to perform the TUG at their self-selected normal speed, using their walking aid if required. The timer is started on the command “ready–set–go” and stopped as the patient returns to a seated position.

Kinematic assessment

Kinematic assessments are performed during over-ground and treadmill walking. Individuals are secured using the FLOAT (“Free Levitation for Overground Active Training”),[47,48] a multidirectional overhead support system that allows patients to move in a large workspace

that is equipped with a 3D motion capture system with infrared cameras (Vicon Motion Systems Ltd., Oxford, UK). The cameras are able to detect the position of reflective markers placed on patients' anatomical landmarks, allowing the quantification of kinematic movement characteristics.[49,50] Additionally, muscle activity is measured with an EMG setup (myon AG, Schwarzenberg, Switzerland). These measures allow the quantification of patients' walking function with high precision and the comparison of gait patterns within (with and without DBS) and between different sessions. In addition to walking assessments, maximal knee and ankle range of motion is evaluated with and without stimulation with the motion capture system during rhythmic flexion/extension tasks performed by the patient in supine or sitting position. Besides quantitative assessment of locomotor function, the FLOAT allows patients to train diverse activities such as level walking, running, stair manoeuvres, chair interactions or walking on uneven terrain with and without stimulation at the limit of their abilities with tailored body weight support.

Long-term Monitoring of Physical Activity

For constant monitoring of physical activity during training and daily life, wearable, wireless sensors (http://zurichmove.com/) are mounted to the patient's wrists, ankles, and wheelchair. Data are transferred via SSL-encrypted links (https) established between sites (e.g. a patient's home or rehab centre) and the Swiss Federal Institute of Technology Zurich (ETH).

ASIA Impairment Scale (AIS)

The American Spinal Injury Association (ASIA) International Standards for Neurological Classification of SCI (ISNCSCI) [51] is an internationally used gold standard method of assessing the neurological status of an individual with SCI. The AIS is carried out by trained medical staff using the ISNCSCI worksheet (https://asia-spinalinjury.org/international-standards-neurological-classification-sci-isncsci-worksheet/).

Modified Ashworth Scale (MAS)

The MAS [52] is a clinical scale used to assess muscle spasticity in patients with lesions of the central nervous system.

Spinal Cord Independence Measure (SCIM III)

The SCIM is a reference tool for the assessment of overall functional ability after SCI. The last version (III) of SCIM contains 19 tasks organized into 3 subscales: Self-care, Respiration & sphincter management, and Mobility.[53] The combined scores on all 19 tasks result in an overall score ranging from 0 to 100, with higher scores reflecting greater functional ability.

Walking Index for Spinal Cord Injury (WISCI II)

The WISCI assesses walking function on an ordinal scale,[54] and captures the extent and nature of assistance a person with SCI requires to walk. Rating is performed according to Ditunno et al.[54]

Assessment of lower urinary tract (LUT) function

To address the burden of neurogenic LUT dysfunction on patient's quality of life after SCI and to analyse the effect of MLR-DBS on recovery of LUT function, a combination of qualitative (bladder diary, QUALIVEEN questionnaire) and quantitative assessments (urodynamic measurements, renal ultrasound) of LUT function are applied in accordance to the European Association of Urology (EAU) Guidelines on Neuro-Urology.[55,56]

- Bladder diary: by completing the Three Day Bladder Chart [57] information on daytime frequency, nighttime frequency, voiding (e.g. spontaneous), catheter use (transurethral, suprapubic, self-catheterization), voided volume, post void residual volume, incontinence episodes, pad use, fluid intake and amount of urine per 24 hours, and pain (visual analogue scale 0-10) is acquired.
- QUALIVEEN questionnaire: all patients fill in the QUALIVEEN questionnaire for self-judgement of LUT dysfunction according to Costa et al.[58]. Scores (0-4) are recorded for "Limitations", "Constraints", "Fears" and "Feelings", and the calculated arithmetic mean is transformed into values of 0-100.
- Urodynamic assessments: Cystometry, uroflowmetry, pressure-flow studies, electromyography and video-urodynamics provide objective information on functioning of the LUT and pelvic floor. Parameters retrieved are: cystometric capacity (mL), compliance (mL/cmH2O), detrusor overactivity (y/n), bladder volume at detrusor overactivity (mL), maximum detrusor pressure amplitude (cmH2O) during storage phase, urinary incontinence, maximum detrusor pressure (cmH2O) during voiding phase, detrusor pressure at maximum flow rate (cmH2O), maximum flow rate (mL/s), voided volume (mL), post-void residual (y/n and mL), pelvic floor electromyographic activity (normal/abnormal), vesico-uretero-renal reflux (y/n).
- Renal and bladder ultrasound: indirect assessment of LUT function, e.g. via post-void residual volume, detrusor thickness or distension of the renal pelvis or ureter.

Assessment of sexual function

The Female Sexual Function Index (FSFI) [59,60] is gold standard for the evaluation of female sexual function in clinical trials. It is questionnaire-based and contains 19-items including sexual arousal, orgasm, satisfaction and pain (score 2-80). The International Index of Erectile Function (IIEF) [61] is a standardized 15-item self-evaluation scale for male patients assessing erectile function, orgasmic function, sexual desire, satisfaction in sexual intercourse and in general.

Epworth Sleepiness Scale (ESS)

The ESS [62] measures a patient's general level of daytime sleepiness. The patient rates the probability of falling asleep on a scale of increasing probability (0-3) for eight different situations.

Fatigue Severity Scale (FSS)

The FSS [63] evaluates the impact of fatigue based on a short questionnaire containing nine statements rating the severity of fatigue symptoms.

Pain assessment

The EMSCI (European Multicenter Study About Spinal Cord Injury) pain assessment form (EPAF) [64,65] and the Spinal Cord Injury Pain Instrument (SCIPI) [66–68] are standardized and validated tools to evaluate pain in individuals with SCI.

Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP)

The GRASSP [69,70] is a standardized upper-limb impairment measure specifically used to assess recovery of upper limb function (strength, sensation, prehension) in individuals with complete or incomplete tetraplegia.

Short Form Health Survey to Assess Quality of Life (SF-36)

Patients with SCI experience tremendous changes in several aspects of everyday life and thus quality of life (QoL) [71] assessments are crucial in clinical trials. We employ the SF-36 [72], a multi-purpose, short-form health survey comprised of 36 questions that compares the relative burden of diseases and differentiates the health benefits produced by a wide range of different treatments. It yields an 8-scale profile of functional health and well-being scores, psychometrically based physical and mental health summary measures, and a preference-based health utility index. QoL is expressed as a score ranging from 0 to 100.

Electrophysiological assessments

Electrophysiological assessments are performed in addition to clinical examinations as they allow prediction of functional outcome and help objectify the extent of the spinal lesion, its stability and potentially recovery of specific functions after SCI.[73,74]

Short-latency somatosensory evoked potentials (SSEPs)

SSEPs are performed to evaluate transmission of ascending signals within the dorsal column of the spinal cord and thus sensory function. The patient is in supine position, and stimulating electrodes are placed on the posterior tibial nerve (below the internal malleolus). Four subcutaneous recording electrodes are placed as follows: at L2 and L5, on the scalp (reference Fz and active Cz', 2 cm behind Cz), and a ground around the ankle. Cortical recording electrodes are positioned in accordance with the International 10–20 system.[75] Stimulation parameters are 200 μs, up to 100 mA at a frequency of 3.1 Hz. The signal is recorded between 30 and 300 Hz with 50 Hz notch filter. Waveforms are measured after 200-800 averages. Dorsal horn negativity (N24) is measured on the lumbar derivation (L5-L2) and represents peripheral conduction time. The post-Rolandic positivity (P45) is measured on the scalp derivation and represents the total conduction time. All measures are recorded before and after interventions. Response latency (ms) and amplitude (μV) are compared between timepoints and conditions (stim/no stim).

DBS evoked potentials (DBS-EPs)

DBS-EP testing is performed similar to SSEP measurements. However, instead of stimulating a peripheral nerve, the evoked cortical response is generated by repetitive low frequency stimulation of the target region (CNF/MLR). Outcome measures are response latency (ms) and amplitude (μV).

Motor evoked potentials (MEPs)

MEPs are tested to evaluate the ability of MLR-DBS enhanced training to induce remodelling of spinal pathways leading to amplification of descending signals. Surface recording electrodes are positioned on the tibialis anterior and the gastrocnemius medialis muscles. Transcranial magnetic stimulation (TMS) is applied on the scalp close to Cz and on the lumbar spine in front of L5. After a test stimulus, the stimulation is increased stepwise up to 100% of the stimulator output and the response is recorded under 5-10% voluntary muscle activation. Total conduction time is measured after scalp stimulation and peripheral conduction time after lumbar stimulation. All measures are recorded before and after interventions. Response latency (ms) and amplitude (μV) are compared between timepoints and conditions.

Local field potentials (LFPs)

LFPs are measured intraoperatively during probe insertion and postoperatively in case of temporary externalization of the lead. Intraoperative LFPs are measured in the target region, starting 10 mm above the target and ending 5 mm below the target. Postoperative measurements are performed at the 4 contacts of the implanted lead. Signals are band pass filtered (1-500 Hz).

Electroencephalogram (EEG)

To reconstruct patterns of specific neuronal activity and their change upon MLR-DBS, non-invasive EEG recordings are performed in the perioperative period and at the last assessment timepoint.

DBS during behavioural testing and rehabilitative training

In the first two weeks after lead implantation, different stimulation parameters (frequency, Hz; pulse width, µs; amplitudes, mV) are tested during rest and locomotor training in order to identify optimal stimulator settings including safety limits for each patient individually. Subsequently, four combinations of parameters eliciting the best motor responses without side effects are chosen and programmed to the patient programming device (programs A-D). Afterwards, the patient undergoes intensive, rehabilitative training with his favourite program (e.g. 20 Hz, 420 µs, suprathreshold intensity). Behavioural testing is performed with and without stimulation during each follow-up visit using the stimulation parameters applied during training.

Study endpoints

The primary endpoint of the DBS-SCI study is improvement of locomotor function, represented by an increased distance covered during the 6MWT when comparing performance at the 6 months timepoint with and without DBS with performance at baseline. Additionally, a variety of secondary endpoint assessments are performed (Table 2). Table 3 summarizes timing and schedule of the respective primary and secondary endpoint assessments.

Table 2 – Primary and secondary endpoint measures.

Primary endpoint measure	Secondary endpoint measures
6 Minute Walking Test (6MWT) at 6 months follow-up vs. baseline	6 MWT at follow-up timepoints other than 6 months post-implantation
	10 Meter Walking Test (10MWT)
	Timed Up and Go Test (TUG)
	Kinematic assessments (FLOAT)
	Spinal Cord Independence Measure (SCIM III)
	Walking Index for Spinal Cord Injury (WISCI II)
	Activity counts (patient's overall activity level)
	Electrophysiological measurements*
	Quality of life (SF-36)
	Lower urinary tract (LUT) function**
	Sexual function (FSFI/IIEF)
	Spasticity (MAS)
	Neurological classification of SCI (AIS)
	Upper limb function (GRASSP)
	Level of fatigue (FSS)
	Level of sleepiness (ESS)
	Pain (EPAF, SCIPI)

FLOAT = Free Levitation for Overground Active Training. MLR = mesencephalic locomotor region. *Local field potentials (LFPs); somatosensory evoked potentials (SSEPs); motor evoked potentials (MEPs); DBS evoked potentials (DBS-EPs); electroencephalogram (EEG). SF-36 = Short Form Health Survey to Assess Quality of Life. **bladder diary, QUALIVEEN questionnaire, urodynamic measurements, bladder and renal ultrasound. FSFI = Female Sexual Function Index. IIEF = International Index of Erectile Function. MAS = Modified Ashworth Scale. AIS = American Spinal Injury Association (ASIA) Impairment Scale. GRASSP = Graded Redefined Assessment of Strength, Sensation and Prehension. FSS = Fatigue Severity Scale. ESS = Epworth Sleepiness Scale. EPAF = EMSCI (European Multicenter Study About Spinal Cord Injury) Pain Assessment Form. SCIPI = Spinal Cord Injury Pain Instrument.

Table 3 – Flowchart summarising scheduling and timing of primary and secondary endpoint assessments.

Site	Study periods	Screening	Baseline	DBS surgery	Post-implantation phase			IPG implantation	Rehabilitation / Follow-up phase					
Visit		1	2	3	4	5	6*	7*	8	Dis-charge	Site	9	10	11
Day (d) / month (mo)		-90 to -30 d	-10 to -1 d	0	1 to 3 d	4 to 7 d	8 to 9 d	6 to 10 d	14 d +/-3 d			mo 1 +/-3 d	mo 3 +/-1 week	mo 6
University Hospital Zurich/ Balgrist University Hospital	**Study inclusion and consent**										Balgrist University Hospital			
	Consenting	X												
	Enrolment	X												
	Patient inclusion by PI		X											
	Imaging													
	X-ray thorax	X							X					
	X-ray skull, abdomen								X					
	Stereotactic cranial CT			2 X										
	Diagnostic MRI (3T)	X												
	Perisurgical examinations													
	Surgical examination (incl. wound check)	X		X	X	X	X	X				X	X	X
	Anaesthesiologic examination		X	X			X	X						
	Neuropsychological assessment	X												X
	Psychiatric assessment	X												X
	Surgical procedures													
	DBS lead implantation			X										
	Implantation of IPG or explantation of DBS lead			X (externalization may be skipped and IPG implanted at visit 3)										
	Education in handling of patient programming device								X					
	Electrophysiological assessments													
	EMG	X		X								X	X	X
	Microelectrode recording			X										
	Nerve conduction	X												X
	Non-invasive EEG	X		X	X	X								X
	MEP, SSEP	X		X	X	X								X
	LFP, DBS-EP			X	X	X								
Balgrist University Hospital	**Clinical assessments**													
	AIS	X	X			X			X			X	X	X
	WISCI II	X	X			X			X			X	X	X
	SCIM III	X	X			X			X			X	X	X
	TUG	X	X			X			X			X	X	X
	Kinematic assessments	X	X			X			X			X	X	X
	6MWT	X	X			X			X			X	X	X**
	10MWT	X	X			X			X			X	X	X
	AE assessment		X	X	X	X	X	X	X			X	X	X
	Questionnaires: QoL, FSFI, IIEF, ESS, FSS, EPAF, SCIPI	X										X	X	X
	Questionnaire: MAS	X	X			X						X	X	X
	LUT assessments (Bladder diary, QUALIVEEN, urodynamics, bladder/renal ultrasound)	X												X
	GRASSP	X												X

*If impulse generator (IPG) is implanted at visit 3, visit 6 and visit 7 will be skipped. **Primary endpoint. DBS = deep brain stimulation. IPG = impulse generator. CT = computed tomography. MRI = magnetic resonance imaging. 3T = 3 Tesla. EMG = electromyography. EEG = electroencephalography. LFP = local field potentials. MEP = motor evoked potentials. SSEP = somatosensory evoked potentials. DBS-EP = DBS-evoked potentials. QoL = quality of life. FSFI = Female Sexual Function Index. IIEF = International Index of Erectile Function. ESS = Epworth Sleepiness Scale. FSS = Fatigue Severity Scale. AE = adverse event. AIS = American Spinal Injury Association (ASIA) Impairment Scale. WISCI II = Walking Index of Spinal Cord Injury. SCIM III = Spinal Cord Independence Measure. TUG = Timed Up and Go test. 6MWT = 6 Minute Walking Test. 10MWT = 10 Meter Walking Test. EPAF = EMSCI (European Multicenter Study About Spinal Cord Injury) Pain Assessment Form. SCIPI = Spinal Cord Injury Pain Instrument. MAS = Modified Ashworth Scale. LUT = lower urinary tract function. GRASSP = Graded Redefined Assessment of Strength, Sensation and Prehension.

Sample size

Based on data on the 6MWT [44,76,77] published in the literature and our clinical experience we estimate a relative effect size of 30% improvement in the 6MWT 6 months after treatment start compared to performance at baseline to be clinically relevant. A sample size of five patients provides us with a power (1-β) of 80% (α = 0.05). Founded on previous experience in DBS of the MLR,[78,79] we judge that the selected sample size will provide acceptable clinical validity for the study objectives.

Statistical analysis

Considering the observational nature of this clinical trial, statistics will be restricted to descriptive statistics.

Trial status

The study has started recruiting patients in March 2017. To date, one patient has been successfully included on November 26, 2018. Another patient has been included on March 15, 2018, but withdrew consent prior to surgery (screening failure).

Patient and public involvement

Patients or the public were not and will not be involved in the design, conduct, reporting, or dissemination plans of this research.

ETHICS AND DISSEMINATION

The study was approved by the local institutional review board (IRB) of the Ethical Committee of the Canton of Zurich (case number BASEC 2016-01104) and Swissmedic (10000316) in January and March 2017. Protocol modifications have to be approved by the local IRB and communicated to trial registries. Before inclusion of a patient, the potential participant is

informed orally by the investigator, and all potential participants are additionally provided with a clear and comprehensive information sheet. Sufficient time is given to the potential participant to decide whether to participate or not. If potential participants agree to participate in the study, they are asked to sign a consent form at the moment of inclusion in the study. The data obtained in the course of the study is treated according to the local data protection law and is handled in strictest confidence. During the study, subjects are identified solely by an anonymized patient identifier. The findings of this trial will be submitted to a peer-reviewed journal and abstracts are presented at relevant national and international scientific conferences. The study was registered on ClinicalTrials.gov (NCT03053791) on February 15, 2017.

