

The Dorsal Root Ganglion as a Novel Neuromodulatory Target to Evoke Strong and Reproducible Motor Responses in Chronic Motor Complete Spinal Cord Injury: A Case Series of Five Patients

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ABSTRACT

Objectives: Current strategies for motor recovery after spinal cord injury (SCI) aim to facilitate motor performance through modulation of afferent input to the spinal cord using epidural electrical stimulation (EES). The dorsal root ganglion (DRG) itself, the first relay station of these afferent inputs, has not yet been targeted for this purpose. The current study aimed to determine whether DRG stimulation can facilitate clinically relevant motor response in motor complete SCI.

Materials and Methods: Five patients with chronic motor complete SCI were implanted with DRG leads placed bilaterally on level L4 during five days. Based on personalized stimulation protocols, we aimed to evoke dynamic (phase 1) and isotonic (phase 2) motor responses in the bilateral quadriceps muscles. On days 1 and 5, EMG-measurements (root mean square [RMS] values) and clinical muscle force measurements (MRC scoring) were used to measure motor responses and their reproducibility.

Results: In all patients, DRG-stimulation evoked significant phase 1 and phase 2 motor responses with an MRC ≥ 4 for all upper leg muscles (rectus femoris, vastus lateralis, vastus medialis, and biceps femoris) ($p < 0.05$ and $p < 0.01$, respectively), leading to a knee extension movement strong enough to facilitate assisted weight bearing. No significant differences in RMS values were observed between days 1 and 5 of the study, indicating that motor responses were reproducible.

Conclusion: The current paper provides first evidence that bilateral L4 DRG stimulation can evoke reproducible motor responses in the upper leg, sufficient for assisted weight bearing in patients with chronic motor complete SCI. As such, a new target for SCI treatment has surfaced, using existing stimulation devices, making the technique directly clinically accessible.

Keywords: Motor dysfunction, neurostimulation, spinal cord injuries, spinal ganglia

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INTRODUCTION

Spinal cord injury (SCI) is one of the most devastating injuries to the human central nervous system, leading to a multitude of problems including loss of autonomic control, muscle atrophy, spasticity, and most prominently, sensory and motor impairments (1, 2). The motor impairments originate from a disconnection between descending pathways and spinal circuits caudal to the lesion, depriving the latter of synaptic input necessary for generation and control of motor responses (3).

One of the current experimental strategies aimed at motor recovery after SCI is epidural neuromodulation of the spinal cord, also known as (epidural) spinal cord stimulation ((e)SCS) or epidural electrical stimulation (EES) (4–8). Both in preclinical (9–11) and clinical experimental settings (4, 5, 12–14), EES in combination with rehabilitation was able to facilitate regain of (voluntary) motor control in motor incomplete and motor complete SCI. Although the exact circuit-level mechanisms responsible for these motor improvements remain to be elucidated, various studies suggest that EES facilitates motor performance through modulation of mostly afferent, dorsal pathways forwarding input to the spinal cord (3, 15, 16). It is thought that with the engagement of these dorsal spinal cord structures through EES in combination with locomotor training, sensory feedback is enhanced, which could form a new source of excitation of spinal circuits caudal to the lesion (3, 17). This claim is further supported by evidence from preclinical work, involving both genetic mutation models (3) and lesion models (9). For example, elimination of sensory input through a genetic mutation in a mouse model of SCI resulted in impairments of locomotor recovery (3). Similarly, in a rat model of SCI, unilateral deafferentation of the hindlimb resulted in serious impairment of EES-induced motor recovery on the deafferented side as compared to the nondeafferented side (9).

The dorsal root ganglion (DRG) harbors the first-order neurons of the sensory pathway and is as such responsible for a range of sensory processes, such as nociception (pain), mechanoreception (pressure) as well as proprioception (body spatial position) (18). The latter subtype of DRG neurons is associated with muscle spindles through which information about muscle contraction is transmitted to the central nervous system for proprioceptive processing (3, 17). These neurons exhibit the most widespread central projection pattern of all DRG sensory neurons and establish unique synaptic contacts with motor neurons and ventral interneurons involved in locomotor behavior such as extensor-flexor alternation regulation (19) and rhythm generation (3) as studied in murine models. Specifically, muscle spindle afferents are thought to be embedded in a so-called “selective central synaptic connectivity matrix,” (3) which facilitates the transfer of muscle-specific information either 1) directly to motor neurons through functionally distinct interneurons or 2) through mediation of reciprocal inhibition between motor neurons (20–22), resulting in recruitment of both monosynaptic and polysynaptic spinal reflex pathways. It is thought that the proprioceptive subtype of DRG neuron is therefore in a prime position to convey

direct excitation to these spinal circuits relevant to motor behavior, especially under conditions of disconnected descending input, as is the case in SCI (3).

Although the importance of the role of afferent input for motor recovery in SCI has been reported before, the DRG itself has not been targeted as a source of stimulation to evoke motor responses in patients with SCI as of yet. Apart from a preliminary study in rats and cats (23, 24), there has been no report in the literature of the potential ability of DRG stimulation to evoke motor responses, let alone in patients with SCI (see literature overview in Supporting Information S1). For chronic pain, however, DRG stimulation is already well known as a safe and effective treatment (25–28), with uniquely beneficial characteristics (28), including selectivity and subdermatomal specificity, physical lead stability, and anatomical accessibility.

In the case of SCI, the use of DRG stimulation would target responsible sensory neurons directly and at each spinal level individually, presenting with potential advantages such as spatial selectivity (28), which remains a challenging frontier for EES as used after SCI (4, 5, 12–14). In fact, with the DRGs anatomically separated at each level, DRG stimulation may improve spatial selectivity as compared to EES, as the stimulation is less likely to spread to other spinal levels, even at high stimulation amplitudes. Moreover, given the application of DRG stimulation in chronic pain (25–28), the necessary devices (pulse generators and leads) are directly clinically accessible once the necessary regulatory hurdles are passed. Therefore, exploring the potential of DRG stimulation to evoke motor responses after SCI would fill in a current lacuna in literature and clinical practice.

The goal of the current study is to provide a first proof-of-principle of the potential of DRG-stimulation as a new target for neuromodulation in a case series of patients with motor complete SCI. More specifically, the current study sets out to explore whether DRG stimulation can lead to selective (*DRG-level specific*), reproducible (*over a period of days*), and clinically relevant (*strong and potentially weight bearing*) motor responses. We had preliminary evidence from a pilot study in chronic pain patients (see summary in Supporting Information S2), demonstrating that *within* the stimulation range of currently available clinical devices, DRG-stimulation could facilitate strong, reproducible motor responses in the lower extremities in these noninjured patients. To best of our knowledge, the current study is the first to explore the above-mentioned goals in SCI patients.

MATERIALS AND METHODS

Participants

For this study, patients with chronic motor complete SCI (ASIA Impairment Scale [AIS] A/B) without any residual motor function in the lower extremities were included from the investigators' practice at Erasmus MC and the Rijndam Rehabilitation Center in Rotterdam, the Netherlands. The level and completeness of injury was confirmed pre-inclusion using neurological examination in accordance to American Spinal Cord Injury Association (ASIA)

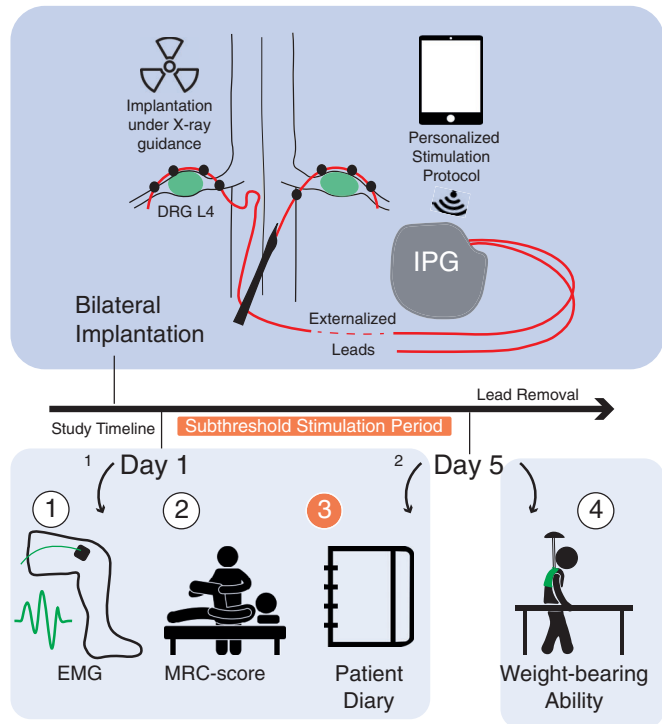


Figure 1 Overview of the experimental design as used in this study. On day 1, patients received surgical implantation of two DRG leads, which were placed bilaterally on level L4. On days 1 and 5, EMG and clinical measurements were performed. At the end of day 1, patients were sent home with both DRG-leads activated at a submotor threshold stimulation level, and a patient diary to fill in during the submotor threshold stimulation period at home (marked orange). On day 5, the ability for assisted weight bearing was also tested with both DRG leads activated according to optimal isotonic stimulation parameters. At the end of day 5, leads were removed in an outpatient clinical setting at the department of pain medicine (as no surgery/admission was necessary for this). [Color figure can be viewed at wileyonlinelibrary.com]

guidelines, as performed by a specialist in rehabilitation medicine (RO). In addition, baseline Medical Research Council (MRC) scores of the legs were assessed by the same specialist (on a scale from 0 to 5, with 0 being “no contraction” and 5 being “normal strength”) (29, 30). Additionally, self-reported problems with spasticity were listed. Patients were included if they suffered from motor complete SCI for >2 years and were >18 years old at the time of inclusion. Preferably, patients with residual, bilateral upper extremity strength were included to ensure possibility of assisted weight-bearing testing (see “Clinical Outcome Measures”). This was, however, not a protocolized inclusion criterion. Patients were excluded if they were implanted with an intrathecal baclofen pump, they suffered from anxiety or depression, had pressure ulcers or severe contractures, were pregnant or had a life expectancy less than one year.

Study Design

The current study consists of a prospective case series and proof-of-principle study. For each individual patient, the study period consisted of a total of five days (Fig. 1). On day 1, the patient underwent the placement of temporary leads, externalized through the skin, to allow for nonsurgical removal at the end of the study period. Subjects received DRG leads on level L4, one on each side. This level was preferred, as the roots at this level

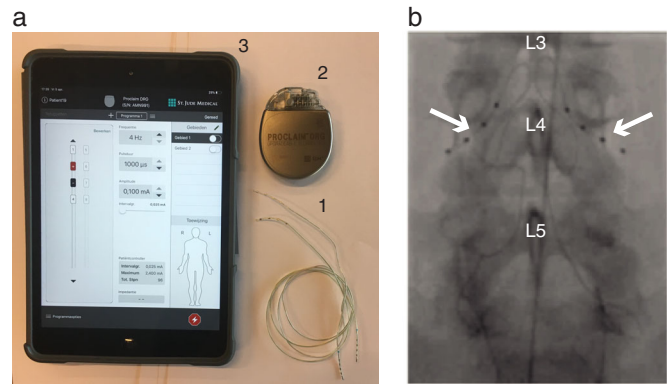


Figure 2 DRG-stimulation system and intra-operative X-ray image. a. Overview of the Abbott DRG-stimulation kit as used in this study. 1) Temporary quadripolar leads as placed in the study patients. Each lead holds a total of four electrodes, which can be programmed separately. 2) The pulse generator that was left externalized but connected to the implanted temporary leads during the study period. 3) The clinician programmer that was used to program the leads individually according to the stimulation protocol. The complete DRG-stimulation system is currently clinically accessible for the treatment of chronic pain. b. Overview of intra-operative X-rays as made during the DRG-lead placement of pt #2. Vertebral segments L3, L4, and L5 are labeled in the X-ray. As can be seen from the X-ray, the leads are placed bilaterally over the L4 level DRG (see white arrows), caudal to the pedicles of the vertebral segment labeled as “L4.” [Color figure can be viewed at wileyonlinelibrary.com]

are known to activate the quadriceps muscles which are involved in knee extension (31), as was confirmed in our explorative study using DRG stimulation to evoke lower-extremity motor responses in patients implanted with a DRG stimulator for the indication of chronic pain (see Supporting Information Fig. S2). After successful implantation, the patient was brought to the Department of Clinical Neurophysiology for surface EMG and clinical muscle force measurements (MRC scoring). After this first measurement session, patients were sent home with a DRG stimulator activated at submotor threshold level to assess potential effects of continuous subthreshold neuromodulation. On day 5, the patients were invited back for a second measurement session to assess the reproducibility of motor response. The same day, the DRG leads were removed in an outpatient setting at the Department of Pain Medicine (as no surgery/hospital admission was necessary for this). The study design was approved by the Erasmus Medical Centre Medical Ethics Review Committee (METC) (MEC-2017-107, NL60957.078.17). Prior to participation, all participants signed a written informed consent as approved by the METC. In addition, all patients provided consent for the publication of personal images.

DRG-Stimulation Device Implantation

The DRG-stimulation device (Abbott, Plano, TX, USA) as used in the current study consists of an external trial pulse generator (Proclaim DRG), two quadripolar percutaneous DRG-leads and a wireless clinician programmer device (Fig. 2). The pulse generator allowed for a maximum range of pulse frequency (F) (4–80 Hz), pulse amplitude (I) (0–6.000 mA), and pulse duration (D) (40–1000 μ sec) (32). The minimally invasive surgical technique has been described earlier by members of the current research group (26) and was performed by an experienced senior member of staff (FH). The patient was placed in prone position with pillows

to minimize the lumbar lordosis. The entire procedure was performed under local anesthetic (lidocaine). Sedation with propofol and remifentanyl was additionally available at the patient's request. Leads were placed via a percutaneous and minimally invasive epidural approach, using a loss of resistance technique with a Tuohy needle. Leads were inserted through a sheath and positioned in the intervertebral foramen under the pedicle on top of the DRG. The lead was stabilized in the epidural space with a double loop. Correct lead position was determined by using fluoroscopy in AP and lateral direction and intraoperative stimulation until motor responses (i.e., leg movement) were present upon visual inspection.

EMG Measurements (Days 1 and 5)

The current study aimed at evoking two types of muscle response. First, we aimed to evoke a so-called phase 1 muscle response, a "dynamic" motor response characterized by a clear alternation between muscle contraction and relaxation. This response is the consequence of a lower-frequency stimulation input, leaving time for relaxation between stimulation pulses. Second, we aimed to evoke a phase 2 "isotonic" muscle response, a muscle response at higher stimulation frequency and amplitude, leading to a continuous, strong muscle contraction with a stable tonus and no visible relaxation of the muscle.

In order to evoke both these "dynamic" muscle responses (*phase 1*), as well as the "isotonic" motor responses (MRC ≥ 4) (*phase 2*), a stimulation protocol was developed based on the previously mentioned explorative study (see Supporting Information Fig. S2). In phase 0, we increased the pulse amplitude (I) to find the first threshold of muscle contraction. This was done under the minimum frequency which can be produced by the pulse generator (4 Hz). The threshold was determined by both visual clinical feedback of the targeted muscles and the appearance of DRG-evoked potentials on the real-time EMG traces (JD). Then, we continued to increase the amplitude in phase 1 to find the optimal settings of I, defined as the I after which the amplitude of the muscle response as seen in the EMG-traces did not increase any further. In phase 2, we aimed at isotonic contractions by taking the optimal I and increasing the pulse frequency (F) until isotonic contractions were observed. If the maximum increase in F still did not allow for isotonic contraction, we increased the pulse duration (D) (also known as pulse width) to facilitate an isotonic contraction (Table 1). All stimulation protocols were performed using a standard electrode configuration ($N+ -N$), assuming an ideal placement of the DRG lead. In case of loss of muscle amplitude during phase 2, stimulation was paused briefly (<5 min) to rest the muscle and picked up at the last set of stimulation parameters to continue above-described protocol. Only in those cases when a full run through phase 0–2 (Table 1) (including pauses) would not lead to isotonic contraction, we would change to new

electrode configurations and run through the protocol again. First, a change in polarity would be attempted ($N- +N$), and if not successful, more "wide-field" stimulation options (e.g., $+NN-$, $-NN+$, etc., on a trial-and-error basis) were tried. After determination of the optimum settings for isotonic stimulation for each leg, bilateral stimulation was attempted. Based on the intrinsic settings of the pulse generator, bilateral stimulation entailed *interleaved* delivery of pulses to the bilateral DRGs (32). The personal activation thresholds and muscle force (MRC scoring) were compared between baseline, days 1 and 5 to assess reproducibility of motor responses.

Submotor Threshold Stimulation Protocol at Home (Days 2–4)

After the first EMG measurements, patients were sent home with both DRG leads activated at a submotor threshold stimulation level (0.10 mA [I], 4 Hz [F], and 1000 μ sec [D]). This combination of stimulation parameters was predefined as a combination of parameters expected to be far *under* the muscle activation threshold, as based on the first pilot study (see Supporting Information S2). The submotor threshold nature of these parameters was confirmed for each patient during the EMG measurement on day 1.

EMG-Data Acquisition and Analysis

Responses from the rectus femoris (RF), vastus lateralis (VL), vastus medialis (VM), biceps femoris (BF), gastrocnemius (GC), tibialis anterior (TA), and the abductor hallucis longus (AHL) muscles were recorded bilaterally with BrainRT EEG software (OSG, Belgium) using silver-silverchloride surface electrodes at a sampling frequency of 1000 Hz. In addition, paraspinal muscles (PS) were measured to detect stimulation artifact signal and stimulation onset.