DISCUSSION

Encouraging results on behavioural effects of MLR-DBS in preclinical models of neurotrauma [16,30] have contributed to the initiation of this first in-man study, which is currently being carried out at the University Hospitals of Zurich. The primary aim of this study is to improve motor function and enable locomotion in wheelchair-bound, subchronic and chronic SCI patients with limited, non-functional ambulatory abilities with MLR-DBS, and to investigate the clinical feasibility and efficacy of MLR-DBS in humans. Ultimately, we aim at maximizing the long-term restitution of lost motor functions in patients with severe motor incomplete SCI. A first patient has been included and implanted successfully, followed by intensive locomotor training with suprathreshold MLR-DBS.

The most important lesson learnt from our previous experience in the treatment of this patient is that MLR-DBS is safe, feasible and well tolerated. No increase in pain, deterioration of residual motor or sensory functions, cognitive or emotional disturbances, increase in spasticity and no incontinence was observed. However, sufficient time has to be allocated to the adjustment of stimulation parameters for efficient training to ensue. Optimal stimulation parameters will have to be determined for each patient individually, however, wider pulses (>400 µs) seem to be more effective for enhancement of locomotion and more convenient than shorter pulse widths. LFP measurements and preliminary results from behavioural testing suggest that lower stimulation frequencies (8-20 Hz) are appropriate.

A particular challenge remains trajectory planning and lead implantation. Many regions of the brainstem, including the MLR subnuclei, are small and poorly described in humans when compared to the rodent PPN and CNF.[23,28,29] Coordinates known from DBS of the PPN with successful reduction of freezing of gait symptoms in patients with Parkinson's disease [24–27] can be adapted based on landmarks in human and rodent stereotactic atlases in order to localize the CNF in relation to the PPN. However, to increase the accuracy of planned trajectories and intraoperative targeting, a more detailed description of the macro- and microanatomy of the human MLR is urgently needed.

Another important step in trial design and treatment development is patient selection. In both rodents [16,42,80] and humans,[41] the reticulospinal system is crucial for functional recovery after SCI, and at least a small number of reticulospinal fibres needs to be preserved in order to reactivate lumbar CPGs via MLR-DBS. Thus, patients who have suffered an anatomically complete SCI are not envisioned eligible for MLR-DBS. Fortunately, the majority of SCIs are anatomically incomplete,[4] and reticulospinal fibres are likely to be at least partially spared after SCI in humans [40] due to their scattered projection pattern in the spinal cord white matter.[38,39] Based on preclinical data and experience gained from the first study participant we suggest that patients with an incomplete SCI and residual proprioceptive function, who are able to stand, but suffer from deficient stepping initiation and walking function are most likely

to benefit from MLR-DBS-enabled and -enhanced training. To allow for an integration of the effects of MLR-DBS into the still plastic spinal system during early phases of rehabilitative training, we are currently adapting the original study protocol so that patients can be included as early as 3 months after injury. Stratification of patients will be based on the expected outcome of walking function predicted by the 6MWT. Patient recruitment and screening are currently ongoing.

Our preliminary results from one study patient show that MLR-DBS is feasible and safe. The efficacy of MLR-DBS to enhance training and promote functional recovery in human SCI patients can now be tested in an appropriate number of individuals.

Acknowledgments

We thank our patient for her courage and enthusiasm to participate in this study, and Medtronic, Minneapolis, MN, USA, who provide the implants required. We also thank all collaborators involved in the study who have agreed to provide treatment and assessments as in-kind contribution of the Departments of Neurosurgery, Neurology, Neuroradiology, Anaesthesiology and Psychiatry of the University Hospital Zurich, the Spinal Cord Injury Center of the Balgrist University Hospital, the Institute for Regenerative Medicine of the University of Zurich, and the Swiss Federal Institute of Technology Zurich. The study has been presented at the "European Society for Stereotactic and Functional Neurosurgery (ESSFN) Meeting" 2018 in Edinburgh, Scotland, and the "EANS Trauma & Critical Care Update meeting" 2018 in Lund, Sweden.

Authors' contributions

LHS and ASH contributed equally to the manuscript and are joint first authors. MES, LR, and ACu are joint senior authors. LHS, ASH, MB, CRB, LI, LR, MES, and ACu designed the study, created and refined the study protocol, and supervise the study. LHS, MFO, ASH, and LR perform surgeries. MB, LF, RW, ACa, CM, and ACu designed assessments of motor function and perform testing and analysis. MS, MH, CRB, and LI designed and conduct electrophysiological measurements. TMK conceptualized and performs assessments of lower urinary tract function. IK and AP assist with study coordination and conduct questionnaire-based assessments. All authors are involved in the development and implementation of the study as well as in data collection and analysis. ASH and LHS designed the figures and drafted the manuscript. All authors critically revised the manuscript and approved its final version.

Funding

Implanted hardware (electrodes, impulse generators, extension wires, and patient programming devices) including replacements for a period of 10 years after implantation in case of e.g. battery depletion is provided by Medtronic, Minneapolis, MN, USA, for five patients free of charge. Beyond that, we do not receive any financial support by Medtronic. The study is financed by the Department of Neurosurgery, University Hospital Zurich, the Spinal Cord Injury Center, Balgrist University Hospital, and the Department of Neurology, University Hospital Zurich. No specific research grant has been declared for this study. The funding sources had no influence on the design of this study and the writing of this manuscript, and will not have any influence on study execution, data analysis, data interpretation, or decision to publish results.

Competing interests

The authors declare that they have no competing interests.

Patient consent for publication

Written informed consent for publication of clinical details and/or clinical images was obtained from the patient. A copy of the consent form is available for review by the editor of this journal.

Ethics approval

Ethical approval has been obtained from the Ethical Committee of the Canton of Zurich (case number BASEC 2016-01104) and Swissmedic (10000316). Protocol modifications have to be approved by the local Ethical Committee of the Canton of Zurich and communicated to trial registries.

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FIGURE LEGENDS

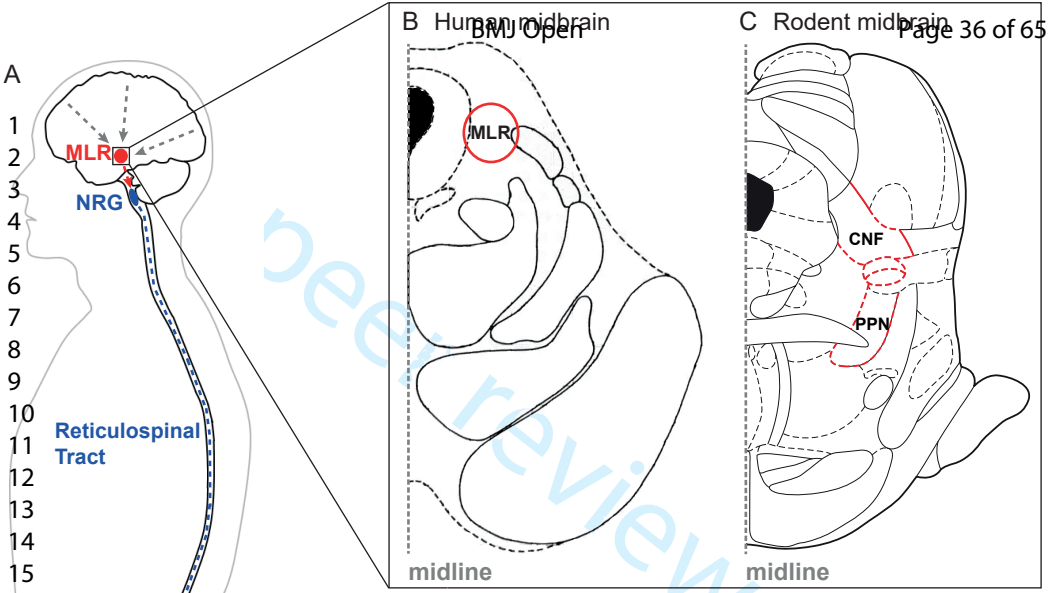
Figure 1 - Schematic illustration of the reticulospinal system. (A) Higher central nervous system centres of motion control send their signals to the mesencephalic locomotor region (MLR). The MLR is bilaterally linked to its downstream target, the gigantocellular reticular nucleus (NRG), which gives rise to the reticulospinal tract and drives the central pattern generators (CPG) for motoneuron activation and locomotion. (B-C) Horizontal section of the human (B) and cross section of the rat (C) midbrain at the level of the superior colliculi depicting the MLR (B – landmarks based on Afshar et al.[81]; C – landmarks based on Paxinos et al.[82]). CNF = cuneiform nucleus. PPN = pedunculopontine nucleus.

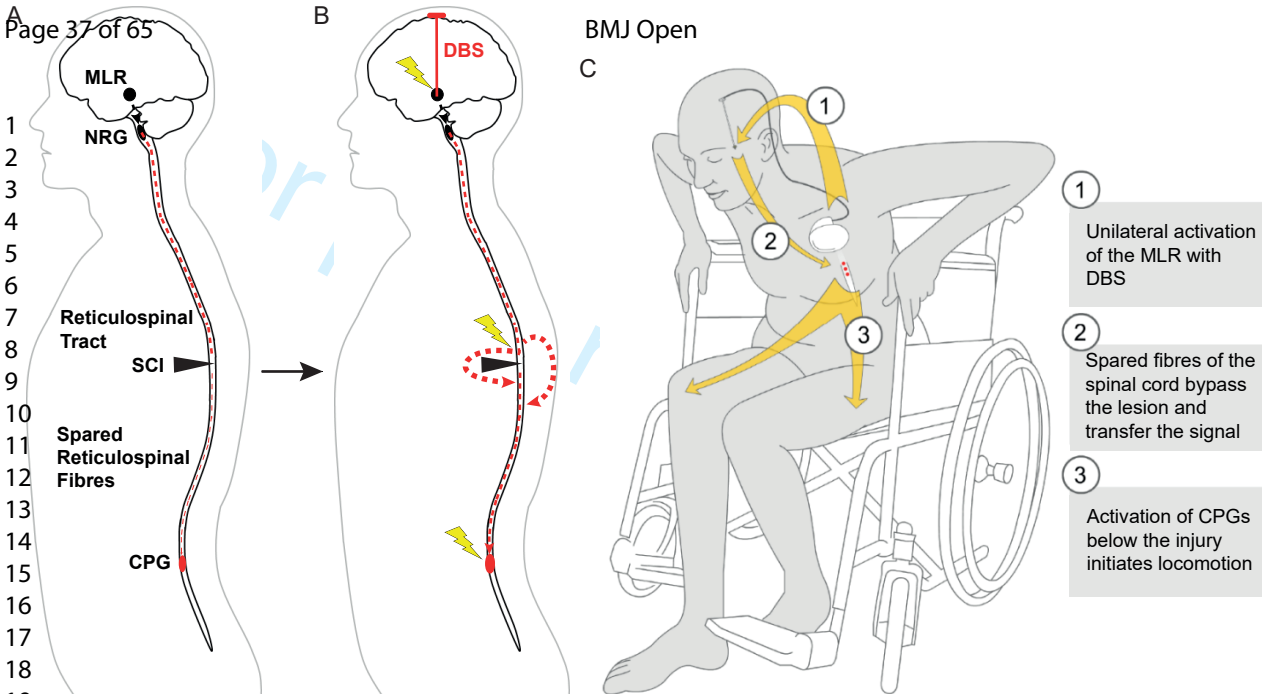
Figure 2 - Schematic illustration of MLR-DBS. (A) After incomplete SCI, spared fibres of the reticulospinal tract are not sufficient to properly convey motor signals to sublesional locomotor circuits (CPG). The CPGs are thus deprived of their central input. However, these local rhythm generators remain intact. (B) MLR-DBS can recruit spared fibres of the reticulospinal tract system, enabling them to reactivate sublesional motor circuits. (C) Summary. MLR = mesencephalic locomotor region. NRG = gigantocellular reticular nucleus. SCI = spinal cord injury. CPG = central pattern generators. DBS = deep brain stimulation. (A-B) was modified from Hofer and Schwab, Curr Opin Neurol, 2019 [3], with permission.

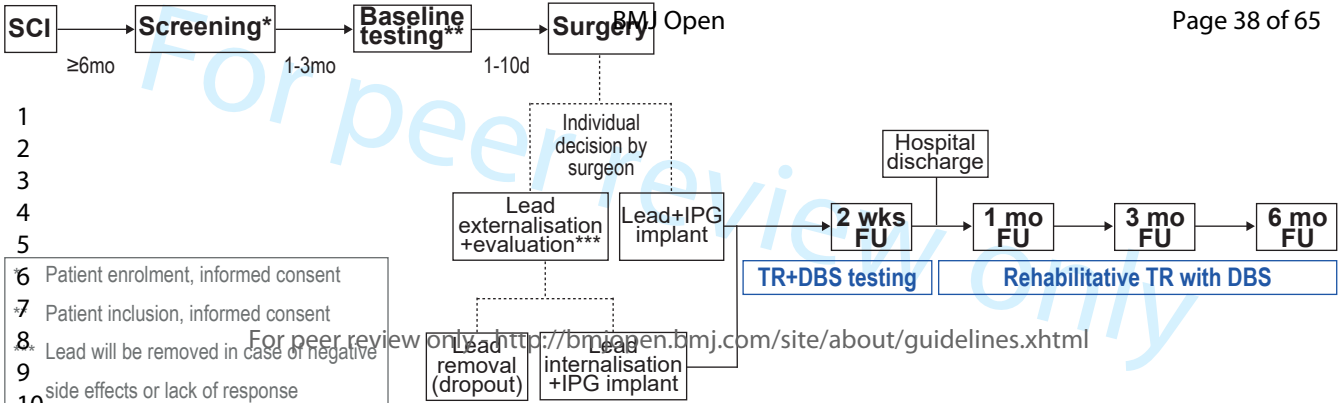
Figure 3 – Study timeline. Patients with a motor incomplete SCI at the level of T10 or above and at least 6 months of recovery after injury are eligible to undergo screening for study participation. Incomplete SCI is confirmed based on clinical examinations, magnetic resonance imaging, and electrophysiological measurements. 1-3 months after study enrolment, baseline testing is performed, followed by unilateral electrode implantation at the less severely affected side 1-10 days later. During surgery, the surgeon decides whether lead and impulse generator (IPG) will be implanted during one session, or whether the lead will be temporarily externalized, depending on intraoperative testing results. In case of lead externalisation, an evaluation period ensues where the patient's responsiveness to MLR-DBS and potential negative side effects are assessed. In case of unsatisfactory results or withdrawal of consent, the lead is removed, and the patient is registered as a study dropout. In case of satisfactory testing, the lead is internalized and the IPG is implanted. After complete implantation, follow-up testing ensues at 2 weeks, 1 month, 3 months and 6 months, respectively. Patients will be discharged from hospital after 2-3 weeks of training (TR) and testing. After hospital discharge, patients will undergo rehabilitative training with DBS at settings predefined during the first 2 weeks after implantation. SCI = spinal cord injury. mo = month(s). d = day(s). wks = weeks. FU = follow-up. TR = training. DBS = deep brain stimulation.

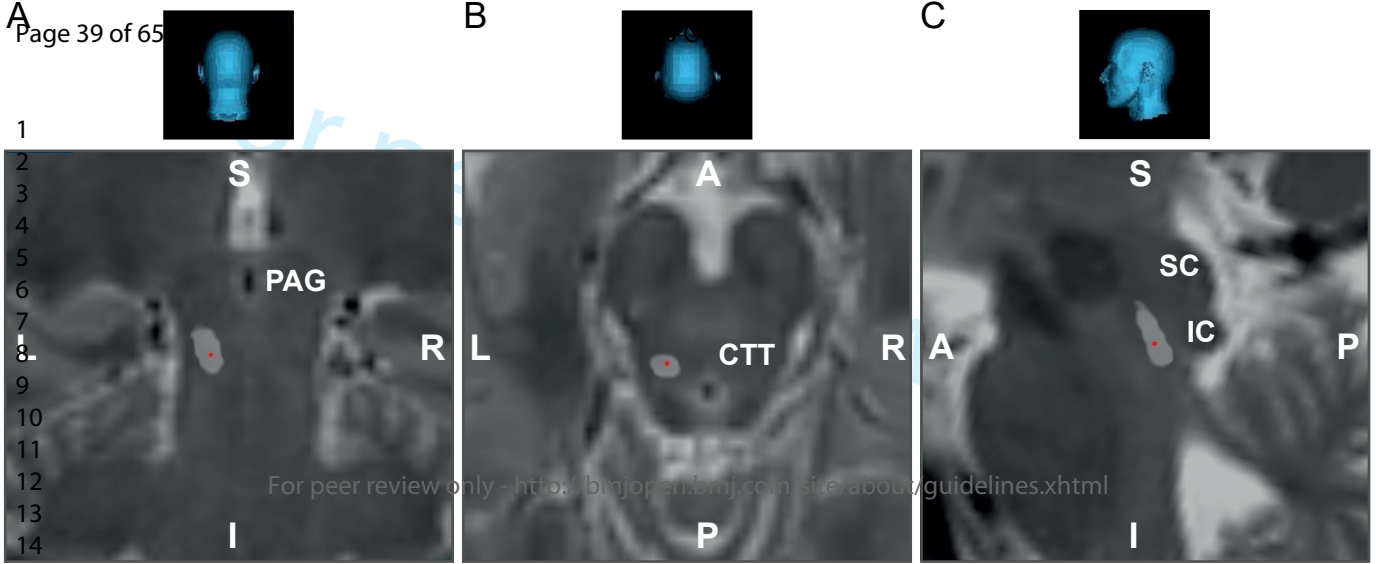
Figure 4 – Target area definition and electrode positioning. The MLR can be targeted by aiming anterior to the inferior colliculi (IC), lateral of the periaqueductal grey (PAG), and slightly posterior to the central tegmental tract (CTT).[81,83] (A) Coronal, (B) axial, and (C) sagittal view of the mesencephalon of the first patient successfully included in the DBS-SCI trial, showing the localization of the implanted lead (red dot in light grey area). S = superior. I = inferior. L = left. R = right. A = anterior. P = posterior.

3









SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym *A phase I/II open-label multicenter trial to evaluate safety and preliminary efficacy of unilateral deep brain stimulation of the mesencephalic locomotor region in patients with incomplete spinal cord injury (DBS-SCI).*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry *Registered on clinicaltrials.gov (NCT03053791, DBS-SCI).*
	2b	All items from the World Health Organization Trial Registration Data Set *See ClinicalTrials registry and full study protocol.*
Protocol version	3	Date and version identifier *Latest approved (Ethical Committee of the Canton of Zurich) study version: version 5, 12.09.2019.*

Funding	4	Sources and types of financial, material, and other support

Implanted hardware (electrodes, impulse generators, extension wires, and patient programming devices) including replacements for a period of 10 years after implantation in case of e.g. battery depletion is provided by Medtronic, Minneapolis, MN, USA, for five patients free of charge. Beyond that, we do not receive any financial support by Medtronic. The study is financed by the Department of Neurosurgery, University Hospital Zurich, the Spinal Cord Injury Center, Balgrist University Hospital, and the Department of Neurology, University Hospital Zurich. No specific research grant has been declared for this study. The funding sources had no influence on the design of this study and the writing of this manuscript, and will not have any influence on study execution, data analysis, data interpretation, or decision to publish results.

Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors

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LHS, ASH, MB, CRB, LI, LR, MES, and ACu designed the study, created and refined the study protocol, and supervise the study. LHS, MFO, ASH, and LR perform surgeries. MB, LF, RW, ACa, CM, and ACu designed assessments of motor function and perform testing and analysis. MS, MH, CRB, and LI designed and conduct electrophysiological measurements. TMK conceptualized and performs assessments of lower urinary tract function. IK and AP assist with study coordination and conduct questionnaire-based assessments. All authors are involved in the development and implementation of the study as well as in data collection and analysis.

5b Name and contact information for the trial sponsor

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5c Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities

The funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. The authors have no competing interests to declare.

5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

N/A

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

Briefly: A spinal cord injury (SCI) is a devastating event with an immediate impact on an individual's health and quality of life. Even though most spinal cord injuries are clinically incomplete, major neurological and functional recovery plateaus after three to four months after injury despite intensive rehabilitative training. To enhance training efficacy and improve long-term outcomes, the combination of rehabilitation with electrical modulation of CNS targets, e.g. electrical spinal cord stimulation or deep brain stimulation, has aroused scientific interest in recent years with some encouraging results. In deep brain stimulation (DBS) the mesencephalic locomotor region (MLR), an evolutionarily conserved brainstem locomotor command center that controls the initiation and maintenance of locomotion, is considered a promising target. Animal experiments have shown that MLR-DBS can acutely induce swimming and walking in rats with spinal white matter destructions of >85%. Promising pre-clinical data and the minimally-invasive nature of DBS have led to the initiation of this study to investigate the therapeutic potential of MLR-DBS to improve recovery of gait in a small cohort of patients.

	6b	Explanation for choice of comparators

The study comprises no comparators, performance will be compared between different timepoints. The presence of an SCI will be documented by neuroimaging and the risk of paraplegia resulting from other origins can be excluded. Therefore, a mere placebo-effect resulting in improvement of the ability to walk is extremely unlikely. A control group undergoing sham-surgeries is not necessary at this early stage of research on this topic.

Objectives	7	Specific objectives or hypotheses *We hypothesize that MLR-DBS can modulate spared fibers of the reticulospinal tract system that bypass the site of injury and reintegrate quiescent sublesional circuits into a functional network that supports walking. We propose that enhancing excitability of sublesional spinal motor circuits increases training efficacy and promotes recovery of motor function in patients with incomplete, subchronic and chronic SCI.*
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) *Briefly: The DBS-SCI trial is a prospective one-armed multi-centre study. The trial is considered successful if the patient's performance in the 6 minutes walking test (6MWT, primary outcome measure) 6 months after treatment start is at least 30% better compared to performance at baseline.*

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained *Briefly: The trial is conducted and data are collected at two sites in Zurich, Switzerland: the University Hospital Zurich (Departments of Neurosurgery and Neurology, both specialized in deep brain stimulation), and the Spinal Cord Injury Center of the Balgrist University Hospital (specialized in the management of acute and chronic SCI including neurorehabilitation). The study is open to national and international patients, however, basic understanding of German or English is required.*

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Addressed in "Inclusion and exclusion criteria" section of manuscript.

Inclusion criteria:

- *Informed consent*
- *Participation in two assessment sessions before enrolment*
- *Willingness and ability to comply with the protocol and to attend all required study training and visits*
- *Female or male*
- *Age 18-75*
- *Motor incomplete SCI*
- *Level of lesion at or above T10, based on AIS level, preservation of sacral function*
- *Focal spinal cord disorder caused by either trauma or non-traumatic and non-progressive condition*
- *Minimum 6 months of recovery after SCI*
- *Completed in-patient rehabilitation program*
- *WISCI II, level >2 (0-20 items): assistance of one or more persons. Ability to walk at least 10 meters*
- *Stable medical and physical condition*
- *Adequate care-giver support and access to appropriate medical care in patient's home community*

Exclusion criteria:

- *Enrolment of the investigator, her/his family members, employees and other dependent persons*
- *Limitation of standing and walking function based on accompanying (CNS) disorders*
- *Cardiovascular disorders*
- *Implanted technical devices*
- *Significant autonomic dysreflexia*
- *Cognitive disorders/brain damage*
- *Drug refractory epilepsy*
- *Severe joint contractures disabling or restricting lower limb movements*
- *Haematological disorders with increased risk of bleeding*
- *Participation in another study with investigational drug within 30 days preceding and during the present study*
- *Congenital or acquired lower limb abnormalities*
- *Women who are pregnant or breast feeding or planning a pregnancy during the course of the study*
- *Lack of safe contraception*
- *Inability to follow the procedures of the study*
- *Known or suspected non-compliance, drug or alcohol abuse*
- *Current or prior malignancy*

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

Interventions and assessments are described in detail in study protocol.

Briefly:

Intervention model: single group assignment (single group of patients with incomplete SCI), single armed study, all patients receive treatment.

Procedure:

- *Implantation of a deep brain stimulation system (electrodes into the mesencephalic locomotor region and Medtronic Activa SC impulse generator into pectoral or abdominal region).*
- *Deep brain stimulation of mesencephalic locomotor region during rehabilitative training with regular follow-ups until 6 months after implantation.*

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

Should a subject's participation in the investigation be discontinued, the reason for discontinuation, e.g. safety concerns, must be documented in the source documents. The Sponsor may terminate the study prematurely according to certain circumstances, for example: ethical concerns, insufficient participant recruitment, when the safety of the participants is doubtful or at risk, alterations in accepted clinical practice that make the continuation of a clinical trial unwise, or early evidence of benefit or harm of the experimental intervention. Participants may withdraw from participation at any time without need to give reasons. If the patient wishes so, the implanted DBS system will be surgically removed. The procedure will not be charged from the patient or his health insurance. The Investigator may decide to withdraw a subject from the investigation at any time. The investigators must make every effort to contact the subject to ascertain the reason for missed appointments if a subject does not return for follow-up assessments. Correspondence with the subject is necessary for regular withdrawal from pending follow-up.

The Study Protocol, Case Report Forms, Informed Consent form and other patient information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Any change affecting the subject requires that the subject is informed about the change(s). An updated signed and dated informed consent shall be obtained from the investigator and the study participant, no later than during the subject's next follow-up visit under the scope of this investigation.

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

Initially, all participants are informed in detail about the study, its background and goals, the importance of training intensity, and the importance of adherence to the study plan. At follow-ups, feedback sessions are performed and experience between participants and investigators is exchanged. Regular correspondence with the subjects additionally ensures adherence to intervention protocols. Subjects are asked to document their daily activities and training sessions, which is regularly reported to the investigators in order to monitor training frequency and intensity (in case of home training or training in an external rehab center). In addition, physical activity during training and daily life is monitored by wireless sensors mounted to the patient's wrists, ankles and wheelchair, and data are regularly transferred via SSL-encrypted links (https) established between sites (e.g. a patient's home or rehab centre) and the Swiss Federal Institute of Technology Zurich (ETH).

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Prior to surgery, all medication that has blood-thinning effect (effect on blood coagulation or platelet function, e.g. Aspirin, Plavix, Marcoumar, Valproic acid, Gingko) is prohibited. The patients are informed by the surgeon prior to surgery about these medications and how they should be discontinued. If there is an indication for continuous intake of an anticoagulant or antiplatelet drug, the patient has to be excluded from the study. Patients with implanted technical devices, e.g. cardiac pacemakers, are not eligible for study participation.

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended *Briefly, the primary outcome measure for improvement of ambulation in this study is the gain of covered distance in the 6 minutes walking test (6MWT) at 6 months post implantation compared to baseline level. Additionally, a variety of quantitative and qualitative secondary outcome measures are performed, e.g. kinematic assessments, electrophysiological measurements and questionnaire-based assessments.*
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) *Briefly, patients with a motor incomplete SCI at the level of T10 or above and at least 6 months of recovery after injury are eligible to undergo screening for study participation. 1-3 months after study enrolment, baseline testing is performed, followed by unilateral electrode implantation at the less severely affected side 1-10 days later (with or without temporary lead externalisation). After complete implantation, follow-up testing ensues at 2 weeks, 1 month, 3 months and 6 months, respectively. Patients will be discharged from hospital after 2-3 weeks of training (TR) and testing. After hospital discharge, patients will undergo rehabilitative training with DBS. See Figure 3 of manuscript.*

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Briefly, we aim to include 5 patients in the study who have to complete all preoperative and postoperative examinations until 6 months after surgery, resulting in a total of 11 timepoints. In case of withdrawal of participation or arising complications (dropouts and incomplete follow-up), we aim to include two more patients (replacement of dropouts/withdrawal). The number of subjects is based on the aim of gaining information on treatment effectiveness with adequate safety. Preliminary studies of PPN stimulation in patients with gait disturbance and falls due to Parkinson's disease have been analyzed in a retrospective review by Morita et al., 2014. Sample sizes ranged from 1 to 14 in 12 publications. We estimate a relative effect size of 30% improvement in the 6MWT 6 months after treatment start compared to performance at baseline to be clinically relevant. A sample size of five patients provides us with a power (1-β) of 80% (α = 0.05). We judge that the selected sample size, based on previous experience in deep brain stimulation of the MLR, will provide acceptable clinical validity for the study objectives.

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
		In summary, all candidate patients, namely patients able to stand with or without walking aid and with a stable neurological condition, are screened and have to meet all of the inclusion and none of the exclusion criteria. Subjects will undergo preoperative examinations (e.g. MRI scans of the head and spine, neuropsychological, psychiatric and sleep status assessments etc.) according to our standard protocols of DBS for movement disorders, based on certification criteria of highly-specialized-medical DBS centers in Switzerland. Neurological assessments for SCI related impairment as defined by the study protocol are performed at the Spinal Cord Injury Center of Balgrist University Hospital. The subject population enrolled in this investigation will be comprised of male and female patients from our out-patient clinic at Balgrist University Hospital or from international volunteers actively contacting the investigators based on information obtained from study registries. Patients who do not meet all in- and exclusion criteria are not eligible to participate in this investigation. There will be no specific gender distribution as gender specific differences concerning efficacy and safety of the investigational diagnostic process are not to be expected.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
		N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
		N/A

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions *N/A*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how *N/A*
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial *N/A*

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

Addressed in "Study design", "Clinical assessments", and "Electrophysiological assessments" sections, and Table 2 and Table 3 of manuscript.

The primary outcome measure (6-minute walking test) is an internationally recognized test to assess walking capacity in spinal cord injured patients, widely used in clinical trials and clinical routine. During the 6MWT, the patient is accompanied by an experienced investigator (physiotherapist).

Using a variety of standardized, well-known and widely used quantitative, qualitative and questionnaire-based methods as secondary outcome measures, the study additionally collects a big data set on motor, sensory, autonomic function and quality of life. For example, the WISCI (Walking Index for Spinal Cord Injury) is frequently used in clinical trials to assess walking function on an ordinal scale, and it captures the extent and nature of assistance a person with SCI requires to walk. To address the burden of neurogenic lower urinary tract dysfunction on patient's quality of life after SCI and to analyse the effect of MLR-DBS on recovery of lower urinary tract function, a combination of qualitative (bladder diary, validated questionnaire Qualiveen) and quantitative assessments (urodynamic measurements, renal ultrasound) of bladder function are applied in accordance to the European Association of Urology (EAU) Guidelines on Neuro-Urology.

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Regular correspondence with the subjects in addition to regular follow-ups promotes retention and adherence to intervention protocols. Patients who prematurely withdraw from the study will be offered complete removal of all implanted material. In case of complete implant removal, the patients will receive a short-term follow-up after 4 to 6 weeks by the surgeon to assess wound-healing and outcome of surgery. Afterwards, the clinical follow-up for SCI will be performed at the Balgrist University Hospital according to clinical standards. In case the patient withdraws from the study but refuses removal of the implants, clinical follow-up will be performed as well at the Department of Neurosurgery, University Hospital of Zurich, and at the Balgrist University Hospital according to clinical standards. In case of withdrawal, the patient's study related data will remain in the study.

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Data management system: All data will be entered in a case report form (CRF). Every patient will receive an anonymized and unique patient identifier. The investigator will compile a confidential list, which relates these patient numbers to the patient's full name. This list will only be accessible to the study team and the monitor. Original patient files may be viewed by monitors, auditors and inspectors. Overall, the PI is responsible for data handling. The PI and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies. Investigational data shall be analyzed by the PI and may be transferred to a location outside of Switzerland and/or any other regulatory authority. All data from the CRFs will be transferred to an electronic database by the study coordinator at USZ. All paper CRFs and other documents will be scanned and stored as PDF files. Data transfer will be overseen and double-checked by the PI personally to prevent copy failures.

Data security, access and backup: According to corresponding national laws the patient must declare in writing that he or she agrees to the recording of his or her medical data, respectively, and if necessary, the reporting to national health authorities. The CRF and submitted source data are archived by the data owner (PI) for at least 15 years as required by national law. The investigator keeps originals of all source data and an original dated and signed duplicate of the patient consent form of each patient together with other essential study documents at the study center in accordance with the national law. The electronic database and scans of paper CRFs and documents will serve as backup and vice versa.

Electronic and central data validation: The investigator confirms with his or her signature on the CRF that all statements and data are complete and correct. All incoming CRF are checked for plausibility and completeness. If necessary, the investigator/study nurse will add missing data or correct inconsistent statements. Any change or correction to data reported on a CRF shall be tracked. Source documents shall be created and maintained by the investigation site team throughout the clinical investigation. The data reported on the CRFs shall be derived from, and be consistent with, these source documents, and any discrepancies shall be explained in writing.