The EMG data were manually annotated into 3 sec data-files in the regions of interest before being subjected to data processing in a custom-written data-analysis tool (Matlab R2017a). Filtering involved detrending (fifth order Butterworth at 1 Hz), notch-filtering (50 Hz), and low-pass filtering (second-order Butterworth at 100 Hz), before being subtracted by background (nonstimulated baseline) EMG signal. For the low-pass filter, the cut-off was determined based on the maximum stimulation frequency expected to be needed in the pilot (40 Hz based on the first pilot, see Supporting Information S2). Apart from the detrending, no other high-pass filter was applied to prevent the loss of signals produced by low-frequency stimulation (4 Hz). All signals and frequency spectra of signals were compared prefiltering and postfiltering to determine the presence of any filtering artifacts and/or the loss of signal detail. To measure muscle movements, we made use of the root mean square (RMS) of the subtracted signal as a measure of the average power of the EMG signal (4, 5).

Table 1 Stimulation Protocol as Used During the EMG Measurements.

Phase	Amplitude (I)	Frequency (F)	Duration (D)	Aim
Phase 0	0–6.0 mA	4 Hz	200 μ sec	Dynamic Contraction–Threshold I
Phase 1	Threshold I–6.0 mA	4 Hz	200 μ sec	Dynamic contraction–Optimal I
Phase 2	Optimal I	4–40 Hz	200 μ sec	Isotonic contraction–F/D optimization
or	Optimal I	Last F	200 μ sec to 1 msec	

I, pulse amplitude; F, pulse frequency; D, pulse duration.

For visualization purposes, RMS values for each muscle (contralateral and ipsilateral to stimulation) in each individual patient during phase 1, phase 2 and bilateral stimulation were displayed using heatmaps. Additionally, filtered 3 sec EMG traces during phase 1, phase 2, and bilateral stimulation on days 1 and 5 were displayed. A selection of individual traces of DRG-evoked potentials was also displayed with respect to each pulse of DRG-stimulation (as extracted from the artifact signal in the PS trace, see above). All filtering and visualizations (heatmap, muscle traces) were performed in Matlab 2017a.

Clinical Outcome Measures

A total of two clinical outcome measures were used to assess the motor responses as evoked by DRG stimulation. Primarily, muscle strength during phase 2 (isotonic) contractions on days 1 and 5 was measured using manual muscle testing (MMT) with the Medical Research Council (MRC)-scoring system (on a scale from 0 to 5, with 0 being "no contraction" and 5 being "normal strength") (29, 30). These scores were performed during phase 2 stimulation of one or both legs, with the subject in supine position. An MRC score of ≥ 4 (with a score of "4" entailing a "movement against gravity and resistance") is necessary for muscle strength during DRG stimulation to be considered feasible in a clinical setting for SCI (e.g., to allow for assisted weight-bearing ability/standing). As a secondary outcome measure, and mostly for demonstrative purposes, the ability for the patient to come to an *assisted* weight-bearing position was assessed on day 5 at the Unit of Physiotherapy with both DRG-stimulators activated on an isotonic level. This outcome measure was considered secondary to the MRC score, as it was expected that a leg extension around the knee joint alone would not be sufficient to come to *independent* standing (i.e., lack of hip stability, postural control). The assisted weight bearing consisted of the following components: 1) a passive patient lift system that was slowly lowered, 2) parallel bars that could be used for the patient to compensate using their arms as the lift was lowered, 3) positioning of the feet by a researcher during the lowering to ensure proper sole-ground contact, and 4) when necessary, ankle-feet orthoses on both legs to promote stability. Patients were tested for assisted weight-bearing ability multiple times, but never longer than five consecutive minutes of standing. The assisted weight-bearing test was *only* performed when deemed safe, that is, if a patient had sufficient remaining upper extremity strength to compensate on the parallel bars.

Statistical Analysis

Group-level RMS values were compared between muscle pairs (ipsilateral vs. contralateral to stimulation site) using a nonparametric Wilcoxon rank sum test for independent samples, both for data on days 1 and 5 of the study. In addition, to assess the stability of the response, group-level RMS values were compared for each individual muscle between day 1 and day 5 using the nonparametric Wilcoxon signed rank test for dependent samples. Differences were considered to be statistically significant when $p < 0.05$. All statistical analyses were performed in Matlab 2017a.

Adverse Events and Side Effects

During the subthreshold stimulation period (days 2–4), all patients were asked to keep a diary regarding: potential (changes in) pain sensations (reported on a VAS scale), signs of autonomic dysreflexia (e.g., elevated heart rate, headache, high blood

pressure), involuntary muscle responses or signs of other (unwanted) side effects. During each measurement session, blood pressure was also measured. Finally, each patient was given a company-provided magnet (St. Jude Medical) and instructions on how to use it to disable (and re-activate) the pulse generator in case of signs of autonomic dysreflexia. Patients were asked to report if, when and how long they had disabled their stimulator during the study period.

RESULTS

Patient Baseline Characteristics

Five male patients with motor complete SCI were included between June 2018 and December 2018 (Table 2). The mean age was 26.6 years old (19–35 years) and the mean time since injury was 6.6 years (4–15 years). All SCIs were a result of trauma. Levels of SCI ranged between C4–Th5, with four patients presenting with AIS A and one with AIS B (pt #2). Three patients (pt #1–3) had sufficient core stability and muscle strength in the upper limbs for testing of assisted weight bearing. All patients presented with an MRC score of 0 for all lower leg muscles at baseline. All patients presented with self-reported spasticity in the legs. None of the patients took any anti-spasticity medication or received botulinum toxin injections at least six months prior to inclusion of the study. None of the patients presented with rigidity or contractures in the lower extremities (Table 2).

Phase 1 (Dynamic) and Phase 2 (Isotonic) Muscle Response (RMS Values)

In all patients, the stimulation protocol evoked both phase 1 (*dynamic*) (Fig. 3) and phase 2 (*isotonic*) motor response (Fig. 4), both on day 1 and day 5 of the study (see Supporting Information S3 Video).

For the phase 1 motor response, only the upper leg muscles (*RF*, *VL*, *VM*, and *BF*) presented with a significant rise in RMS values when comparing the stimulated right leg (ipsilateral) to the contralateral left leg on both day 1 and day 5 of the study ($p < 0.05$ in all cases) (Fig. 3a,b). None of the lower leg muscles showed a significant increase in RMS-value during stimulation. No significant difference in RMS values for each individual muscle was observed between measurements on day 1 vs. measurements on day 5 (Fig. 3c), indicating a stable and reproducible response. An overview of EMG-traces for all muscles during phase 1 stimulation in each patient individually is depicted in the Supporting Information Figure S4. There was no significant difference in these results when the left leg rather than the right leg was ipsilateral to stimulation (*data not shown*).

For the phase 2 motor response, the upper leg muscles (*RF*, *VL*, *VM*, and *BF*) again presented with the most significant rise in RMS value when comparing the stimulated right leg (ipsilateral) to the contralateral left leg on both day 1 and day 5 of the study ($p < 0.01$ in all cases) (Fig. 4a,b). Of the lower leg muscles, only the TA showed a significant difference in RMS-values between the ipsilateral vs. contralateral leg on both day 1 and 5 of the study (Fig. 4c) ($p < 0.05$ and $p < 0.01$ for the two days, respectively), but with lower overall RMS amplitudes as compared to the upper leg muscles. Nevertheless, lower leg muscle involvement could be observed under higher-amplitude stimulation, as also visible in Supporting Information S3 Video (more on this in the Discussion). No significant difference in RMS values for each individual muscle was observed between measurements on day 1 vs.

Table 2 Overview of the Baseline Characteristics of the Five Patients With Chronic Motor Complete Spinal Cord Injury Included in the Current Study.

Subject	Age (y)	Gender	Post-injury (y)	Neuro Level	AIS-grade	AIS-Score				Sensory (C2-S4-5, max. 2 per level) (max. 56 in total per side)		Motor (lower Extr) (max. 5 per muscle, per side)		Motor (upper Extr) (max. 5 per muscle, per side)		DAP	VAC	Self-reported spasticity	Comments
						R	L	R	L	R	L	R	L	Level	Level				
1	23	M	4	Th4	A	22	23	23	23	L2 L3 L4 L5 S1	0 0	0 0	C5 C6 C7 C8 L1	5 5	5 5	No	No	Yes	
2	19	M	5	C8	B	15	20	15	15	L2 L3 L4 L5 S1	0 0	0 0	C5 C6 C7 C8 L1	5 5	5 5	Yes	No	Yes	
3	35	M	15	Th3	A	23	26	21	24	L2 L3 L4 L5 S1	0 0	0 0	C5 C6 C7 C8 L1	5 5	5 5	No	No	Yes	
4	32	M	4	Th5	A	24	24	24	24	L2 L3 L4 L5 S1	0 0	0 0	C5 C6 C7 C8 L1	5 5	5 5	No	No	Yes	Plexus brachialis lesion (L), full paralysis, NT for AIS-score
5	24	M	5	C4	A	8	6	6	6	L2 L3 L4 L5 S1	0 0	0 0	C5 C6 C7 C8 L1	4 0	4 0	No	No	Yes	

AIS, ASIA Impairment Score; R, right; L, left; LT, light touch; PP, pinprick; NT, not testable; DAP, deep anal pressure; VAC, voluntary anal contraction.

measurements on day 5 (Fig. 4c), indicating a stable and reproducible response. When looking at this response in the EMG traces of, for example, the VL, a clear activation can be appreciated on both day 1 and day 5 (Fig. 4e,f). An overview of EMG traces for all muscles during phase 2 stimulation in each patient individually is depicted in the Supporting Information Figure S4. There was no significant difference in these results when the left leg was ipsilateral to stimulation (*data not shown*), or when bilateral phase 2 stimulation was performed (see later on).