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol *Statistics will be restricted to descriptive statistics. The trial is considered successful if the patient's performance in the 6MWT has improved by at least 30% at 6 months after treatment start compared to baseline (two-samples t-test).*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) *N/A*
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) *N/A*

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed *Monitoring visits at the investigator's site prior to the start and during the course of the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors at an early time point. The Sponsor-Investigator organizes professional independent monitoring for the study. All original data including all patient files, progress notes and copies of laboratory and medical test results will be available for monitoring. The monitor will review all or a part of the CRF/eCRFs and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents. The investigator's site will collaborate with the Clinical Trials Center (CTC) of the University Hospital Zurich to ensure monitoring. A study specific monitoring plan, developed according to the CTC's SOP on monitoring activities, regulates extent, frequency and nature of monitoring activities.* *A quality assurance audit/inspection of this study may be conducted by the cantonal ethical committee (CEC) and by Swissmedic. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study. The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/documents and will answer any questions arising. All involved parties will keep the patient data strictly confidential.*
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial *N/A. The regulatory authorities receive an annual safety and interim report.*

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct *Every abnormal finding that appears for the first time or worsens during the course of the study will be recorded on the CRF and reported as adverse event. Adverse events (e.g. wound infections) will be interrogated for at each contact between the responsible investigator and the study subject. All pathological and clinically relevant findings in physical and neurological examinations, vital signs, clinical chemistry, hematology, and during surgery will be documented as adverse events. Complications related to assessments (e.g. falls during walking tests) will be reported as adverse events.*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor *A quality assurance audit of this study may be conducted by the cantonal ethical committee and by Swissmedic. The quality assurance auditor will be independent from the investigators and sponsor, and have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study. The investigator will grant the auditor access to the source data/documents and will answer any questions arising during the audit. All involved parties will keep patient data strictly confidential.*

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval *Ethical approval has already been obtained from the Ethical Committee of the Canton of Zurich (case number BASEC 2016-01104) and Swissmedic (10000316) in 2017. Latest approved protocol version: version 5, 12.09.2019.*
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) *Amendments are sent to and evaluated by the Cantonal Ethical Committee and Swissmedic. Substantial amendments are only implemented after approval by the Cantonal Ethical Committee and Swissmedic, respectively. Any change affecting the study participants requires that the subject is informed about the change(s). An updated signed and dated informed consent will be obtained from the subject by the investigator, no later than during the subject's next follow-up visit under the scope of this investigation.* *As addressed in the "Discussion" section of the manuscript, an amendment to the study protocol is currently being written in order to include patients already 3 months after injury (instead of 6).*

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	*Before inclusion of a patient, the potential participant is informed by the investigator about the nature and purpose of the trial, the procedures involved, expected duration, potential risks and benefits, and any discomfort that might occur. Each participant will be informed that the participation is voluntary and that he/she may withdraw consent from the study at any time. Withdrawal of consent will not affect the patient's subsequent medical assistance and treatment. The participant is informed that his/her medical records may be examined by authorized individuals other than their treating physician. All participants are provided with a participant information sheet and a consent form describing the study and providing sufficient information for patients to make an informed decision about their participation in the study. Sufficient time will be given to the participant to decide whether to participate or not. Depending on the date of screening, the time frame is 20-80 days before hospitalization.* *The patient information sheet and the consent form have been reviewed and approved by the Cantonal Ethical Committee and Swissmedic. The formal consent of a participant is obtained before the participant undergoes any study procedure. The participant has to read and consider the statement before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is also signed and dated by the investigator (or his designee), and will be retained as part of the study records.*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	*N/A*

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial *All data will be entered in a database as recorded in the CRF and every patient will receive an anonymized and unique patient identifier. The investigator will compile a confidential list, which relates these patient numbers to the patient's personal information. This separately stored list will only be accessible to the study team and the monitor. Original patient files may be viewed by monitors, auditors and inspectors.*
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site *The authors have no conflicts of interest to declare. Investigators and collaborators receive no financial or other compensation for work rendered in accordance with the study, despite their regular income from their respective affiliations.*
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators *After termination of the study, study data will be available for analysis only for persons or institutes assigned by the PI, according to local regulations. Direct access to source documents will be permitted for* purposes of monitoring, audits and inspections. *The PI maintains all essential clinical investigation documents from prior, during and after the clinical investigation on file at the site. Originals of all study-related report forms, administrative documents, medical records, and a list allowing patient identification will be stored in the study headquarters University Hospital Zurich and Balgrist University Hospital for at least 15 years after completion of the trial.*

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation *Any damage developed in relation to study participation is covered by the study's insurance. So as not to forfeit their insurance cover, the participants themselves must strictly follow the instructions of the study personnel. Participants must not be involved in any other medical treatment without permission of the PI (emergency excluded). Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly in the event of health problems or other injuries sustained during or after the course of study. The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential. The patient and his health insurance will not be charged for screening, treatment and follow-up (until 6 months after surgery), but there will be no compensation for participation in the study. Clinical examinations and treatments after completion of the 6 months' follow-up will be charged from the patient´s health insurance.*
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions *The findings of this trial will be submitted to a peer-reviewed journal and abstracts are presented at relevant national and international conferences. Results will be communicated to participants in layman's terms.*

	31b	Authorship eligibility guidelines and any intended use of professional writers *Publication(s) and/or presentation(s) of the study results is encouraged. Neither the sponsor nor the investigators have the right to prevent publication, except for patent or copyright reasons. Staff members who gave relevant scientific support to the study design, conductance and/or analysis of results will be included as coauthors, if applicable. A copy of all publications will be sent to the coauthors. The PI will decide about authorship and the sequence of co-authors, including the last author, based on the amount and importance of the contribution to the study as judged by the PI. No professional writers will be used.*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code *N/A*
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates *Please see Appendix 1.*
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable *N/A*

Appendix 1 - Model consent form

Informed consent for participation in a clinical study

- Please read this document carefully
- Please ask in case of questions or further interest.

Study identifier: (of the local ethics committee)	BASEC 2016_01104
Study title:	Deep Brain Stimulation in patients with incomplete spinal cord injury for improvement of gait Tiefe Hirnstimulation zur Verbesserung des Gehens bei Patienten mit Rückenmarksverletzungen
Responsible institution (Sponsor) (complete address):	Neurochirurgische Klinik, UniversitätsSpital Zürich, Frauenklinikstrasse 10, CH-8091 Zürich
Study site:	UniversitätsSpital Zürich and Uniklinik Balgrist Zürich
Principal investigator: Name, First name:	Lennart Stieglitz MD, Chief of service, Specialist for Neuromodulation Armin Curt MD, Chairman Center for Paraplegia
Participant: Name and first name, date of birth	☐ female ☐ male

- I was informed in detail orally as well as in written form about the purpose, the conduction, about expected effects, possible side-effects, risks and benefits of the study by the signing surgeon.
- My questions concerning my participation in the study were answered satisfyingly. I received the study information of 07.06.2019 Version 2 (two parts) and receive a copy of this informed consent form. I accept the content of the above mentioned study information.
- I participate in this study voluntarily. I can withdraw from participation at any time and will not suffer disadvantages concerning my ongoing medical treatment hence.
- I was informed about other possible treatment options.
- I was given enough time to decide about my participation.
- I was informed, that an insurance company will cover damages resulting from participation in the study, in case I can prove the connection clearly.
- I agree that my general practitioner is informed about my participation in the study: Yes ☐ No ☐.
- In case of incidental findings I want to a) ☐ be informed unconditionally; b) ☐ not informed or c) ☐ I want to leave the decision with the following person: .....
- I know, that my personal data may only be used in coded form for scientific purposes. I agree, that the responsible specialists of the initiator of the study and the local authorities (cantonal ethics committee) may be granted insight into the original data for control purposes, but only under strict compliance with confidentiality.
- I am aware, that the obligations mentioned in the study information are to be obliged during the study. The principal investigator may exclude me from the study at any time with my best interests in mind.

Place, date	Signature study participant

Confirmation of the investigator: Hereby I confirm that I informed the participant in detail about the character, importance and relevance of the study. I will fulfill all legal obligations in connection with this study. Should I learn of aspects that could affect the willingness of the participant to participate during the course of the study, I will inform him/her immediately.

Ort, Datum	Signature of the investigator

BMJ Open

Deep brain stimulation for locomotion in incomplete human spinal cord injury (DBS-SCI) – protocol of a prospective one-armed multi-centre study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-047670.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Aug-2021
Complete List of Authors:	Stieglitz, Lennart; University Hospital Zurich, Department of Neurosurgery Hofer, Anna-Sophie; University Hospital Zurich, Department of Neurosurgery; University of Zurich Institute for Regenerative Medicine Bolliger, Marc; Balgrist University Hospital, Spinal Cord Injury Center Oertel, Markus; University Hospital Zurich, Department of Neurosurgery Filli, Linard; Balgrist University Hospital, Spinal Cord Injury Center Willi, Romina; Balgrist University Hospital, Spinal Cord Injury Center Cathomen, Adrian; Balgrist University Hospital, Spinal Cord Injury Center Meyer, Christian; Balgrist University Hospital, Spinal Cord Injury Center Schubert, Martin; Balgrist University Hospital, Spinal Cord Injury Center Hubli, Michèle ; Balgrist University Hospital, Spinal Cord Injury Center Kessler, Thomas; Balgrist University Hospital, Department of Neuro-Urology Baumann, Christian; University Hospital Zurich, Department of Neurology Imbach, Lukas; University Hospital Zurich, Department of Neurology Krüsi, Iris; Balgrist University Hospital, Spinal Cord Injury Center Prusse, Andrea; Balgrist University Hospital, Spinal Cord Injury Center Schwab, Martin; University of Zurich Institute for Regenerative Medicine Regli, Luca; University Hospital Zurich, Department of Neurosurgery Curt, Armin; Balgrist University Hospital, Spinal Cord Injury Center
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	REHABILITATION MEDICINE, Neurological injury < NEUROLOGY, Spine < ORTHOPAEDIC & TRAUMA SURGERY, NEUROSURGERY, Clinical trials < THERAPEUTICS

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Deep brain stimulation for locomotion in incomplete human spinal cord injury (DBS-SCI) – protocol of a prospective one-armed multi-centre study

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Word count: 5422 words

ABSTRACT

Introduction: Spinal cord injury (SCI) is a devastating condition with immediate impact on the individual's health and quality of life. Major functional recovery reaches a plateau three to four months after injury despite intensive rehabilitative training. To enhance training efficacy and improve long-term outcomes, the combination of rehabilitation with electrical modulation of the spinal cord and brain has recently aroused scientific interest with encouraging results. The mesencephalic locomotor region (MLR), an evolutionarily conserved brainstem locomotor command and control centre, is considered a promising target for deep brain stimulation (DBS) in patients with SCI. Experiments showed that MLR-DBS can induce locomotion in rats with spinal white matter destructions of >85%.

Methods and analysis: In this prospective one-armed multi-centre study, we investigate the safety, feasibility, and therapeutic efficacy of MLR-DBS to enable and enhance locomotor training in severely affected, subchronic and chronic American Spinal Injury Association Impairment Scale C patients in order to improve functional recovery. Patients undergo an intensive training program with MLR-DBS while being regularly followed-up until 6 months post-implantation. The acquired data of each timepoint are compared to baseline while the primary endpoint is performance in the 6 Minute Walking Test (6MWT). The clinical trial protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials checklist.

Ethics and dissemination: This first in-man study investigates the therapeutic potential of MLR-DBS in SCI patients. One patient has already been implanted with electrodes and underwent MLR stimulation during locomotion. Based on the preliminary results which promise safety and feasibility, recruitment of further patients is currently ongoing. Ethical approval has been obtained from the Ethical Committee of the Canton of Zurich (case number BASEC 2016-01104) and Swissmedic (10000316). Results will be published in peer-reviewed journals and presented at conferences.

Trial registration: Registered on ClinicalTrials.gov (NCT03053791) on February 15, 2017.

Keywords: Spinal cord injury, deep brain stimulation, mesencephalic locomotor region, locomotion, training, rehabilitation

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This prospective one-armed multi-centre proof-of-concept study investigates the safety, feasibility and therapeutic potential of MLR-DBS to improve walking function after severe incomplete SCI.
- Patients with completed in-patient rehabilitation with highly limited ambulatory capacity are screened and considered for study enrolment.
- The study comprises a variety of clinical and electrophysiological assessments before, during, and after electrode implantation.
- Patients undergo intensive rehabilitative training with MLR-DBS and are followed-up on a regular basis until 6 months post-implantation.
- The primary endpoint is improvement of locomotion measured by the 6MWT 6 months after electrode implantation compared to baseline performance.

INTRODUCTION

In the event of spinal cord injury (SCI) a person's life turns upside down within a split second, and a multitude of body functions are either severely impaired or completely lost instantly. Reacquiring lost functions including locomotion is of high importance for affected patients.[1] However, it remains a largely unmet medical need due to the lack of treatment options to sufficiently rewire interrupted fibre tracts and enhance repair of the damaged human spinal cord. Despite decades of basic research, neuro-rehabilitative training currently remains the only treatment option that increases the chances of long-term improvement of sensory-motor functions.[2,3] Even though most SCIs spare some descending and ascending fibre tracts, leaving the sublesional spinal cord [4] only incompletely disconnected from the brain, functional recovery remains limited in most cases.[3,5,6] The number of spared descending fibres is often insufficient to convey appropriate control signals to sublesional locomotor circuits, e.g. central pattern generators (CPGs), which are thus deprived of supraspinal input and modulation,[7] and fail to induce rhythmic motor patterns.[8,9] However, these local rhythm generators remain functional and can be reactivated, e.g. by direct electrical stimulation in combination with training.[10–12] To increase the efficiency and efficacy of neurorehabilitation, locomotor training has therefore been combined with electrical epidural and transcutaneous stimulation of the spinal cord in small cohorts of patients in recent years, yielding promising results.[3,13–15] Another encouraging approach to recruit inactive, yet intact, sublesional motor circuits involves the electrical activation of spared descending reticulospinal tract fibres (Figure 1).[16] The majority of reticulospinal fibres arise from the medial medullary reticular formation, which relays the output of its upstream target, the mesencephalic locomotor region (MLR),[17–19] to the spinal cord. The MLR is a phylogenetically conserved key locomotor control centre in the brainstem, and is comprised of two main nuclei, the pedunculopontine (PPN) and the cuneiform nucleus (CNF).[20–22] The PPN is associated with exploratory behaviour,[23] and deep brain stimulation (DBS) of the PPN in patients with Parkinson's disease can result in a reversal of freezing of gait.[24–27] On the other hand, the CNF is known to be a main control region for locomotion initiation, maintenance and speed regulation.[23,28,29] Recently, the MLR has gained scientific and clinical interest as target for DBS to improve deficient gait after SCI [16] and stroke [30] with the CNF being proposed as main therapeutic target in recent rodent studies.[23,28,29] Acute electrical activation of the rat MLR has been shown to enable close to physiological hindlimb movements during walking and swimming in a rodent model of chronic incomplete SCI resembling an American Spinal Injury Association Impairment Scale (AIS) D score in humans.[16] In animals with severely paralyzed hindlimbs (AIS A-C in humans) stroke movements re-appeared with gravity-support during swimming with MLR-DBS. In an acute rodent stroke model, MLR-DBS was able to improve walking speed and limb coordination.[30] DBS in humans is considered safe, reversible and minimally-invasive, and is

being routinely and successfully applied in the treatment of various movement disorders [31–36] with great technical progress in recent years.[37–39] While DBS of the PPN in Parkinson's disease has not only yielded clearly positive therapeutic effects,[40] the CNF might be a promising target for locomotion initiation.

Function and anatomy of the brainstem motor systems are highly conserved across mammalian species.[41] Due to their dispersed projection pattern throughout the spinal cord white matter,[42,43] reticulospinal fibres are likely to be partially spared after incomplete SCI in humans,[44] and are crucial for functional recovery after SCI.[45,46]

Encouraging results from animal studies [16,30,47] have led to the initiation of a first in-man study that investigates MLR-DBS enabled intensive rehabilitative training and its potential to enhance locomotion in non-ambulatory, subchronic and chronic SCI patients. The study protocol is presented in this article.

We hypothesize that MLR-DBS can modulate the activity of spared reticulospinal fibres that bypass the site of injury and reintegrate quiescent sublesional circuits into a functional network that supports walking (Figure 2). We propose that enhancing excitability of sublesional spinal motor circuits increases training efficacy and promotes recovery of motor function in patients with incomplete, subchronic and chronic SCI.

METHODS AND ANALYSIS

Study design

This prospective one-armed phase I/II multi-centre study is being conducted as cooperation of the University of Zurich, the University Hospital Zurich and the Balgrist University Hospital Zurich. Patients are screened and selected by SCI specialists and physiotherapists at the Balgrist University Hospital. Incomplete SCI is confirmed based on clinical examinations, magnetic resonance imaging (MRI), and electrophysiological measurements, and each patient's established drug therapy is recorded. After patient inclusion and baseline examinations, a DBS lead is stereotactically unilaterally implanted into the cuneiform part of the MLR, followed by infraclavicular or abdominal implantation of an impulse generator (IPG, Figure 3). The side of lead placement is chosen based on the functional and anatomical lesion extent, with preference for the less severely affected side to transmit as much descending brainstem motor signal as possible beyond the lesion via the primarily uncrossed reticulospinal fibres. The patients are followed-up on a regular basis until 6 months post-implantation, and the acquired data of each timepoint are compared with baseline findings. The primary outcome measure for improvement of ambulation in this study is the difference in covered distance in the 6 Minute Walking Test (6MWT) at 6 months post-implantation compared to baseline level. The trial is considered successful if the patient's performance in the 6MWT 6 months after treatment start is at least 30% [48] higher compared to performance at baseline. For the design of the clinical trial protocol we followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.[49]

Study population

Female and male patients (18-75 years) with completed in-patient rehabilitation and at least 6 months of recovery after SCI are screened and considered for study enrolment. We aim at including 5 patients, who have to complete all preoperative and postoperative examinations until 6 months after electrode implantation, resulting in a total of 11 timepoints. In case of withdrawal of participation, dropouts and incomplete follow-up, we will include a maximum of 2 additional patients (replacement of dropouts/withdrawal). The study is open to national and international patients. Basic understanding of German or English is required. Patients who prematurely withdraw from the study will be offered complete removal of all implanted material, and will be followed-up according to clinical standards. The patients' study related data will remain in the study.

Inclusion and exclusion criteria

To be eligible for the study, a participant must fulfil all inclusion criteria and none of the exclusion criteria (Table 1).

Table 1 – Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Informed consent	Enrolment of the investigator, her/his family members, employees and other dependent persons
Participation in two assessment sessions before enrolment (screening and baseline)	Limitation of standing and walking function based on accompanying (CNS) disorders
Willingness and ability to comply with the protocol and to attend required study training and visits	Cardiovascular disorders restricting physical training or peripheral nerve disorders
Female or male subject	Implanted technical devices (pacemaker, defibrillator, others)
Age 18-75	History of significant autonomic dysreflexia
Motor incomplete SCI	Cognitive disorders/brain damage
Level of lesion at or above T10, based on AIS level, preservation of sacral function	Drug refractory epilepsy
Focal spinal cord disorder caused by either trauma or non-traumatic and non-progressive condition (like haemorrhage, benign tumour)	Severe joint contractures disabling or restricting lower limb movements
Minimum 6 months of recovery after SCI	Haematological disorders with increased risk of bleeding during surgical interventions
Completed in-patient rehabilitation program	Participation in another study with investigational drug within 30 days preceding and during the present study
WISCI II, level >2 (0-20 items): assistance of one or more persons. Ability to walk at least 10 meters	Congenital or acquired lower limb abnormalities (affection of joints and bone)
Stable medical and physical condition	Women who are pregnant or breast feeding or planning a pregnancy during the course of the study
Adequate care-giver support and access to appropriate medical care in patient's home community	Lack of safe contraception
	Inability of the participant to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc.
	Known or suspected non-compliance, drug or alcohol abuse
	Current or prior malignancy

CNS = central nervous system. SCI = spinal cord injury. AIS = ASIA (American Spinal Injury Association) Impairment Scale. WISCI = Walking Index for Spinal Cord Injury. PI = principal investigator.