Bilateral Stimulation

In all patients, after isotonic stimulation parameters were determined for each leg, double lead stimulation was attempted in a supine position (Fig. 5). This was performed to ensure the potential of evoking bilateral isotonic motor responses simultaneously, required for weight bearing (see Supporting Information S3 Video). Double lead stimulation required an adjustment in isotonic stimulation parameters in both A and/or F in a total of two patients (pt #1 and #5) (see Fig. 6). However, there was no significant difference in RMS values during bilateral isotonic stimulation between the left and right leg or between day 1 and day 5 of stimulation (Fig. 5a–c).

Muscle Force (MRC Scoring) and Weight-Bearing Ability

In all patients, isotonic stimulation presented with an extension of the leg around the knee (see Supporting Information S3 Video). In all patients, this was accompanied by an MRC score of ≥4 on day 1 and day 5 (Table 3). In three of the patients (pt #1–3), bilateral activation of the leads allowed for testing of assisted weight bearing on day 5, with the help of their upper limb strength to stabilize on the parallel bars (see Fig. 6 and Supporting Information S3 Video). For two patients (pt #4 and #5), the lack of arm strength and core stability did not allow for safe testing of assisted weight bearing on day 5.

Activation Thresholds Day 1 vs. Day 5

Great heterogeneity in activation thresholds of phase 1 (0.5–2.5 mA) as well phase 2 (2.3–6.0 mA) motor responses could be observed across, as well as within patients when comparing day 1 vs. day 5 parameters (see Supporting Information Fig. S4). An overview of the activation thresholds for all the measured muscles can be found in Table 4.

Amplitude Response Curves

Amplitude response curves could be made for all patients on both day 1 and day 5 during phase 2 of stimulation, depending on the range of parameters as used for stimulation for each individual patient (due to heterogeneity in activation thresholds across patients, different ranges of parameters could be covered per patient, see Supporting Information S4). Noticeably, muscle recruitment patterns across different amplitudes resulted in heterogeneous curves across and within patients between day 1 vs. day 5. However, in all patients, the upper leg muscles consisting of VL, VM, RF (of the *m. quadriceps femoris*) and BF were recruited most, followed by the TA (activated mostly in pt #3 and pt #4) and the AH (activated mostly in pt #1, #3, and pt#4). In addition, in patient 3 (TA) and patient 4 and 5 (AH), contralateral muscles were at times recruited during increase of amplitude (see Supporting Information S4 for extended figures).

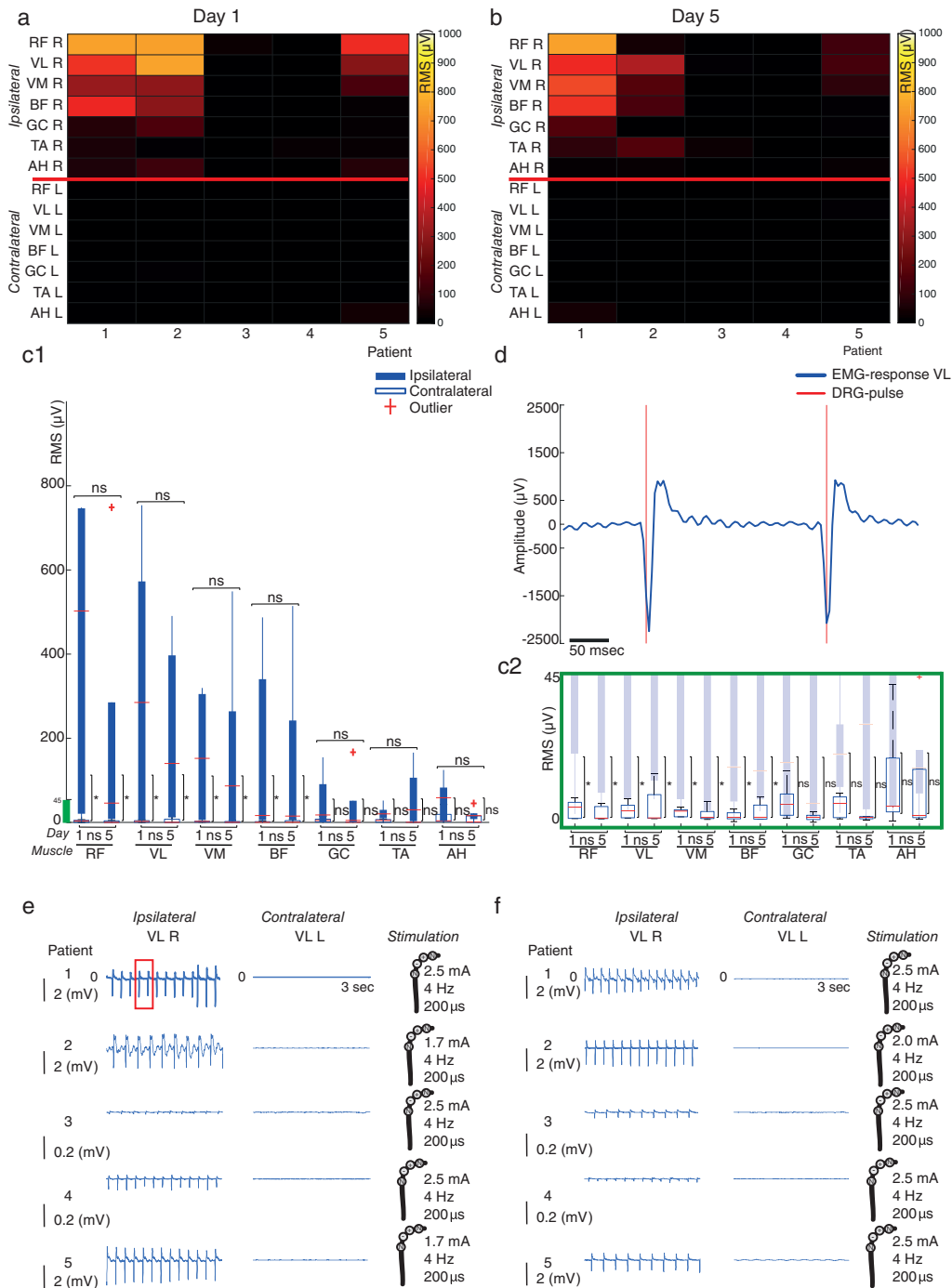


Figure 3 Overview of patient- and group-level analysis of muscle response during phase 1 of our stimulation protocol (increase in amplitude during stimulation aimed at dynamic muscle response). a,b. Heat plots representing the muscle response of ipsilateral vs. contralateral muscles *per individual patient* during phase 1 of stimulation on day 1 vs. day 5 of the study. At first glance, the highest RMS values were achieved in the upper leg muscles in patients 1, 2, and 5. c. 1) Boxplots depicting the *group-level* RMS values of ipsilateral (filled blue boxes) and contralateral (blue contoured boxes) muscles responses on day 1 and day 5 of stimulation. At a group level, the right upper leg muscles (RF, VL, VM, and BF) ipsilateral to stimulation present with significantly higher RMS values as compared to their contralateral counterparts in the left leg on both days 1 and 5 ($p < 0.05$ in all cases using a Wilcoxon rank sum test, see vertical lines). For the lower leg muscles, differences in RMS values were nonsignificant on both days 1 and 5. None of the muscles, either ipsi- or contralateral, showed a significant difference in RMS value between day 1 and day 5 of stimulation ($p > 0.05$ in all cases using a Wilcoxon signed rank test, see horizontal lines). c. 2) Zoom-in on a section of the boxplots in C.1 (see green range on the y-axis), depicting more clearly the contralateral muscle responses on day 1 and day 5 of stimulation (blue contoured boxes). All contralateral responses were $< 50 \mu\text{V}$ in amplitude. d. Zoom-in on 500 msec of the data selected from a ROI depicted by the red box in panel e. Individual traces of DRG-evoked potentials are now visible with respect to the DRG-pulse pattern. A total of two pulses is visible in this time window, matching with the 4 Hz pulse frequency delivered by the stimulator. e,f. Example EMG-traces of the ipsi- and contralateral VL muscle during phase 1 stimulation on days 1 and 5 of the study. Differences between stimulated vs. nonstimulated side are clearly visible, with the frequency used during phase 1 stimulation reflecting in the frequency of the muscle contractions. Corresponding stimulation parameters and electrode configuration are depicted in the right columns. See supplement 4 for patient-specific details. I, pulse amplitude; F, pulse frequency; D, pulse duration; BF, biceps femoris; PS, paraspinal; RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis; GC, gastrocnemius; TA, tibialis anterior, AH, abductor hallucis; RMS, root mean square; R, right; L, left. * $p < 0.05$, ns = not significant. [Color figure can be viewed at wileyonlinelibrary.com]