Target area definition

While the rodent CNF and its microstructure are nowadays well characterized,[23,28,29] the human CNF is poorly described, and presented only in a very limited number of stereotactic atlases. However, due to the high phylogenetic conservation,[41] the CNF can be defined by surrounding landmarks and coordinates available from lead implantation into the PPN and rodent stereotactic atlases (Figure 4).

Surgery

All individuals included in the study undergo unilateral stereotactic implantation of an intracranial lead (model 3389-28; Medtronic, Minneapolis, MN, USA) via a unilateral burrhole under local anaesthesia. The distal end of the DBS lead features narrow (0.5 mm) spacing between each of the four stimulation contacts of 1.5 mm length each. After mounting of the stereotactic frame, high resolution cranial computed tomography (CT) scans are performed and fused with the individual's MRI scan to retrieve stereotactic coordinates based on the pre-planned trajectory. Depending on the patient's preferences and the surgeon's decision, patients either receive a full implant consisting of a DBS lead, an extension and an IPG within one surgical session, or receive a lead only, which is externalized for maximal 10 days for evaluation of side effects and responsiveness to stimulation. In the latter scenario, the patient undergoes a second surgery with either removal of the lead (dropout of the study participant) or completion of the DBS system. For completion, the lead is connected to a Medtronic Activa SC model 37603 IPG using a Medtronic model 37086-60 or 37086-95 extension cable. The IPG is implanted subcutaneously in the pectoral or abdominal region, respectively, depending on the patient's physiognomy and preference.

Intraoperatively, at first electrophysiological mapping of the CNF is performed. Microelectrodes are precisely inserted along a predefined trajectory aiming towards the CNF with the Neuro Omega neuromodulation system and manual drive (Alpha Omega Engineering, Nazareth, Israel) attached to the stereotactic device. During electrode insertion (0.5 mm steps), microelectrode recordings (30 s at each position) of single and multi-unit activity (local field potentials, LFPs) are performed during resting state, imagination of walking, passive and active lower limb movement within 10 mm prior and maximum 5 mm after the projected target point. Signals are band pass filtered (1-500 Hz). Depending on the patient's anatomy up to five microelectrodes can be inserted simultaneously, in case of a presumed elevated risk of haemorrhage, the surgeon can decide to exclusively use macroelectrodes instead of microelectrodes. The centre of the region showing neuronal responsiveness to walking imagination, passive and active lower movement is subsequently stimulated while the patient performs a selection of motor tasks with the lower limbs hanging off the surgery table, accompanied by simultaneous electromyographic (EMG) recordings. Since this study is the

first to investigate DBS of the CNF in human patients, no guidelines for optimal stimulation parameters are available. However, there is growing and comparable evidence from preclinical studies in various animal models suggesting low frequency stimulations (≤50 Hz) at medium to broad pulse widths (200-1000 µs) [16,50,51] which is likely to be transferable to humans due to the evolutionarily conserved nature of the mesencephalic locomotor region across mammalian species. We thus initially stimulate with 20 Hz and 400 µs pulse width at increasing voltages, and frequency and pulse widths are then adjusted based on the individuals' intraoperative behavioural response. Up to three different parameter settings of fixed frequency and pulse width with varying voltages are extensively tested intraoperatively. Stimulation amplitude is slowly increased, and changes in range of motion with and without stimulation are measured by goniometers attached to knee and ankle while the patient performs rhythmic knee and ankle flexion/extension movements. Furthermore, speech and cognition are tested with and without stimulation, and the appearance of side effects, in particular pain sensations and paraesthesia, is closely monitored and documented. Additional electrophysiological measurements, including motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs), are performed for neuromonitoring, and event (i.e. lower extremity motor response) related potentials (ERPs) are analysed. Ultimately, the coordinates resulting in best motor performance (e.g. greatest range of motion of knee joint, highest frequency of rhythmic knee flexions/extensions) at the lowest stimulation parameters without provoking side effects are chosen, and the quadripolar DBS lead is implanted with contact 2 located within the centre of the identified area, fixed to the skull, and either temporarily externalized or connected to an extension and IPG. All subjects subsequently receive a postoperative cranial CT scan to verify correct lead position and exclude surgery-associated complications (e.g. haemorrhages). Each patient recovers from surgery in the intermediate care unit overnight.

Clinical assessments

6 Minute Walking Test (6MWT)

During the 6MWT,[48] the patient is asked to cover a maximal distance within 6 minutes on even ground without any obstacles. The patient is accompanied by an experienced investigator (i.e. physiotherapist) to prevent falling, and may rest at his own discretion and use a walking aid (consistent across all timepoints). The distance covered (m), time and number of rests (min, count) is documented. Each assessment is video recorded.

10 Meter Walking Test (10MWT)

The 10MWT [52] is a widely used assessment tool to measure maximal walking speed (m/s). The patient is instructed to walk 10 m as quickly as possible, but safely, and is given 5 m for

acceleration and deceleration. Patients may use assistive devices (consistent across all timepoints).

Timed-Up and Go Test (TUG)

The TUG is a basic evaluation tool of functional mobility. It measures the time (s) needed to rise from a chair, walk 3 m, turn around and return to a seated position. Participants are asked to perform the TUG at their self-selected normal speed, using their walking aid if required. The timer is started on the command “ready–set–go” and stopped as the patient returns to a seated position.

Kinematic assessment

Kinematic assessments are performed during over-ground and treadmill walking. Individuals are secured using the FLOAT (“Free Levitation for Overground Active Training”),[53,54] a multidirectional overhead support system that allows patients to move in a large workspace that is equipped with a 3D motion capture system with infrared cameras (Vicon Motion Systems Ltd., Oxford, UK). The cameras are able to detect the position of reflective markers placed on patients’ anatomical landmarks, allowing the quantification of kinematic movement characteristics.[55,56] Additionally, muscle activity is measured with an EMG setup (myon AG, Schwarzenberg, Switzerland). These measures allow the quantification of patients’ walking function with high precision and the comparison of gait patterns within (with and without DBS) and between different sessions. In addition to walking assessments, maximal knee and ankle range of motion is evaluated with and without stimulation with the motion capture system during rhythmic flexion/extension tasks performed by the patient in supine or sitting position. Besides quantitative assessment of locomotor function, the FLOAT allows patients to train diverse activities such as level walking, running, stair manoeuvres, chair interactions or walking on uneven terrain with and without stimulation at the limit of their abilities with tailored body weight support.

Long-term Monitoring of Physical Activity

For constant monitoring of physical activity during training and daily life, wearable, wireless sensors (http://zurichmove.com/) are mounted to the patient’s wrists, ankles, and wheelchair. Data are transferred via SSL-encrypted links (https) established between sites (e.g. a patient’s home or rehab centre) and the Swiss Federal Institute of Technology Zurich (ETH).

ASIA Impairment Scale (AIS)

The American Spinal Injury Association (ASIA) International Standards for Neurological Classification of SCI (ISNCSCI) [57] is an internationally used gold standard method of assessing the neurological status of an individual with SCI. The AIS is carried out by trained

medical staff using the ISNCSCI worksheet (https://asia-spinalinjury.org/international-standards-neurological-classification-sci-isncsci-worksheet/).

Modified Ashworth Scale (MAS)

The MAS [58] is a clinical scale used to assess muscle spasticity in patients with lesions of the central nervous system. It is the most commonly used tool to evaluate changes of muscle tone in response to therapeutic interventions, e.g. anti-spasticity medication. Here, we aim to investigate the effects of MLR-DBS by itself on muscle tone and thus do not routinely modify each patient's established anti-spasticity treatment unless medically indicated. However, potential drug-stimulation interactions are considered in data interpretation.

Spinal Cord Independence Measure (SCIM III)

The SCIM is a reference tool for the assessment of overall functional ability after SCI. The last version (III) of SCIM contains 19 tasks organized into 3 subscales: Self-care, Respiration & sphincter management, and Mobility.[59] The combined scores on all 19 tasks result in an overall score ranging from 0 to 100, with higher scores reflecting greater functional ability.

Walking Index for Spinal Cord Injury (WISCI II)

The WISCI assesses walking function on an ordinal scale,[60] and captures the extent and nature of assistance a person with SCI requires to walk. Rating is performed according to Ditunno et al.[60]

Assessment of lower urinary tract (LUT) function

To address the burden of neurogenic LUT dysfunction on patient's quality of life after SCI and to analyse the effect of MLR-DBS on recovery of LUT function, a combination of qualitative (bladder diary, QUALIVEEN questionnaire) and quantitative assessments (urodynamic measurements, renal ultrasound) of LUT function are applied in accordance to the European Association of Urology (EAU) Guidelines on Neuro-Urology.[61,62]

- Bladder diary: by completing the Three Day Bladder Chart [63] information on daytime frequency, nighttime frequency, voiding (e.g. spontaneous), catheter use (transurethral, suprapubic, self-catheterization), voided volume, post void residual volume, incontinence episodes, pad use, fluid intake and amount of urine per 24 hours, and pain (visual analogue scale 0-10) is acquired.
- QUALIVEEN questionnaire: all patients fill in the QUALIVEEN questionnaire for self-judgement of LUT dysfunction according to Costa et al.[64]. Scores (0-4) are recorded

for “Limitations”, “Constraints”, “Fears” and “Feelings”, and the calculated arithmetic mean is transformed into values of 0-100.

- Urodynamic assessments: Cystometry, uroflowmetry, pressure-flow studies, electromyography and video-urodynamics provide objective information on functioning of the LUT and pelvic floor. Parameters retrieved are: cystometric capacity (mL), compliance (mL/cmH2O), detrusor overactivity (y/n), bladder volume at detrusor overactivity (mL), maximum detrusor pressure amplitude (cmH2O) during storage phase, urinary incontinence, maximum detrusor pressure (cmH2O) during voiding phase, detrusor pressure at maximum flow rate (cmH2O), maximum flow rate (mL/s), voided volume (mL), post-void residual (y/n and mL), pelvic floor electromyographic activity (normal/abnormal), vesico-uretero-renal reflux (y/n).
- Renal and bladder ultrasound: indirect assessment of LUT function, e.g. via post-void residual volume, detrusor thickness or distension of the renal pelvis or ureter.

Assessment of sexual function

The Female Sexual Function Index (FSFI) [65,66] is gold standard for the evaluation of female sexual function in clinical trials. It is questionnaire-based and contains 19-items including sexual arousal, orgasm, satisfaction and pain (score 2-80). The International Index of Erectile Function (IIEF) [67] is a standardized 15-item self-evaluation scale for male patients assessing erectile function, orgasmic function, sexual desire, satisfaction in sexual intercourse and in general.

Epworth Sleepiness Scale (ESS)

The ESS [68] measures a patient’s general level of daytime sleepiness. The patient rates the probability of falling asleep on a scale of increasing probability (0-3) for eight different situations.

Fatigue Severity Scale (FSS)

The FSS [69] evaluates the impact of fatigue based on a short questionnaire containing nine statements rating the severity of fatigue symptoms.

Pain assessment

The EMSCI (European Multicenter Study About Spinal Cord Injury) pain assessment form (EPAF) [70,71] and the Spinal Cord Injury Pain Instrument (SCIPI) [72–74] are standardized and validated tools to evaluate pain in individuals with SCI.

Graded Redefined Assessment of Strength, Sensation and Prehension (GRASSP)

The GRASSP [75,76] is a standardized upper-limb impairment measure specifically used to assess recovery of upper limb function (strength, sensation, prehension) in individuals with complete or incomplete tetraplegia.

Short Form Health Survey to Assess Quality of Life (SF-36)

Patients with SCI experience tremendous changes in several aspects of everyday life and thus quality of life (QoL) [77] assessments are crucial in clinical trials. We employ the SF-36 [78], a multi-purpose, short-form health survey comprised of 36 questions that compares the relative burden of diseases and differentiates the health benefits produced by a wide range of different treatments. It yields an 8-scale profile of functional health and well-being scores, psychometrically based physical and mental health summary measures, and a preference-based health utility index. QoL is expressed as a score ranging from 0 to 100.

Electrophysiological assessments

Electrophysiological assessments are performed in addition to clinical examinations as they allow prediction of functional outcome and help objectify the extent of the spinal lesion, its stability and potentially recovery of specific functions after SCI.[79,80] Intraoperative somatosensory and motor evoked potentials are recorded for neuromonitoring purposes due to the close relationship of the CNF with surrounding brainstem structures.

Short-latency somatosensory evoked potentials (SSEPs)

SSEPs are performed to evaluate transmission of ascending signals within the dorsal column of the spinal cord and thus sensory function. The patient is in supine position, and stimulating electrodes are placed on the posterior tibial nerve (below the internal malleolus). Four subcutaneous recording electrodes are placed as follows: at L2 and L5, on the scalp (reference Fz and active Cz', 2 cm behind Cz), and a ground around the ankle. Cortical recording electrodes are positioned in accordance with the International 10–20 system.[81] Stimulation parameters are 200 µs, up to 100 mA at a frequency of 3.1 Hz. The signal is recorded between 30 and 300 Hz with 50 Hz notch filter. Waveforms are measured after 200-800 averages. Dorsal horn negativity (N24) is measured on the lumbar derivation (L5-L2) and represents peripheral conduction time. The post-Rolandic positivity (P45) is measured on the scalp derivation and represents the total conduction time. All measures are recorded before, during and after electrode implantation, and before and after first (week 1 after implantation) and last (6 months after implantation) 6MWT assessments. Response latency (ms) and amplitude (µV) are compared between timepoints and conditions (stim/no stim).

DBS evoked potentials (DBS-EPs)

DBS-EP testing is performed similar to SSEP measurements. However, instead of stimulating a peripheral nerve, the evoked cortical response is generated by repetitive low frequency stimulation of the target region (CNF/MLR). Outcome measures are response latency (ms) and amplitude (μV).

Motor evoked potentials (MEPs)

MEPs are tested to evaluate the ability of MLR-DBS enhanced training to induce remodelling of spinal pathways leading to amplification of descending signals. Surface recording electrodes are positioned on the tibialis anterior and the gastrocnemius medialis muscles. Transcranial magnetic stimulation (TMS) is applied on the scalp close to Cz and on the lumbar spine in front of L5. After a test stimulus, the stimulation is increased stepwise up to 100% of the stimulator output and the response is recorded under 5-10% voluntary muscle activation. Total conduction time is measured after scalp stimulation and peripheral conduction time after lumbar stimulation. All measures are recorded before, during and after electrode implantation, and before and after first (week 1 after implantation) and last (6 months after implantation) 6MWT assessments. Response latency (ms) and amplitude (μV) are compared between timepoints and conditions.

Local field potentials (LFPs)

LFPs are measured intraoperatively during probe insertion and postoperatively in case of temporary externalization of the lead. Intraoperative LFPs are measured in the target region, starting 10 mm above the target and ending 5 mm below the target. Postoperative measurements are performed at the 4 contacts of the implanted lead. Signals are band pass filtered (1-500 Hz).

Electroencephalogram (EEG)

To reconstruct patterns of specific neuronal activity and their change upon MLR-DBS, non-invasive EEG recordings are performed in the perioperative period and at the last assessment timepoint.

DBS during behavioural testing and rehabilitative training

In the first two weeks after lead implantation, different stimulation parameters (frequency, Hz; pulse width, μs; amplitudes, mV) are tested during rest and locomotor training in order to identify optimal stimulator settings including safety limits for each patient individually. The most promising monopolar stimulation settings identified intraoperatively (frequency, pulse width) are applied systematically first via lead contact 2 with varying voltages. In case of failure to induce motor responses or occurrence of side effects at already low voltages parameters will be adapted (frequency, pulse width, polarity, lead contact) sequentially depending on each

patient's efficacy and side effect profile. Subsequently, one set of parameters eliciting the best motor responses without side effects is chosen for rehabilitative training (e.g. 20 Hz, 420 µs, suprathreshold intensity) and programmed to the patient programming device (up to three additional combinations could be additionally programmed to the device if needed). After two weeks, patients are discharged home or to a rehabilitation clinic located close to home. Training intensity is monitored and ensured by regular follow-ups by phone and by online activity monitoring via wearable sensors mounted to the patient's wrists, ankles and wheelchair. Behavioural testing is performed with and without stimulation during each follow-up visit using the stimulation parameters applied during training.

Study endpoints

The primary endpoint of the DBS-SCI study is improvement of locomotor function, represented by an increased distance covered during the 6MWT when comparing performance at the 6 months timepoint with and without DBS with performance at baseline. Additionally, a variety of secondary endpoint assessments are performed (Table 2). Table 3 summarizes timing and schedule of the respective primary and secondary endpoint assessments.

Table 2 – Primary and secondary endpoint measures.