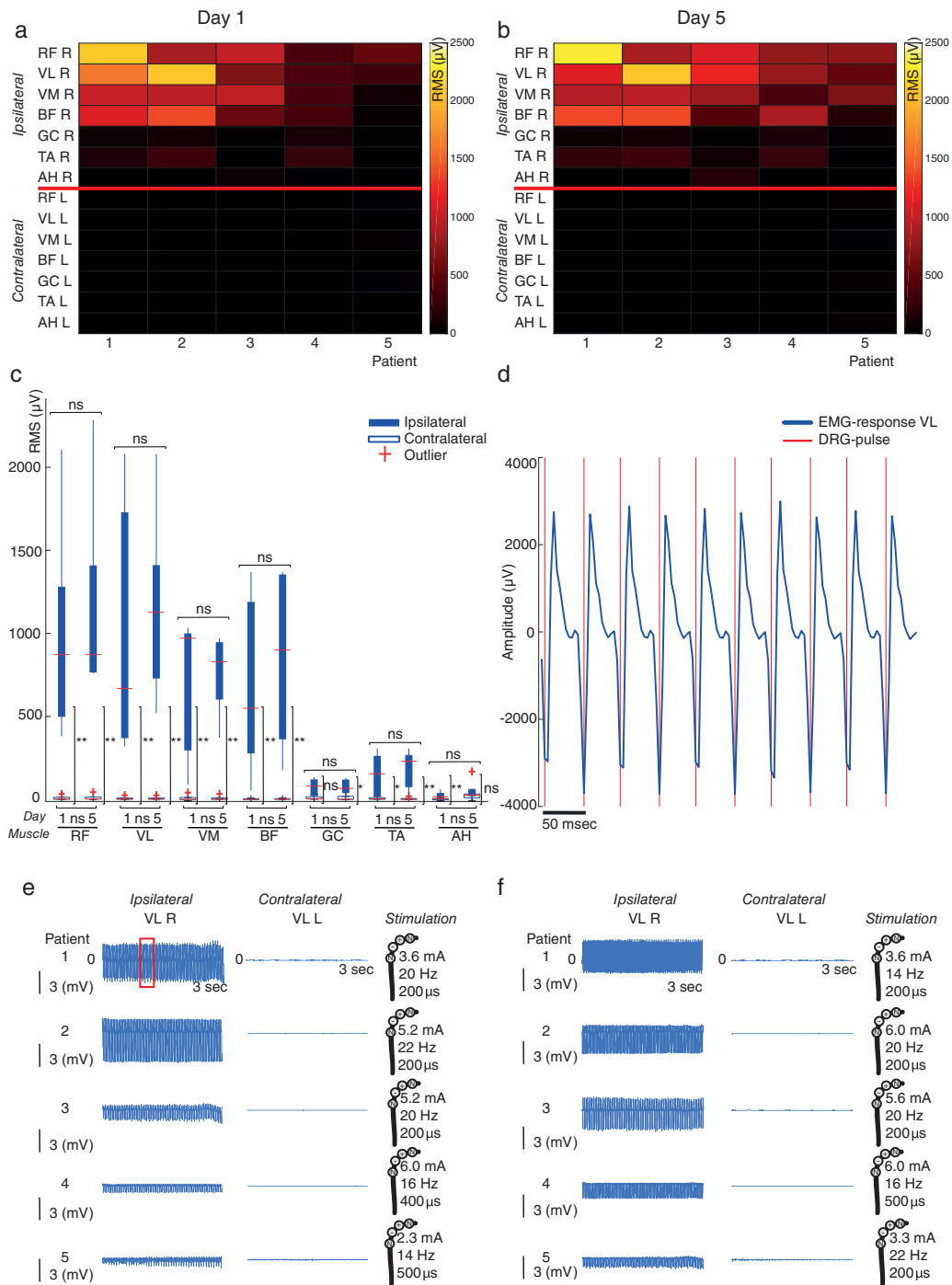


Figure 4 Overview of patient- and group-level analysis of muscle response during the end of phase 2 of our stimulation protocol (isotonic muscle response). a,b. Heat plots representing the muscle response of ipsilateral vs. contralateral muscles *per individual patient* during isotonic motor response (the end of phase 2 of stimulation) on day 1 vs. day 5 of the study. Again, the highest RMS values were achieved in the upper leg muscles for all patients, although the lower leg muscles display higher amplitudes as well when comparing to phase 1 stimulation (Fig. 3). c. Boxplots depicting the *group-level* RMS values of ipsilateral (filled blue boxes) and contralateral (blue contoured boxes) muscle responses on day 1 and day 5 of stimulation. At a group level, the right upper legs muscles (RF, VL, VM, and BF) ipsilateral to stimulation present with significantly higher RMS values as compared to their contralateral counterparts in the left leg on both day 1 and 5 ($p < 0.01$ in all cases using a Wilcoxon rank sum test, see vertical lines). The lower leg muscles present with less clear activation patterns, with on day 1 a significant rise in RMS values for the ipsilateral TA and AH ($p < 0.05$ and $p < 0.01$, respectively), while on day 5, this was the case for the ipsilateral GC and TA ($p < 0.05$ and $p < 0.01$, respectively). However, overall RMS-values for lower leg muscles were lower in amplitude as compared to the upper leg muscles as also seen in panels a and b. None of the muscles, either ipsi- or contralateral, showed a significant difference in RMS-value between day 1 and day 5 of stimulation ($n > 0.05$ in all cases using a Wilcoxon signed rank test, see horizontal lines). d. Zoom-in on 500 msec of the data selected from a ROI depicted by the red box in panel e. Individual traces of DRG-evoked potentials are now visible with respect to the DRG-pulse pattern. A total of ten pulses is visible in this time window, matching with the 20 Hz pulse frequency delivered by the stimulator. e,f. Example EMG-traces of the ipsi- and contralateral VL muscle during isotonic stimulation on day 1 and day 5 of the study. Differences between stimulated vs. nonstimulated side are clearly visible, with continuous activation of the muscle depicted on the side ipsilateral to stimulation. Corresponding stimulation parameters and electrode configuration are depicted in the right columns. See supplement 4 for patient-specific details. I, pulse amplitude; F, pulse frequency; D, pulse duration, BF, biceps femoris; PS, paraspinial; RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis; GC, gastrocnemius, TA, tibialis anterior, AH, abductor hallucis; RMS, root mean square; R, right; L, left. * $p < 0.05$, ** $p < 0.01$, ns = not significant. [Color figure can be viewed at wileyonlinelibrary.com]