Primary endpoint measure	Secondary endpoint measures
6 Minute Walking Test (6MWT) at 6 months follow-up vs. baseline	6 MWT at follow-up timepoints other than 6 months post-implantation
	10 Meter Walking Test (10MWT)
	Timed Up and Go Test (TUG)
	Kinematic assessments (FLOAT)
	Spinal Cord Independence Measure (SCIM III)
	Walking Index for Spinal Cord Injury (WISCI II)
	Activity counts (patient's overall activity level)
	Electrophysiological measurements*
	Quality of life (SF-36)
	Lower urinary tract (LUT) function**
	Sexual function (FSFI/IIEF)
	Spasticity (MAS)
	Neurological classification of SCI (AIS)
	Upper limb function (GRASSP)
	Level of fatigue (FSS)
	Level of sleepiness (ESS)
	Pain (EPAF, SCIPI)

FLOAT = Free Levitation for Overground Active Training. MLR = mesencephalic locomotor region. *Local field potentials (LFPs); somatosensory evoked potentials (SSEPs); motor evoked potentials (MEPs); DBS evoked potentials (DBS-EPs); electroencephalogram (EEG). SF-36 = Short Form Health Survey to Assess Quality of Life. **bladder diary, QUALIVEEN questionnaire, urodynamic measurements, bladder and renal ultrasound. FSFI = Female Sexual Function Index. IIEF = International Index of Erectile Function. MAS = Modified Ashworth Scale. AIS = American Spinal Injury Association (ASIA) Impairment Scale. GRASSP = Graded Redefined Assessment of Strength, Sensation and Prehension. FSS = Fatigue Severity Scale. ESS = Epworth Sleepiness Scale. EPAF = EMSCI (European Multicenter Study About Spinal Cord Injury) Pain Assessment Form. SCIPI = Spinal Cord Injury Pain Instrument.

Table 3 – Flowchart summarising scheduling and timing of primary and secondary endpoint assessments.

Site	Study periods	Screening	Baseline	DBS surgery	Post-implantation phase			IPG implantation	Rehabilitation / Follow-up phase					
Visit		1	2	3	4	5	6*	7*	8	Dis-charge	Site	9	10	11
Day (d) / month (mo)		-90 to -30 d	-10 to -1 d	0	1 to 3 d	4 to 7 d	8 to 9 d	6 to 10 d	14 d +/-3 d			mo 1 +/-3 d	mo 3 +/-1 week	mo 6
University Hospital Zurich/ Balgrist University Hospital	**Study inclusion and consent**										Balgrist University Hospital			
	Consenting	X												
	Enrolment	X												
	Patient inclusion by PI		X											
	Imaging													
	X-ray thorax	X							X					
	X-ray skull, abdomen								X					
	Stereotactic cranial CT			2 X										
	Diagnostic MRI (3T)	X												
	Perisurgical examinations													
	Surgical examination (incl. wound check)	X		X	X	X	X	X				X	X	X
	Anaesthesiologic examination		X	X			X	X						
	Neuropsychological assessment	X												X
	Psychiatric assessment	X												X
	Surgical procedures													
	DBS lead implantation			X										
	Implantation of IPG or explantation of DBS lead			X (externalization may be skipped and IPG implanted at visit 3)										
	Education in handling of patient programming device								X					
	Electrophysiological assessments													
	EMG	X		X								X	X	X
	Microelectrode recording			X										
	Nerve conduction	X												X
	Non-invasive EEG	X		X	X	X								X
	MEP, SSEP	X		X	X	X								X
	LFP, DBS-EP			X	X	X								
Balgrist University Hospital	**Clinical assessments**													
	AIS	X	X			X			X			X	X	X
	WISCI II	X	X			X			X			X	X	X
	SCIM III	X	X			X			X			X	X	X
	TUG	X	X			X			X			X	X	X
	Kinematic assessments	X	X			X			X			X	X	X
	6MWT	X	X			X			X			X	X	X**
	10MWT	X	X			X			X			X	X	X
	AE assessment		X	X	X	X	X	X	X			X	X	X
	Questionnaires: QoL, FSFI, IIEF, ESS, FSS, EPAF, SCIPI	X										X	X	X
	Questionnaire: MAS	X	X			X						X	X	X
	LUT assessments (Bladder diary, QUALIVEEN, urodynamics, bladder/renal ultrasound)	X												X
	GRASSP	X												X

*If impulse generator (IPG) is implanted at visit 3, visit 6 and visit 7 will be skipped. **Primary endpoint. DBS = deep brain stimulation. IPG = impulse generator. CT = computed tomography. MRI = magnetic resonance imaging. 3T = 3 Tesla. EMG = electromyography. EEG = electroencephalography. LFP = local field potentials. MEP = motor evoked potentials. SSEP = somatosensory evoked potentials. DBS-EP = DBS-evoked potentials. QoL = quality of life. FSFI = Female Sexual Function Index. IIEF = International Index of Erectile Function. ESS = Epworth Sleepiness Scale. FSS = Fatigue Severity Scale. AE = adverse event. AIS = American Spinal Injury Association (ASIA) Impairment Scale. WISCI II = Walking Index of Spinal Cord Injury. SCIM III = Spinal Cord Independence Measure. TUG = Timed Up and Go test. 6MWT = 6 Minute Walking Test. 10MWT = 10 Meter Walking Test. EPAF = EMSCI (European Multicenter Study About Spinal Cord Injury) Pain Assessment Form. SCIPI = Spinal Cord Injury Pain Instrument. MAS = Modified Ashworth Scale. LUT = lower urinary tract function. GRASSP = Graded Redefined Assessment of Strength, Sensation and Prehension.

Sample size

Based on data on the 6MWT [48,82,83] published in the literature and our clinical experience we estimate a relative effect size of 30% improvement in the 6MWT 6 months after treatment start compared to performance at baseline to be clinically relevant. A sample size of five patients provides us with a power (1-β) of 80% (α = 0.05). Founded on previous experience in DBS of the MLR,[84,85] we judge that the selected sample size will provide acceptable clinical validity for the study objectives.

Statistical analysis

Considering the observational nature of this clinical trial, statistics will be restricted to descriptive statistics.

Trial status

The study has started recruiting patients in March 2017. To date, one patient has been successfully included on November 26, 2018. Another patient has been included on March 15, 2018, but withdrew consent prior to surgery (screening failure).

Patient and public involvement

Patients or the public were not and will not be involved in the design, conduct, reporting, or dissemination plans of this research.

ETHICS AND DISSEMINATION

The study was approved by the local institutional review board (IRB) of the Ethical Committee of the Canton of Zurich (case number BASEC 2016-01104) and Swissmedic (10000316) in January and March 2017. Protocol modifications have to be approved by the local IRB and communicated to trial registries. Before inclusion of a patient, the potential participant is

informed orally by the investigator, and all potential participants are additionally provided with a clear and comprehensive information sheet. Sufficient time is given to the potential participant to decide whether to participate or not. If potential participants agree to participate in the study, they are asked to sign a consent form at the moment of inclusion in the study. The data obtained in the course of the study is treated according to the local data protection law and is handled in strictest confidence. During the study, subjects are identified solely by an anonymized patient identifier. The findings of this trial will be submitted to a peer-reviewed journal and abstracts are presented at relevant national and international scientific conferences. The study was registered on ClinicalTrials.gov (NCT03053791) on February 15, 2017.

DISCUSSION

Encouraging results on behavioural effects of MLR-DBS in preclinical models of neurotrauma [16,30] have contributed to the initiation of this first in-man study, which is currently being carried out at the University Hospitals of Zurich. The primary aim of this study is to improve motor function and enable locomotion in wheelchair-bound, subchronic and chronic SCI patients with limited, non-functional ambulatory abilities with MLR-DBS, and to investigate the clinical feasibility and efficacy of MLR-DBS in humans. Ultimately, we aim at maximizing the long-term restitution of lost motor functions in patients with severe motor incomplete SCI. A first patient has been included and implanted successfully, followed by intensive locomotor training with suprathreshold MLR-DBS.

The most important lesson learnt from our previous experience in the treatment of this patient is that MLR-DBS is safe, feasible and well tolerated. No increase in pain, deterioration of residual motor or sensory functions, cognitive or emotional disturbances, increase in spasticity and no incontinence was observed. However, sufficient time has to be allocated to the identification of optimal stimulation parameters for efficient training to ensue as reference values from human patients are not yet available. Optimal stimulation parameters will have to be determined for each patient individually, however, based on the existing literature and our experience gained from one patient wider pulses (>400 µs) seem to be more effective for enhancement of locomotion and more convenient than shorter pulse widths. LFP measurements and preliminary results from behavioural testing suggest that lower stimulation frequencies (8-20 Hz) are appropriate, which is in line with preclinical data.[86] Due to the heterogeneity and complexity of chronic spinal cord injury with individual therapeutic needs, standardization of rehabilitative training is challenging. While assessments performed during each patient's stay at the Balgrist University Hospital are standardized, rehabilitative training performed prior to study inclusion varies individually as we recruit patients internationally and include patients after completion of a rehabilitation program as we require a stable neurological baseline condition prior to electrode implantation. After we discharge our patients they train individually under our regular surveillance and constant activity monitoring to ensure a minimum training intensity of each patient. However, given that locomotion parameters like e.g. speed, stepping frequency and body weight support are highly dependent on stimulation parameters chosen and since parameters for locomotion induction vary depending on e.g. lesion size, training cannot be completely identical among study participants. This is therefore a limitation innate to this type of intervention. In addition, the patient's symptoms, especially the individual severity degree of muscle spasticity, have an influence on the feasible training intensity and potentially also on the effect of the stimulation. In this study, medications of each patient are recorded but modified only if required for medical reasons as we first need to

investigate the effect of stimulation as a single-therapy before being able to test combination therapies in follow-up studies.

Given that this proof-of-concept study is the first to investigate effects of DBS of the cuneiform nucleus, the sample size of this study was intentionally chosen to be small. However, our patients undergo a variety of clinically relevant assessments generating important knowledge for follow-up studies of a greater scale. With the 6 Minute Walking Test as primary outcome we have chosen a simple, internationally standardized and comparable test that can be performed anywhere without requiring sophisticated equipment. It measures the maximal distance covered while walking overground independently with a chosen walking aid for 6 minutes. This test is highly clinically relevant as one can also record the patient's functionality in everyday life and analyse its changes over time. We expect a significant increase in the distance walked within 6 minutes and a reduction in the need for assistance when walking 6 months post-implantation compared to baseline. Based on preclinical studies that have shown a positive effect of MLR-DBS on temporal execution of stepping movements we additionally expect an increase in maximal walking speed (10 Minute Walking Test), improved overall functional mobility (Time Up and Go Test), more efficient step cycle initiation and implementation (kinematic assessments), and increased overall physical activity (activity counts). As reports on improvements of lower urinary tract function in response to locomotor training are increasing,[87,88] we are additionally measuring a variety of indicators for lower urinary tract function, where we expect changes in efficiency of bladder emptying. The variety of clinical scores generate non-parametric data and are obtained to identify and monitor side effects (e.g. pain) rather than to statistically analyse therapeutic effects. All assessments performed in this study comprise standard tests applied internationally in SCI research that enable us to capture the variety of consequences of an injury to the spinal cord, e.g. sensori-motor disturbances, autonomic nervous system dysfunction, and decreased quality of life.

A particular challenge remains trajectory planning and lead implantation. Many regions of the brainstem, including the MLR subnuclei, are small and poorly described in humans when compared to the rodent PPN and CNF.[23,28,29] Coordinates known from DBS of the PPN with successful reduction of freezing of gait symptoms in patients with Parkinson's disease [24–27] can be adapted based on landmarks in human and rodent stereotactic atlases in order to localize the CNF in relation to the PPN. However, to increase the accuracy of planned trajectories and intraoperative targeting, a more detailed description of the macro- and microanatomy of the human MLR is urgently needed.

Another important step in trial design and treatment development is patient selection. In both rodents [16,46,89] and humans,[45] the reticulospinal system is crucial for functional recovery after SCI, and at least a small number of reticulospinal fibres needs to be preserved in order to reactivate lumbar CPGs via MLR-DBS. Thus, patients who have suffered an anatomically

complete SCI are not envisioned eligible for MLR-DBS. Fortunately, the majority of SCIs are anatomically incomplete,[4] and reticulospinal fibres are likely to be at least partially spared after SCI in humans [44] due to their scattered projection pattern in the spinal cord white matter.[42,43] Based on preclinical data and experience gained from the first study participant we suggest that patients with an incomplete SCI and residual proprioceptive function, who are able to stand, but suffer from deficient stepping initiation and walking function are most likely to benefit from MLR-DBS-enabled and -enhanced training. To allow for an integration of the effects of MLR-DBS into the anatomically still plastic spinal system during early phases after spinal cord injury, we are currently adapting the original study protocol so that patients can be included as early as 3 months after injury provided a stable neurological condition for the detection of stimulation-induced effects. Stratification of patients will be based on the expected outcome of walking function predicted by the 6MWT. Patient recruitment and screening are currently ongoing.

Our preliminary results from one study patient show that MLR-DBS is feasible and safe. The efficacy of MLR-DBS to enhance training and promote functional recovery in human SCI patients can now be tested in an appropriate number of individuals.

Acknowledgments

We thank our patient for her courage and enthusiasm to participate in this study, and Medtronic, Minneapolis, MN, USA, who provide the implants required. We also thank all collaborators involved in the study who have agreed to provide treatment and assessments as in-kind contribution of the Departments of Neurosurgery, Neurology, Neuroradiology, Anaesthesiology and Psychiatry of the University Hospital Zurich, the Spinal Cord Injury Center of the Balgrist University Hospital, the Institute for Regenerative Medicine of the University of Zurich, and the Swiss Federal Institute of Technology Zurich. The study has been presented at the "European Society for Stereotactic and Functional Neurosurgery (ESSFN) Meeting" 2018 in Edinburgh, Scotland, and the "EANS Trauma & Critical Care Update meeting" 2018 in Lund, Sweden.

Authors' contributions

LHS and ASH contributed equally to the manuscript and are joint first authors. MES, LR, and ACu are joint senior authors. LHS, ASH, MB, CRB, LI, LR, MES, and ACu designed the study, created and refined the study protocol, and supervise the study. LHS, MFO, ASH, and LR perform surgeries. MB, LF, RW, ACa, CM, and ACu designed assessments of motor function and perform testing and analysis. MS, MH, CRB, and LI designed and conduct electrophysiological measurements. TMK conceptualized and performs assessments of lower urinary tract function. IK and AP assist with study coordination and conduct questionnaire-based assessments. All authors are involved in the development and implementation of the study as well as in data collection and analysis. ASH and LHS designed the figures and drafted the manuscript. All authors critically revised the manuscript and approved its final version.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Implanted hardware (electrodes, impulse generators, extension wires, and patient programming devices) including replacements for a period of 10 years after implantation in case of e.g. battery depletion is provided by Medtronic, Minneapolis, MN, USA, for five patients free of charge. Beyond that, we do not receive any financial support by Medtronic. The study is financed by the Department of Neurosurgery, University Hospital Zurich, the Spinal Cord Injury Center, Balgrist University Hospital, and the Department of Neurology, University Hospital Zurich.

Competing interests

The authors declare that they have no competing interests.

Patient consent for publication

Written informed consent for publication of clinical details and/or clinical images was obtained from the patient. A copy of the consent form is available for review by the editor of this journal.

Ethics approval

Ethical approval has been obtained from the Ethical Committee of the Canton of Zurich (case number BASEC 2016-01104) and Swissmedic (10000316). Protocol modifications have to be approved by the local Ethical Committee of the Canton of Zurich and communicated to trial registries.

FIGURE LEGENDS

Figure 1 - Schematic illustration of the reticulospinal system. (A) Higher central nervous system centres of motion control send their signals to the mesencephalic locomotor region (MLR). The MLR is bilaterally linked to its downstream target, the gigantocellular reticular nucleus (NRG), which gives rise to the reticulospinal tract and drives the central pattern generators (CPG) for motoneuron activation and locomotion. (B-C) Horizontal section of the human (B) and cross section of the rat (C) midbrain at the level of the superior colliculi depicting the MLR (B – landmarks based on Afshar et al.[90]; C – landmarks based on Paxinos et al.[91]). CNF = cuneiform nucleus. PPN = pedunculopontine nucleus.

Figure 2 - Schematic illustration of MLR-DBS. (A) After incomplete SCI, spared fibres of the reticulospinal tract are not sufficient to properly convey motor signals to sublesional locomotor circuits (CPG). The CPGs are thus deprived of their central input. However, these local rhythm generators remain intact. (B) MLR-DBS can recruit spared fibres of the reticulospinal tract system, enabling them to reactivate sublesional motor circuits. (C) Summary. MLR = mesencephalic locomotor region. NRG = gigantocellular reticular nucleus. SCI = spinal cord injury. CPG = central pattern generators. DBS = deep brain stimulation. (A-B) was modified from Hofer and Schwab, Curr Opin Neurol, 2019 [3], with permission.

Figure 3 – Study timeline. Patients with a motor incomplete SCI at the level of T10 or above and at least 6 months of recovery after injury are eligible to undergo screening for study participation. Incomplete SCI is confirmed based on clinical examinations, magnetic resonance imaging, and electrophysiological measurements. 1-3 months after study enrolment, baseline testing is performed, followed by unilateral electrode implantation at the less severely affected side 1-10 days later. During surgery, the surgeon decides whether lead and impulse generator (IPG) will be implanted during one session, or whether the lead will be temporarily externalized, depending on intraoperative testing results. In case of lead externalisation, an evaluation period ensues where the patient's responsiveness to MLR-DBS and potential negative side effects are assessed. In case of unsatisfactory results or withdrawal of consent, the lead is removed, and the patient is registered as a study dropout. In case of satisfactory testing, the lead is internalized and the IPG is implanted. After complete implantation, follow-up testing ensues at 2 weeks, 1 month, 3 months and 6 months, respectively. Patients will be discharged from hospital after 2-3 weeks of training (TR) and testing. After hospital discharge, patients will undergo rehabilitative training with DBS at settings predefined during the first 2 weeks after implantation. SCI = spinal cord injury. mo = month(s). d = day(s). wks = weeks. FU = follow-up. TR = training. DBS = deep brain stimulation.

Figure 4 – Target area definition and electrode positioning. The MLR can be targeted by aiming anterior to the inferior colliculi (IC), lateral of the periaqueductal grey (PAG), and slightly posterior to the central tegmental tract (CTT).[90,92] (A) Coronal, (B) axial, and (C) sagittal view of the mesencephalon of the first patient successfully included in the DBS-SCI trial, showing the localization of the implanted lead (red dot in light grey area). S = superior. I = inferior. L = left. R = right. A = anterior. P = posterior.

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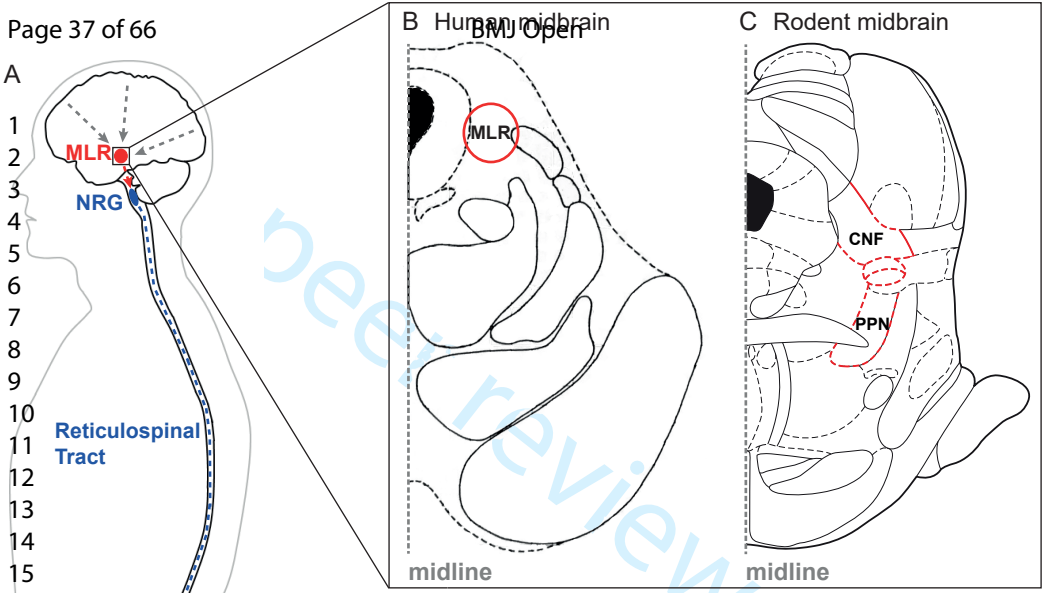

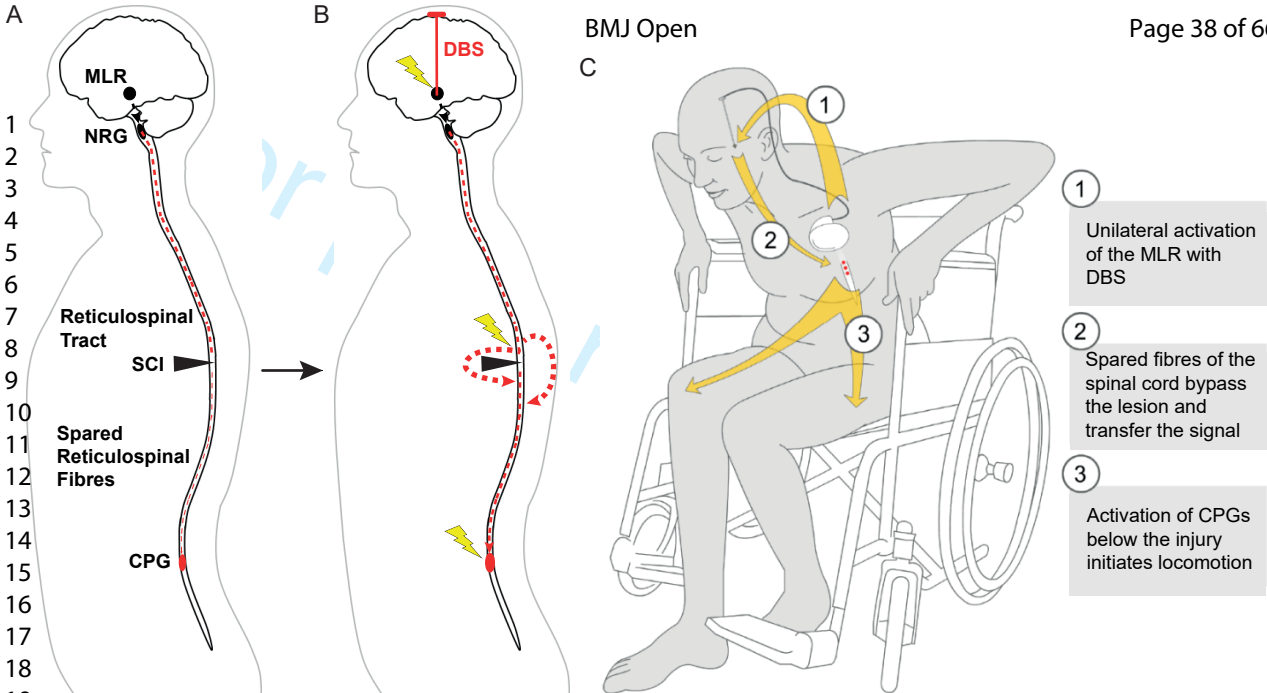

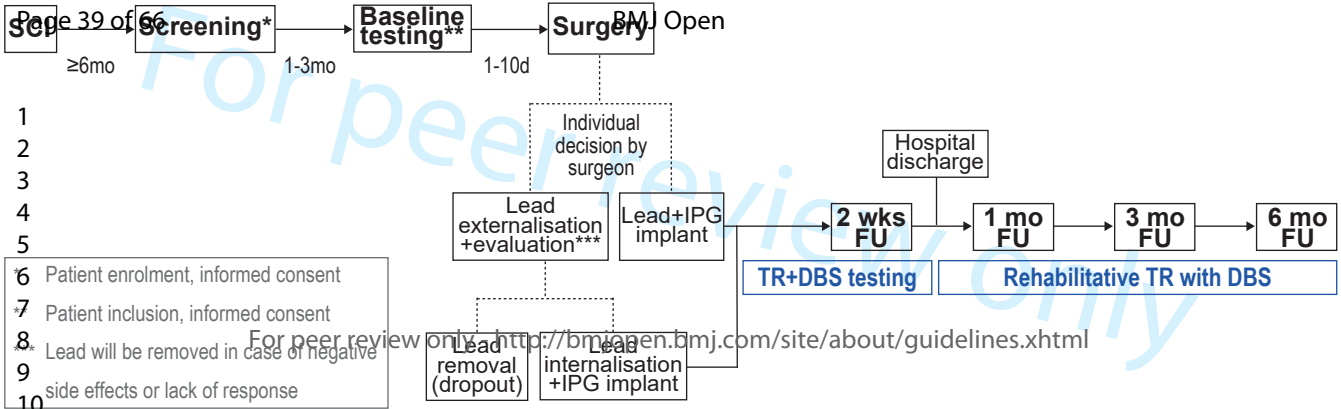

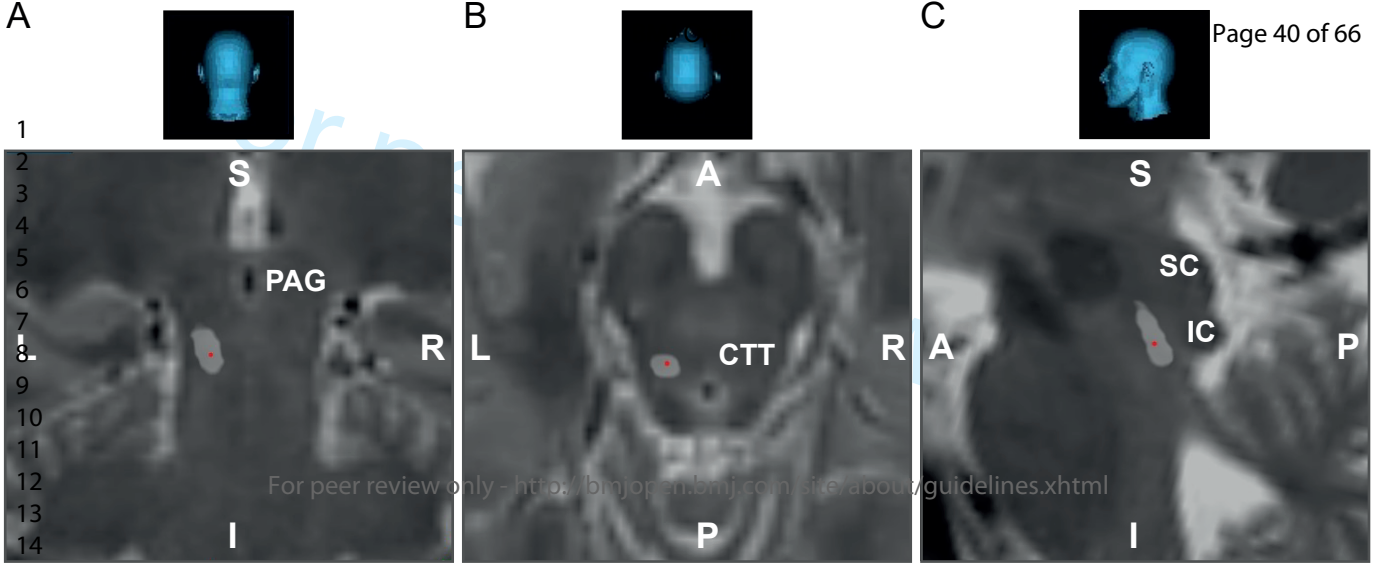

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym *A phase I/II open-label multicenter trial to evaluate safety and preliminary efficacy of unilateral deep brain stimulation of the mesencephalic locomotor region in patients with incomplete spinal cord injury (DBS-SCI).* *See ClinicalTrials.gov and full study protocol for original study title, manuscript title is found on manuscript page 1.*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry *Registered on clinicaltrials.gov (NCT03053791, DBS-SCI).* *See manuscript pages 1 and 19.*
	2b	All items from the World Health Organization Trial Registration Data Set *See ClinicalTrials registry and full study protocol.*
Protocol version	3	Date and version identifier *Latest approved (Ethical Committee of the Canton of Zurich) study version: version 5, 12.09.2019.* *See ClinicalTrials.gov and full study protocol.* *See manuscript page 18 for initial study approval.*

Funding	4	Sources and types of financial, material, and other support

Implanted hardware (electrodes, impulse generators, extension wires, and patient programming devices) including replacements for a period of 10 years after implantation in case of e.g. battery depletion is provided by Medtronic, Minneapolis, MN, USA, for five patients free of charge. Beyond that, we do not receive any financial support by Medtronic. The study is financed by the Department of Neurosurgery, University Hospital Zurich, the Spinal Cord Injury Center, Balgrist University Hospital, and the Department of Neurology, University Hospital Zurich. No specific research grant has been declared for this study. The funding sources had no influence on the design of this study and the writing of this manuscript, and will not have any influence on study execution, data analysis, data interpretation, or decision to publish results.

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LHS, ASH, MB, CRB, LI, LR, MES, and ACu designed the study, created and refined the study protocol, and supervise the study. LHS, MFO, ASH, and LR perform surgeries. MB, LF, RW, ACa, CM, and ACu designed assessments of motor function and perform testing and analysis. MS, MH, CRB, and LI designed and conduct electrophysiological measurements. TMK conceptualized and performs assessments of lower urinary tract function. IK and AP assist with study coordination and conduct questionnaire-based assessments. All authors are involved in the development and implementation of the study as well as in data collection and analysis.

See manuscript page 23.

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See ClinicalTrials.gov and full study protocol.

5c Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities

The funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. The authors have no competing interests to declare.

See manuscript page 23.

5d Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

N/A

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention

Briefly: A spinal cord injury (SCI) is a devastating event with an immediate impact on an individual's health and quality of life. Even though most spinal cord injuries are clinically incomplete, major neurological and functional recovery plateaus after three to four months after injury despite intensive rehabilitative training. To enhance training efficacy and improve long-term outcomes, the combination of rehabilitation with electrical modulation of CNS targets, e.g. electrical spinal cord stimulation or deep brain stimulation, has aroused scientific interest in recent years with some encouraging results. In deep brain stimulation (DBS) the mesencephalic locomotor region (MLR), an evolutionarily conserved brainstem locomotor command center that controls the initiation and maintenance of locomotion, is considered a promising target. Animal experiments have shown that MLR-DBS can acutely induce swimming and walking in rats with spinal white matter destructions of >85%. Promising pre-clinical data and the minimally-invasive nature of DBS have led to the initiation of this study to investigate the therapeutic potential of MLR-DBS to improve recovery of gait in a small cohort of patients.

See manuscript pages 2 and 4-5.

	6b	Explanation for choice of comparators

The study comprises no comparators, performance will be compared between different timepoints. The presence of an SCI will be documented by neuroimaging and the risk of paraplegia resulting from other origins can be excluded. Therefore, a mere placebo-effect resulting in improvement of the ability to walk is extremely unlikely. A control group undergoing sham-surgeries is not necessary at this early stage of research on this topic.

See manuscript page 6.

Objectives	7	Specific objectives or hypotheses *We hypothesize that MLR-DBS can modulate spared fibers of the reticulospinal tract system that bypass the site of injury and reintegrate quiescent sublesional circuits into a functional network that supports walking. We propose that enhancing excitability of sublesional spinal motor circuits increases training efficacy and promotes recovery of motor function in patients with incomplete, subchronic and chronic SCI.* *See manuscript pages 5 and 20.*
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) *Briefly: The DBS-SCI trial is a prospective one-armed multi-centre study. The trial is considered successful if the patient's performance in the 6 minutes walking test (6MWT, primary outcome measure) 6 months after treatment start is at least 30% better compared to performance at baseline.* *See manuscript pages 2 and 6.*

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained *Briefly: The trial is conducted and data are collected at two sites in Zurich, Switzerland: the University Hospital Zurich (Departments of Neurosurgery and Neurology, both specialized in deep brain stimulation), and the Spinal Cord Injury Center of the Balgrist University Hospital (specialized in the management of acute and chronic SCI including neurorehabilitation). The study is open to national and international patients, however, basic understanding of German or English is required.* *See manuscript page 6 and 20.*

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)

Addressed in "Inclusion and exclusion criteria" section of manuscript.

Inclusion criteria:

- *Informed consent*
- *Participation in two assessment sessions before enrolment*
- *Willingness and ability to comply with the protocol and to attend all required study training and visits*
- *Female or male*
- *Age 18-75*
- *Motor incomplete SCI*
- *Level of lesion at or above T10, based on AIS level, preservation of sacral function*
- *Focal spinal cord disorder caused by either trauma or non-traumatic and non-progressive condition*
- *Minimum 6 months of recovery after SCI*
- *Completed in-patient rehabilitation program*
- *WISCI II, level >2 (0-20 items): assistance of one or more persons. Ability to walk at least 10 meters*
- *Stable medical and physical condition*
- *Adequate care-giver support and access to appropriate medical care in patient's home community*

Exclusion criteria:

- *Enrolment of the investigator, her/his family members, employees and other dependent persons*
- *Limitation of standing and walking function based on accompanying (CNS) disorders*
- *Cardiovascular disorders*
- *Implanted technical devices*
- *Significant autonomic dysreflexia*
- *Cognitive disorders/brain damage*
- *Drug refractory epilepsy*
- *Severe joint contractures disabling or restricting lower limb movements*
- *Haematological disorders with increased risk of bleeding*
- *Participation in another study with investigational drug within 30 days preceding and during the present study*
- *Congenital or acquired lower limb abnormalities*
- *Women who are pregnant or breast feeding or planning a pregnancy during the course of the study*
- *Lack of safe contraception*
- *Inability to follow the procedures of the study*
- *Known or suspected non-compliance, drug or alcohol abuse*
- *Current or prior malignancy*

See manuscript pages 6-7.

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered *Interventions and assessments are described in detail in study protocol.* *Briefly:* *Intervention model: single group assignment (single group of patients with incomplete SCI), single armed study, all patients receive treatment.* *Procedure:* • *Implantation of a deep brain stimulation system (electrodes into the mesencephalic locomotor region and Medtronic Activa SC impulse generator into pectoral or abdominal region).* • *Deep brain stimulation of mesencephalic locomotor region during rehabilitative training with regular follow-ups until 6 months after implantation.* See manuscript pages 6, 8-15, Table 2, Table 3, Figure 3.