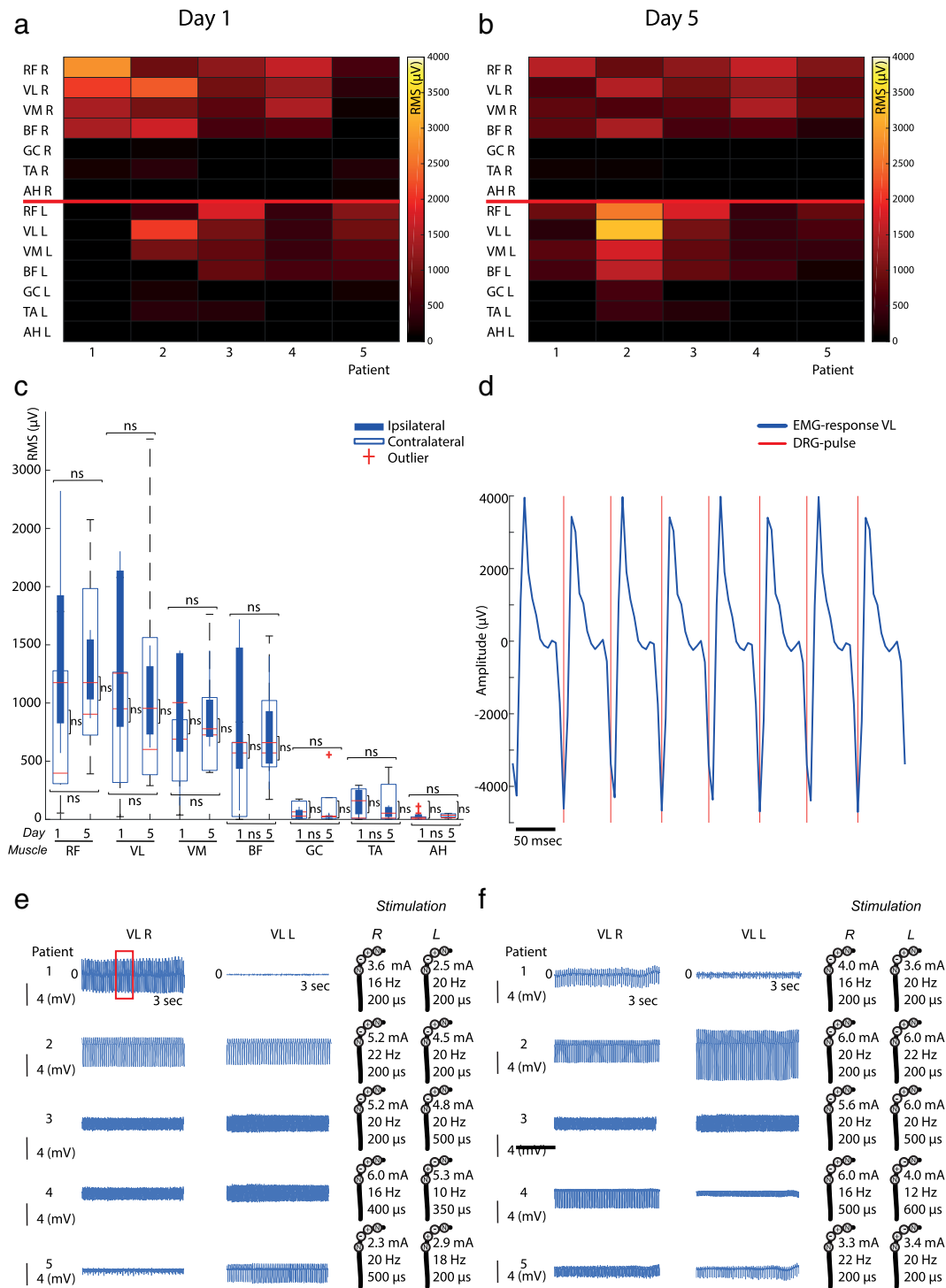


Figure 5 Overview of patient- and group-level analysis of muscle response during bilateral isotonic stimulation. a,b. Heat plots representing the muscle response *per individual patient* during bilateral isotonic stimulation on day 1 vs. day 5 of the study. As can be seen clearly from the heatplots, especially upper leg muscles, now in both the right and left leg, seem to be involved. c. Boxplots depicting the *group-level* RMS values of ipsilateral (filled blue boxes) and contralateral (blue contoured boxes) muscles responses on day 1 and day 5 of stimulation. None of the muscles in the right leg presented with significantly higher RMS-values as compared to their contralateral counterparts in the left leg on both day 1 and 5 ($p > 0.05$ in all cases using a Wilcoxon rank sum test, see vertical lines). Overall RMS values for lower leg muscles were lower in amplitude as compared to the upper leg muscles. None of the muscles, either in the left or right leg, showed a significant difference in RMS-value between day 1 and day 5 of stimulation ($p > 0.05$ in all cases using a Wilcoxon signed rank test, see horizontal lines). d. Zoom-in on 500 msec of the data selected from a ROI depicted by the red box in panel e. Individual traces of DRG-evoked potentials are now visible with respect to the DRG-pulse pattern. A total of eight pulses is visible in this time window, matching with the 16 Hz pulse frequency delivered by the stimulator. e,f. Example EMG traces of the VL muscle during bilateral isotonic stimulation on day 1 and day 5 of the study. Corresponding stimulation parameters and electrode configuration are depicted in the right columns. For all patients, bilateral isotonic stimulation lead to a muscle response with an MRC score of 4 and higher. See supplement 4 for patient-specific details. I, pulse amplitude; F, pulse frequency; D, pulse duration; BF, biceps femoris; PS, paraspinous; RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis; GC, gastrocnemius; TA, tibialis anterior; AH, abductor hallucis; RMS, root mean square; R, right; L, left. * $p < 0.05$, ** $p < 0.01$, ns, not significant. [Color figure can be viewed at wileyonlinelibrary.com]

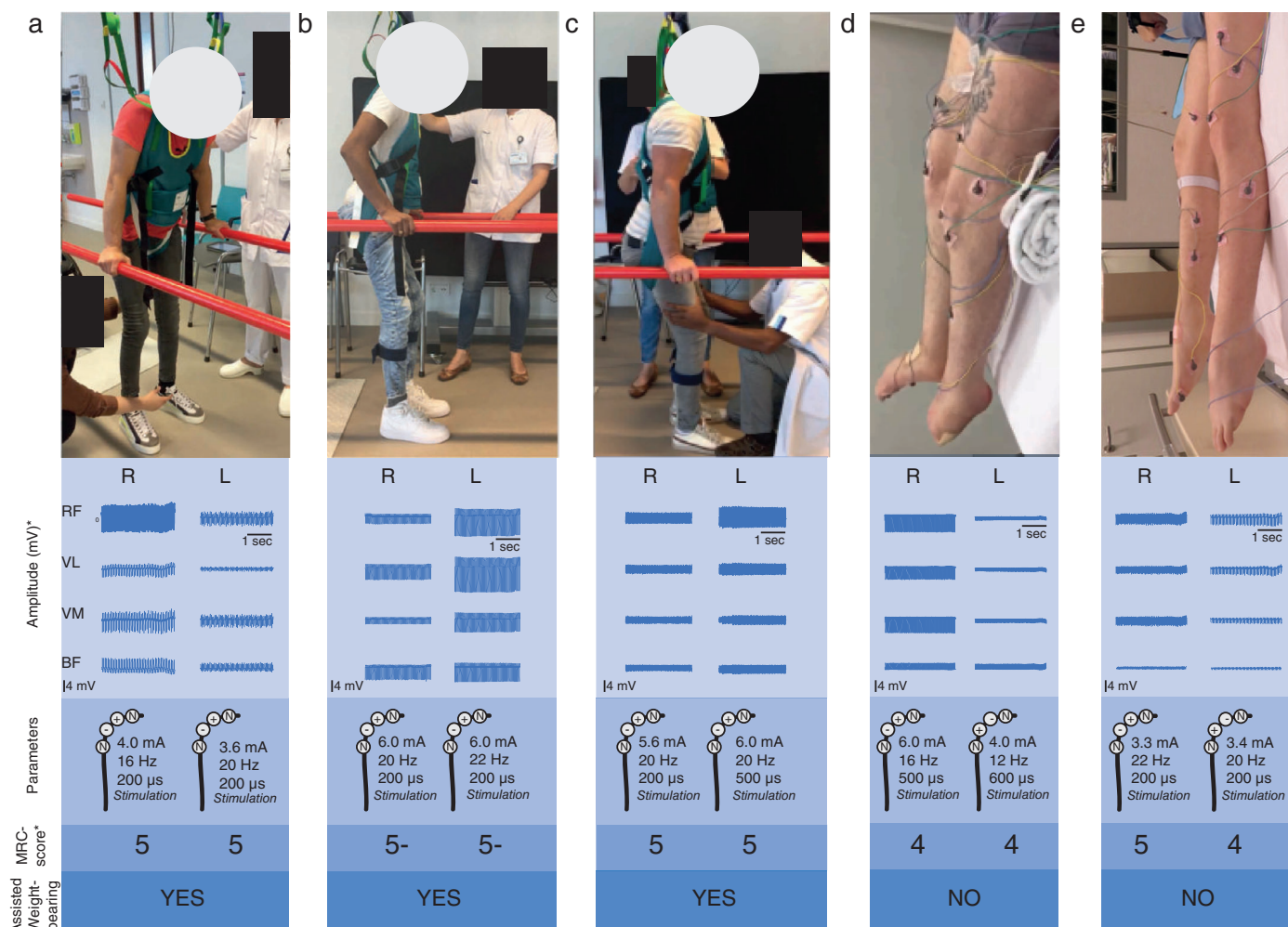


Figure 6 Overview of assisted weight-bearing results in the $n = 5$ patients included in this case series. Weight-bearing assistance consisted of 1) a passive patient lift, 2) parallel bars for upper extremity compensation, 3) positioning of the feet by a researcher and when necessary 4) bilateral ankle-foot orthoses. a. Results for patient #1, who was able to achieve assisted weight bearing. In supine position, the MRC-scores for the right (5) and left (5) leg respectively, also predicted a strong isotonic contraction with potential for weight bearing. b. Results for patient #2, who was able to achieve assisted weight bearing. In supine position, the MRC-scores for the right (5-) and left (5-) leg, respectively, also predicted a strong isotonic contraction with potential for weight-bearing. c. Results for patient #3, who was able to achieve assisted weight bearing. In supine position, the MRC-scores for the right (5) and left (5) leg, respectively, predicted a strong isotonic contraction with potential for weight bearing. In upright position, the patient's posture did not seem as stable as pt. 1 and pt. 2. d. Results of patient #4, who was not able to participate in the assisted weight-bearing test due to lack of upper extremity strength. The image depicts bilateral isotonic response in supine position on day 5. The MRC-scores for the right (4) and left (4) leg did, however, predict potential weight bearing, although the scores were slightly lower as compared to the other patients. e. Results of patient #5, who was not able to participate in the assisted weight-bearing test due to lack of upper extremity strength. The image depicts bilateral isotonic response in supine position on day 5. The MRC scores for the right (5) and left (4) leg did, however, predict potential weight bearing. *All EMG recordings and MRC-scorings were performed in supine position on day 5, prior to testing of assisted weight bearing. MRC, Medical Research Council; I, pulse amplitude; F, pulse frequency; D, pulse duration; mV, millivolt; RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis; BF, biceps femoris; R, right; L, left. [Color figure can be viewed at wileyonlinelibrary.com]