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)

Should a subject's participation in the investigation be discontinued, the reason for discontinuation, e.g. safety concerns, must be documented in the source documents. The Sponsor may terminate the study prematurely according to certain circumstances, for example: ethical concerns, insufficient participant recruitment, when the safety of the participants is doubtful or at risk, alterations in accepted clinical practice that make the continuation of a clinical trial unwise, or early evidence of benefit or harm of the experimental intervention. Participants may withdraw from participation at any time without need to give reasons. If the patient wishes so, the implanted DBS system will be surgically removed. The procedure will not be charged from the patient or his health insurance. The Investigator may decide to withdraw a subject from the investigation at any time. The investigators must make every effort to contact the subject to ascertain the reason for missed appointments if a subject does not return for follow-up assessments. Correspondence with the subject is necessary for regular withdrawal from pending follow-up.

The Study Protocol, Case Report Forms, Informed Consent form and other patient information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Any change affecting the subject requires that the subject is informed about the change(s). An updated signed and dated informed consent shall be obtained from the investigator and the study participant, no later than during the subject's next follow-up visit under the scope of this investigation.

See original study protocol and manuscript pages 6, 18-19, and 35.

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)

Initially, all participants are informed in detail about the study, its background and goals, the importance of training intensity, and the importance of adherence to the study plan. At follow-ups, feedback sessions are performed and experience between participants and investigators is exchanged. Regular correspondence with the subjects additionally ensures adherence to intervention protocols. Subjects are asked to document their daily activities and training sessions, which is regularly reported to the investigators in order to monitor training frequency and intensity (in case of home training or training in an external rehab center). In addition, physical activity during training and daily life is monitored by wireless sensors mounted to the patient's wrists, ankles and wheelchair, and data are regularly transferred via SSL-encrypted links (https) established between sites (e.g. a patient's home or rehab centre) and the Swiss Federal Institute of Technology Zurich (ETH).

See original study protocol and manuscript pages 6, 14, 20.

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Prior to surgery, all medication that has blood-thinning effect (effect on blood coagulation or platelet function, e.g. Aspirin, Plavix, Marcoumar, Valproic acid, Gingko) is prohibited. The patients are informed by the surgeon prior to surgery about these medications and how they should be discontinued. If there is an indication for continuous intake of an anticoagulant or antiplatelet drug, the patient has to be excluded from the study. Patients with implanted technical devices, e.g. cardiac pacemakers, are not eligible for study participation.

See original study protocol and manuscript pages 6-7 and 11.

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended *Briefly, the primary outcome measure for improvement of ambulation in this study is the gain of covered distance in the 6 minutes walking test (6MWT) at 6 months post implantation compared to baseline level. Additionally, a variety of quantitative and qualitative secondary outcome measures are performed, e.g. kinematic assessments, electrophysiological measurements and questionnaire-based assessments.* *See manuscript pages 6, 15, Table 2, Table 3, and Figure 3.*
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) *Briefly, patients with a motor incomplete SCI at the level of T10 or above and at least 6 months of recovery after injury are eligible to undergo screening for study participation. 1-3 months after study enrolment, baseline testing is performed, followed by unilateral electrode implantation at the less severely affected side 1-10 days later (with or without temporary lead externalisation). After complete implantation, follow-up testing ensues at 2 weeks, 1 month, 3 months and 6 months, respectively. Patients will be discharged from hospital after 2-3 weeks of training (TR) and testing. After hospital discharge, patients will undergo rehabilitative training with DBS. See Figure 3 of manuscript.* *See manuscript pages 6, Table 3, and Figure 3.*

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Briefly, we aim to include 5 patients in the study who have to complete all preoperative and postoperative examinations until 6 months after surgery, resulting in a total of 11 timepoints. In case of withdrawal of participation or arising complications (dropouts and incomplete follow-up), we aim to include two more patients (replacement of dropouts/withdrawal). The number of subjects is based on the aim of gaining information on treatment effectiveness with adequate safety. Preliminary studies of PPN stimulation in patients with gait disturbance and falls due to Parkinson's disease have been analyzed in a retrospective review by Morita et al., 2014. Sample sizes ranged from 1 to 14 in 12 publications. We estimate a relative effect size of 30% improvement in the 6MWT 6 months after treatment start compared to performance at baseline to be clinically relevant. A sample size of five patients provides us with a power (1-β) of 80% (α = 0.05). We judge that the selected sample size, based on previous experience in deep brain stimulation of the MLR, will provide acceptable clinical validity for the study objectives.

See manuscript pages 6, 18, 21.

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

In summary, all candidate patients, namely patients able to stand with or without walking aid and with a stable neurological condition, are screened and have to meet all of the inclusion and none of the exclusion criteria. Subjects will undergo preoperative examinations (e.g. MRI scans of the head and spine, neuropsychological, psychiatric and sleep status assessments etc.) according to our standard protocols of DBS for movement disorders, based on certification criteria of highly-specialized-medical DBS centers in Switzerland. Neurological assessments for SCI related impairment as defined by the study protocol are performed at the Spinal Cord Injury Center of Balgrist University Hospital. The subject population enrolled in this investigation will be comprised of male and female patients from our out-patient clinic at Balgrist University Hospital or from international volunteers actively contacting the investigators based on information obtained from study registries. Patients who do not meet all in- and exclusion criteria are not eligible to participate in this investigation. There will be no specific gender distribution as gender specific differences concerning efficacy and safety of the investigational diagnostic process are not to be expected.
See manuscript pages 6-7.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
		N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
		N/A

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions *N/A*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how *N/A*
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial *N/A*

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

Addressed in "Study design", "Clinical assessments", and "Electrophysiological assessments" sections, and Table 2 and Table 3 of manuscript.

The primary outcome measure (6-minute walking test) is an internationally recognized test to assess walking capacity in spinal cord injured patients, widely used in clinical trials and clinical routine. During the 6MWT, the patient is accompanied by an experienced investigator (physiotherapist).

Using a variety of standardized, well-known and widely used quantitative, qualitative and questionnaire-based methods as secondary outcome measures, the study additionally collects a big data set on motor, sensory, autonomic function and quality of life. For example, the WISCI (Walking Index for Spinal Cord Injury) is frequently used in clinical trials to assess walking function on an ordinal scale, and it captures the extent and nature of assistance a person with SCI requires to walk. To address the burden of neurogenic lower urinary tract dysfunction on patient's quality of life after SCI and to analyse the effect of MLR-DBS on recovery of lower urinary tract function, a combination of qualitative (bladder diary, validated questionnaire Qualiveen) and quantitative assessments (urodynamic measurements, renal ultrasound) of bladder function are applied in accordance to the European Association of Urology (EAU) Guidelines on Neuro-Urology.

See manuscript pages 6, 9-15, Table 2, Table 3.

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Regular correspondence with the subjects in addition to regular follow-ups promotes retention and adherence to intervention protocols. Patients who prematurely withdraw from the study will be offered complete removal of all implanted material. In case of complete implant removal, the patients will receive a short-term follow-up after 4 to 6 weeks by the surgeon to assess wound-healing and outcome of surgery. Afterwards, the clinical follow-up for SCI will be performed at the Balgrist University Hospital according to clinical standards. In case the patient withdraws from the study but refuses removal of the implants, clinical follow-up will be performed as well at the Department of Neurosurgery, University Hospital of Zurich, and at the Balgrist University Hospital according to clinical standards. In case of withdrawal, the patient's study related data will remain in the study.
See original study protocol and manuscript page 6, 14-15, 20, and 35.

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Data management system: All data will be entered in a case report form (CRF). Every patient will receive an anonymized and unique patient identifier. The investigator will compile a confidential list, which relates these patient numbers to the patient's full name. This list will only be accessible to the study team and the monitor. Original patient files may be viewed by monitors, auditors and inspectors. Overall, the PI is responsible for data handling. The PI and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies. Investigational data shall be analyzed by the PI and may be transferred to a location outside of Switzerland and/or any other regulatory authority. All data from the CRFs will be transferred to an electronic database by the study coordinator at USZ. All paper CRFs and other documents will be scanned and stored as PDF files. Data transfer will be overseen and double-checked by the PI personally to prevent copy failures.

Data security, access and backup: According to corresponding national laws the patient must declare in writing that he or she agrees to the recording of his or her medical data, respectively, and if necessary, the reporting to national health authorities. The CRF and submitted source data are archived by the data owner (PI) for at least 15 years as required by national law. The investigator keeps originals of all source data and an original dated and signed duplicate of the patient consent form of each patient together with other essential study documents at the study center in accordance with the national law. The electronic database and scans of paper CRFs and documents will serve as backup and vice versa.

Electronic and central data validation: The investigator confirms with his or her signature on the CRF that all statements and data are complete and correct. All incoming CRF are checked for plausibility and completeness. If necessary, the investigator/study nurse will add missing data or correct inconsistent statements. Any change or correction to data reported on a CRF shall be tracked. Source documents shall be created and maintained by the investigation site team throughout the clinical investigation. The data reported on the CRFs shall be derived from, and be consistent with, these source documents, and any discrepancies shall be explained in writing.

See original study protocol.

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol *Statistics will be restricted to descriptive statistics. The trial is considered successful if the patient's performance in the 6MWT has improved by at least 30% at 6 months after treatment start compared to baseline (two-samples t-test).* *See manuscript page 18.*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) *N/A*
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) *N/A*

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed *Monitoring visits at the investigator's site prior to the start and during the course of the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors at an early time point. The Sponsor-Investigator organizes professional independent monitoring for the study. All original data including all patient files, progress notes and copies of laboratory and medical test results will be available for monitoring. The monitor will review all or a part of the CRF/eCRFs and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents. The investigator's site will collaborate with the Clinical Trials Center (CTC) of the University Hospital Zurich to ensure monitoring. A study specific monitoring plan, developed according to the CTC's SOP on monitoring activities, regulates extent, frequency and nature of monitoring activities.* *A quality assurance audit/inspection of this study may be conducted by the cantonal ethical committee (CEC) and by Swissmedic. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study. The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/documents and will answer any questions arising. All involved parties will keep the patient data strictly confidential.* *See original study protocol.*
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial *N/A. The regulatory authorities receive an annual safety and interim report.*

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct *Every abnormal finding that appears for the first time or worsens during the course of the study will be recorded on the CRF and reported as adverse event. Adverse events (e.g. wound infections) will be interrogated for at each contact between the responsible investigator and the study subject. All pathological and clinically relevant findings in physical and neurological examinations, vital signs, clinical chemistry, hematology, and during surgery will be documented as adverse events. Complications related to assessments (e.g. falls during walking tests) will be reported as adverse events.* *See original study protocol.*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor *A quality assurance audit of this study may be conducted by the cantonal ethical committee and by Swissmedic. The quality assurance auditor will be independent from the investigators and sponsor, and have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study. The investigator will grant the auditor access to the source data/documents and will answer any questions arising during the audit. All involved parties will keep patient data strictly confidential.* *See original study protocol.*

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval *Ethical approval has already been obtained from the Ethical Committee of the Canton of Zurich (case number BASEC 2016-01104) and Swissmedic (10000316) in 2017. Latest approved protocol version: version 5, 12.09.2019.* *See manuscript pages 2, 18-29, 24.*
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) *Amendments are sent to and evaluated by the Cantonal Ethical Committee and Swissmedic. Substantial amendments are only implemented after approval by the Cantonal Ethical Committee and Swissmedic, respectively. Any change affecting the study participants requires that the subject is informed about the change(s). An updated signed and dated informed consent will be obtained from the subject by the investigator, no later than during the subject's next follow-up visit under the scope of this investigation.* *As addressed in the "Discussion" section of the manuscript, an amendment to the study protocol is currently being written in order to include patients already 3 months after injury (instead of 6).* *See manuscript pages 18-19, and 22.*

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) *Before inclusion of a patient, the potential participant is informed by the investigator about the nature and purpose of the trial, the procedures involved, expected duration, potential risks and benefits, and any discomfort that might occur. Each participant will be informed that the participation is voluntary and that he/she may withdraw consent from the study at any time. Withdrawal of consent will not affect the patient's subsequent medical assistance and treatment. The participant is informed that his/her medical records may be examined by authorized individuals other than their treating physician. All participants are provided with a participant information sheet and a consent form describing the study and providing sufficient information for patients to make an informed decision about their participation in the study. Sufficient time will be given to the participant to decide whether to participate or not. Depending on the date of screening, the time frame is 20-80 days before hospitalization.* *The patient information sheet and the consent form have been reviewed and approved by the Cantonal Ethical Committee and Swissmedic. The formal consent of a participant is obtained before the participant undergoes any study procedure. The participant has to read and consider the statement before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is also signed and dated by the investigator (or his designee), and will be retained as part of the study records.* *See original study protocol and manuscript pages 18-19.*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable *N/A*

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial *All data will be entered in a database as recorded in the CRF and every patient will receive an anonymized and unique patient identifier. The investigator will compile a confidential list, which relates these patient numbers to the patient's personal information. This separately stored list will only be accessible to the study team and the monitor. Original patient files may be viewed by monitors, auditors and inspectors.* *See original study protocol.*
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site *The authors have no conflicts of interest to declare. Investigators and collaborators receive no financial or other compensation for work rendered in accordance with the study, despite their regular income from their respective affiliations.* *See manuscript page 23.*
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators *After termination of the study, study data will be available for analysis only for persons or institutes assigned by the PI, according to local regulations. Direct access to source documents will be permitted for* purposes of monitoring, audits and inspections. *The PI maintains all essential clinical investigation documents from prior, during and after the clinical investigation on file at the site. Originals of all study-related report forms, administrative documents, medical records, and a list allowing patient identification will be stored in the study headquarters University Hospital Zurich and Balgrist University Hospital for at least 15 years after completion of the trial.* *See original study protocol.*

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	*Any damage developed in relation to study participation is covered by the study's insurance. So as not to forfeit their insurance cover, the participants themselves must strictly follow the instructions of the study personnel. Participants must not be involved in any other medical treatment without permission of the PI (emergency excluded). Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly in the event of health problems or other injuries sustained during or after the course of study. The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential. The patient and his health insurance will not be charged for screening, treatment and follow-up (until 6 months after surgery), but there will be no compensation for participation in the study. Clinical examinations and treatments after completion of the 6 months' follow-up will be charged from the patient´s health insurance.* *See original study protocol*.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	*The findings of this trial will be submitted to a peer-reviewed journal and abstracts are presented at relevant national and international conferences. Results will be communicated to participants in layman's terms.* *See manuscript pages 2 and 19.*

	31b	Authorship eligibility guidelines and any intended use of professional writers *Publication(s) and/or presentation(s) of the study results is encouraged. Neither the sponsor nor the investigators have the right to prevent publication, except for patent or copyright reasons. Staff members who gave relevant scientific support to the study design, conductance and/or analysis of results will be included as coauthors, if applicable. A copy of all publications will be sent to the coauthors. The PI will decide about authorship and the sequence of co-authors, including the last author, based on the amount and importance of the contribution to the study as judged by the PI. No professional writers will be used.* *See original study protocol.*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code *N/A*
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates *Please see Appendix 1.*
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable *N/A*

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Appendix 1 - Model consent form

Universität Zürich[UZH] | UniversitätsSpital Zürich | ETH zürich | Der Balgrist

Informed consent for participation in a clinical study

- Please read this document carefully
- Please ask in case of questions or further interest.

Study identifier: (of the local ethics committee)	BASEC 2016_01104
Study title:	Deep Brain Stimulation in patients with incomplete spinal cord injury for improvement of gait Tiefe Hirnstimulation zur Verbesserung des Gehens bei Patienten mit Rückenmarksverletzungen
Responsible institution (Sponsor) (complete address):	Neurochirurgische Klinik, UniversitätsSpital Zürich, Frauenklinikstrasse 10, CH-8091 Zürich
Study site:	UniversitätsSpital Zürich and Uniklinik Balgrist Zürich
Principal investigator: Name, First name:	Lennart Stieglitz MD, Chief of service, Specialist for Neuromodulation Armin Curt MD, Chairman Center for Paraplegia
Participant: Name and first name, date of birth	☐ female ☐ male

- I was informed in detail orally as well as in written form about the purpose, the conduction, about expected effects, possible side-effects, risks and benefits of the study by the signing surgeon.
- My questions concerning my participation in the study were answered satisfyingly. I received the study information of 07.06.2019 Version 2 (two parts) and receive a copy of this informed consent form. I accept the content of the above mentioned study information.
- I participate in this study voluntarily. I can withdraw from participation at any time and will not suffer disadvantages concerning my ongoing medical treatment hence.
- I was informed about other possible treatment options.
- I was given enough time to decide about my participation.
- I was informed, that an insurance company will cover damages resulting from participation in the study, in case I can prove the connection clearly.
- I agree that my general practitioner is informed about my participation in the study: Yes ☐ No ☐.
- In case of incidental findings I want to a) ☐ be informed unconditionally; b) ☐ not informed or c) ☐ I want to leave the decision with the following person: .....
- I know, that my personal data may only be used in coded form for scientific purposes. I agree, that the responsible specialists of the initiator of the study and the local authorities (cantonal ethics committee) may be granted insight into the original data for control purposes, but only under strict compliance with confidentiality.
- I am aware, that the obligations mentioned in the study information are to be obliged during the study. The principal investigator may exclude me from the study at any time with my best interests in mind.

Place, date	Signature study participant

Confirmation of the investigator: Hereby I confirm that I informed the participant in detail about the character, importance and relevance of the study. I will fulfill all legal obligations in connection with this study. Should I learn of aspects that could affect the willingness of the participant to participate during the course of the study, I will inform him/her immediately.

Ort, Datum	Signature of the investigator