Frequency Response Curves

Frequency response curves could be made for all patients on both day 1 and day 5 within the range of 4–24 Hz, depending on the parameters as used for stimulation for each individual patient (due to heterogeneity in activation thresholds across patients, different ranges of parameters could be covered per patient, see Supporting Information S4). Noticeably, rise in frequency was accompanied by less clear rises in RMS values, in line with results of our first explorative study in chronic pain patients (see Supporting Information S2). What is more, a rise in frequency at times was accompanied by a drop in EMG-amplitude, different per patient (see Supporting Information S4), potentially explained by muscle fatigue (more on this in the discussion). Increase in

frequency at times resulted in recruitment of contralateral muscles such as in patient 1 (AH) and patient 2 (TA).

Adverse Events and Side Effects

None of the patients reported any (serious) adverse events during the study period (including signs of autonomic dysreflexia), nor were any (serious) adverse events observed by the research team. No abnormal changes in blood pressure were measured during stimulation. None of the patients presented with lead/wound infection during/after the study. None of the patients (including pt #2 with AIS B) reported any painful sensory perception during stimulation. None of the patients reported using the

Table 3 Overview of the MRC Scores During Phase 2 (isotonic) Contractions of Five Patients on Days 1 and 5 of the Current Study.

Patient	MRC* score baseline	MRC* score day 1	MRC* score day 5
1-Right	0	5	5
1-Left	0	4	5
2-Right	0	5-	5-
2-Left	0	4	5-
3-Right	0	5	5
3-Left	0	5	5
4-Right	0	4	4
4-Left	0	4	4
5-Right	0	5	5
5-Left	0	4	4

*MRC, Medical Research Council.

Table 4 - Overview of the Activation Thresholds of All Patients (n = 5) on Days 1 and 5.

Patient and side of stimulation	Parameter	Phase 1 (dynamic)		Phase 2 (isotonic)	
		Day 1	Day 5	Day 1	Day 5
1-Right	I (mA)	0.9	0.5	3.6	3.6
	F (Hz)	4	4	20	14
	D (µsec)	200	200	200	200
1-Left	I	1.0	1.2	2.5	4.4
	F	4	4	20	16
	D	200	200	200	200
2-Right	I	1.2	1.2	5.2	6.0
	F	4	4	22	20
	D	200	200	200	200
2-Left	I	0.8	2.0	4.5	6.0
	F	4	4	20	20
	D	200	200	200	200
3-Right	I	1.2	0.95	5.2	5.6
	F	4	4	20	20
	D	200	200	200	200
3-Left	I	1.5	1.5	4.8	6.0
	F	4	4	20	20
	D	200	200	500	500
4-Right	I	0.8	0.6	6.0	6.0
	F	4	4	16	16
	D	200	200	400	500
4-Left	I	2.5	2.3	5.0	4.0
	F	4	4	10	20
	D	200	200	350	600
5-Right	I	0.8	1.2	2.3	3.3
	F	4	4	14	22
	D	200	200	500	200
5-Left	I	1.2	1.1	2.5	3.4
	F	4	4	20	20
	D	200	200	200	200

I, pulse amplitude (mA); F, pulse frequency (Hz); D, pulse duration (µsec).

magnet to disable the pulse generator during the subthreshold stimulation period.

DISCUSSION

This study is the first of its kind to demonstrate the potential of the DRG as a new target for reproducible and potentially weight-

bearing muscle recruitment in patients with motor complete SCI. In all patients, bilateral DRG-stimulation on the L4 level was able to evoke bilateral isotonic motor responses recruiting predominantly upper leg muscles (Fig. 4), leading to knee extension. In three of our patients with sufficient core-stability and arm strength, these motor responses were strong enough to reach assisted weight bearing (Fig. 6 and Table 3). All muscle responses were reproducible over a five-day period (Figs. 3–5).

In its currently studied form, isotonic DRG stimulation could be potentially beneficial for independent transfers requiring weight-bearing ability. The dynamic muscle responses as studied in the context of this manuscript could be a potentially interesting, internalized alternative to functional electrical stimulation (FES) of muscles used to combat muscle atrophy and bone density loss (33, 34).

Noticeable, however, was the significant intersubject variability in threshold values for activation of phase 1 and phase 2 movements, pointing out the need for personalized stimulation parameters, as is also common in EES (7). What is more, a rise in frequency at times was accompanied by a drop in EMG-amplitude, as especially visible in our frequency response curves (see Supporting Information S4). This seemed only to occur in those occasions when at high amplitude (end of phase 1) a step-wise increase in frequency was performed with longer pauses between each step. This might indicate the presence of muscle fatigue, which could pose a challenge for future endeavors aiming at long-lasting weight bearing for safe and independent transfers. However, as the drop in amplitude seemed to occur at particular frequencies, different per patient (see Supporting Information S4), this phenomenon might also be explained by a more frequency-specific drop in muscle amplitude. Future studies aiming for multilead stimulation and more long-lasting, nonassisted weight-bearing, should focus on overcoming potential muscle fatigue problems, for example, by combining stimulation with (muscle) training, as is already common in EES (35–37).

Stimulation, Training, and Assisted Weight Bearing

In contrast to most EES studies so far (4, 5, 8, 12–14), our short-term DRG-stimulation was not aimed at subject-driven volitional movement, but rather stimulation-driven motor responses, recruiting the synaptic reflexes directly. We sent our patients home with the DRG-stimulator still activated at submotor threshold level to assess a potential change in stimulation parameters needed for muscle recruitment and/or changes in evoked muscle force (Fig. 1). The sub-threshold stimulation did not lead to any significant changes in RMS-values of any of the motor responses on day 5 as compared to day 1 (Figs. 3–5) as measured in the EMG in supine position.

This is not surprising as the potential neuromodulation induced plasticity or changes in muscle recruitment require longer periods of time and rehabilitation, as known from EES literature (4, 5, 8, 12–14). However, a recent study reported immediate effects of EES on restoration of volitional motor control in patients with chronic motor complete SCI (7) without any prior rehabilitation, suggesting a second plasticity-independent mechanism. The potential of DRG stimulation to achieve this immediate regain of volitional control has not been addressed in our study and remains to be elucidated.

Similarly, our assisted weight-bearing test was performed without any prior (activity based) training and under immediate DRG-stimulation only. The assisted weight-bearing test in our study was considered secondary to the MRC score as an outcome measure, as it was expected that a leg extension around the knee joint alone would not be sufficient to come to *independent* standing (i.e. due to lack of hip stability, postural control). We have indeed seen that in those patients lacking complete bilateral arm function (pt. #4 and #5), we were not able to successfully perform the assisted weight-bearing measurements (see Fig. 6). Previous work using EES over the lumbosacral spinal cord in combination with stand training for a period of months in four clinically motor complete patients with SCI, demonstrated regain of the patients' ability for full weight-bearing standing with minimal need for self-balance

and external knee or hip extension assistance when the epidural stimulation was on (35). In a follow-up paper studying one of these patients throughout more than three years of activity-based training with EES, the authors report the patient's ability to stand with the stimulator turned off, indicating involvement of neuronal plasticity (36). Similarly, an individual case of motor complete SCI implanted with a lumbosacral epidural stimulator was reported to present with an independent standing ability within two weeks of EES motor training (37). Additionally, combined training and non-invasive transcutaneous spinal cord stimulation (tSCS) between vertebral levels T11–T12 or L1–L2 in a range of patients with different levels of SCI (AIS A–C) demonstrated a regain of self-assisted standing with minimal assistance provided to the knees or hips (38). In our case, no training component was involved in the study procedure, and the assisted weight-bearing test was performed on day 5 only. Nevertheless, the targeted L4-level related knee extension in supine position, was also present in a standing position for pt. #1–3. Where the above-mentioned techniques of EES and tSCS also reported additional nonassisted hip extension, we observed the absence of hip stability in our patients, although not quantified. This could be explained by the fact that we aimed to target L4 specifically, while the previously mentioned experiments had access to the full lumbosacral spinal cord. Future experiments using multilead DRG-stimulation, combined with the previously mentioned training, could allow for better comparisons. As we will discuss later on in the limitations section of this discussion, these future studies will have to include a wider range of quantifiable measures and assistance methods to assess weight-bearing standing ability using DRG stimulation more objectively.

Heterogeneity, Selectivity, and Current Spread

In this context, it is also interesting to note the heterogeneity in muscle recruitment across patients, as well as the recruitment of non-L4 specific distal muscles (e.g., the AHL) (Fig. 4) and contralateral muscles, although the latter nonsignificant using group-level statistics (Figs. 3–5). This cross talk is known in literature on DRG-stimulation for the treatment of chronic neuropathic pain and is thought to occur as electrical current spreads through the Lissauer tract. As such, in chronic pain treatment, it is not unusual to target specific dermatomes related to the perceived pain by stimulating spinal levels usually not ascribed to these dermatomes (39). The involvement of these distal muscles, however, coincided with relatively small amplitudes in the EMG. Nevertheless, distal muscle involvement was visible (e.g., plantar flexion as seen in Supporting Information S3 Video) as discussed in the Results section. This discrepancy most likely involves EMG scaling of large, proximal muscles of the lower limb compared to smaller, distal muscles. Although first reaction to the above-described potential current spread would be to counter-act such cross talk to enhance spatial selectivity necessary for the temporal dynamics underlying locomotion, it could also be valuable to harness such cross talk to elicit multijoint movements, such as a combination of knee extension and plantar flexion described above.

Another possible scenario to consider within the realm of current spread, is direct ventral root (VR) activation, which would cancel out the potential benefits of dorsal recruitment as mentioned in the introduction. Rather than having artificial afferent input enter the spinal cord dorsally and drive motor response through mono- and polysynaptic spinal circuitry, the VR-activation scenario would entail a direct activation of muscles, without spinal modulatory involvement (20–22). However, it is important to note that direct VR stimulation

would be a less likely scenario to favor. First of all, given the dorsal placement of the lead per conventional guidelines in pain treatment, the DRG should be the primary target (see also Fig. 2b). In fact, computational literature modeling the effects of DRG-stimulation tells us that it is highly likely that even the most ideal dorsal placement of the lead, results in an electrical field impacting only a portion of the DRG's fibers (24) and neuronal population (40). Our data show that we were able to evoke motor responses using amplitudes as low as 500 μ A (Table 4), which would make a direct VR activation unlikely given the anatomical distance >5 mm between the dorsal aspect of the L4 DRG and the VR in the average human (41, 42). Finally, the observed contralateral recruitment of muscles, although sparse, is an argument in favor of recruitment of muscles through spinal reflexes, rather than through direct VR stimulation. At higher stimulation amplitudes, however, the possibility of VR recruitment becomes more likely and should therefore be considered in future experimental and especially computational studies.

Lastly, it is interesting to note that all patients presented with self-reported transfer-evoked spasticity at time of inclusion, without any rigidity or contractures in the muscles and joints. Although an enigmatic mechanism in itself, spasticity is thought to be the result of a combination hyperexcitability of interneurons in the spinal cord and decrease of postsynaptic inhibition (43, 44). Part of our future efforts will focus on determining to what extent the presence of spasticity, as well as other ways to interrogate the sensory system (e.g., motor reflexes), would be important for presurgical screening and prediction of DRG-stimulation treatment success.

The Potential Advantage of DRG Stimulation

Looking for new targets such as the DRG for neuromodulation in a SCI setting can be advantageous for several reasons. First of all, the percutaneous technique of the surgical placement of the DRG leads is considered less invasive than the laminectomy necessary for EES when using paddle electrodes. The lead-placement over the DRG in the neuroforamen, enhances the physical stability, decreasing the risk of lead migration due to postural changes as seen in EES (28), while remaining equally as safe as EES (45). Furthermore, the opportunity to place the lead over the DRG may also promote further spatial selectivity, as it would facilitate stimulation to each spinal level separately (28), which remains a challenging but essential frontier in EES (46). What is more, the somatotopic make-up of the DRG (28, 47) shows further potential for intra-DRG selectivity, and as such, for selectivity of muscle groups relevant for different stages of human locomotion. In the context of chronic pain, these selectivity advantages of DRG stimulation have led to superiority of the DRG in terms of clinical outcome as compared to EES (28). In other experimental animals reports targeting the DRG for sensory feedback, so-called "microstimulation" of the DRG confirms the level of selective recruitment which can be achieved (48).

In the current study, we demonstrate significant changes in RMS values of predominantly upper leg muscles involved in knee extension, indicating a reasonable level of spatial selectivity. In addition, this selectivity remained stable over a period of five days. However, we believe that the potential spatial selectivity could not be harnessed completely, with at times lower leg muscles or contralateral muscles being recruited (although predominantly nonsignificant and lower in their RMS values). The most likely room for further improvement of selectivity lies in increasing the limited spatial selectivity inherent to the quadripolar DRG leads. Intra-operative electrophysiology during placement of next-generation,

spatially selective leads, could further facilitate harnessing of DRG-somatotomy using microstimulation techniques.

With the potential advantageous aspects to DRG-stimulation in mind, it is warranted to consider future research looking into DRG stimulation as a means for regaining of standing and/or walking. The obvious trade-off of EES as compared to DRG-stimulation in this effort is the fact that multilevel DRG stimulation with spatially selective leads will have to be enabled in order to recruit all relevant muscles involved in locomotion. First of all, multiple leads will have to be implanted bilaterally which might cancel out the previously mentioned minimally invasive nature of lead placement. Additionally, pulse generators currently available on the market will need to be adjusted to facilitate the multilead stimulation. Combination placements of both SCS and DRG-leads to increase recruitment selectivity in clinically relevant levels (e.g., for postural stability or bladder control), would be an additional interesting possibility to investigate.

Study Limitations

The current study is prone to several limitations. First, only male, relatively young patients were included. It is important to further investigate the observed responses against the backdrop of patient heterogeneity within SCI (7). Second, our experimental design required a measurement session on the same day as lead implantation. As such, electrical stimulation settings might have been influenced by tissue reaction after placement, including edema, as is also the case in lead placement for chronic pain (27). Last, the clinical measurements of muscle force using the MRC-score were accompanied by an assisted weight-bearing ability test with the help of parallel bars and a patient lift system (our secondary outcome). This test was limited in its conclusions, especially given the lack of activation of other essential muscles necessary for stability and standing, as well as the compensatory use of arm muscle strength during standing. Additionally, the component of assistance could not be quantified due to the fact that only a *passive* patient lift was available, and no force sensors were used to measure force in the upper extremities during parallel bar compensation. Additional muscle force measurements, such as by using dynamometers, will aid in objectifying the actual muscle strength in future studies.

Conclusion

DRG-stimulation using the stimulators and leads available on the market for chronic pain, allowed for strong and reproducible isotonic motor responses in the upper leg muscles of patients with chronic motor complete SCI, enough to potentially enable weight bearing. With the minimally invasive surgical placement of the lead in mind, as well as the potential clinical benefits of spatial selectivity, future research on DRG-stimulation in a SCI setting is warranted.

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Authorship Statement

Sadaf Soloukey, Judith D. de Rooij, Frank J. P. M. Huygen, and Biswadji S. Harhangi were involved in the study design. Sadaf Soloukey, Judith D. de Rooij, Rutger Osterthun, Judith Drenthen, Frank J. P. M. Huygen, and Biswadji S. Harhangi were involved in the data collection. Sadaf Soloukey and Chris I. De Zeeuw were involved in the data analysis. Sadaf Soloukey and Biswadji S. Harhangi were involved in the writing of the manuscript. All authors were involved in data interpretation and editing of the manuscript. All authors approved the final manuscript. All authors had complete access to the study data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the supporting information tab for this article.

COMMENT

This is a very interesting and important study as it is the first to test the effects of dorsal root ganglion (DRG) stimulation on the recovery of motor function after spinal cord injury (SCI). These results are very timely as a growing number of groups are using epidural spinal cord stimulation (eSCS) to boost motor function after spinal cord injury. Although the mechanism of action remains unclear, the commonly held view is that eSCS activates large diameter primary afferent neurons, activating motor neurons trans-synaptically. This paper demonstrates a different approach for stimulating primary afferent neurons by placing electrodes on the DRG. This study tested this approach in 5 subjects with severe spinal cord injury and the results demonstrate clear and significant effects on muscle activation, providing early evidence supporting the potential benefits of this method. This work offers an innovative approach for recovering motor function after SCI, which is currently untreatable and results in permanent and often severe deficits in mobility and quality of life.

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