Received: August 16, 2020 Revised: January 11, 2021 Accepted: January 28, 2021

(onlinelibrary.wiley.com) DOI: 10.1111/ner.13379

How to Identify Responders and Nonresponders to Dorsal Root Ganglion-Stimulation Aimed at Eliciting Motor Responses in Chronic Spinal Cord Injury: Post Hoc Clinical and Neurophysiological Tests in a Case Series of Five Patients

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ABSTRACT

Objective: While integrity of spinal pathways below injury is generally thought to be an important factor in the success-rate of neuromodulation strategies for spinal cord injury (SCI), it is still unclear how the integrity of these pathways conveying the effects of stimulation should be assessed. In one of our institutional case series of five patients receiving dorsal root ganglion (DRG)-stimulation for elicitation of immediate motor response in motor complete SCI, only two out of five patients presented as responders, showing immediate muscle activation upon DRG-stimulation. The current study focuses on post hoc clinical-neurophysiological tests performed within this patient series to illustrate their use for prediction of spinal pathway integrity, and presumably, responder-status.

Materials and Methods: In a series of three nonresponders and two responders (all male, American Spinal Injury Association [ASIA] impairment scale [AIS] A/B), a test-battery consisting of questionnaires, clinical measurements, as well as a series of neurophysiological measurements was performed less than eight months after participation in the initial study.

Results: Nonresponders presented with a complete absence of spasticity and absence of leg reflexes. Additionally, nonresponders presented with close to no compound muscle action potentials (CMAPs) or Hofmann(H)-reflexes. In contrast, both responders presented with clear spasticity, elicitable leg reflexes, CMAPs, H-reflexes, and sensory nerve action potentials, although not always consistent for all tested muscles.

Conclusions: Post hoc neurophysiological measurements were limited in clearly separating responders from nonresponders. Clinically, complete absence of spasticity-related complaints in the nonresponders was a distinguishing factor between responders and nonresponders in this case series, which mimics prior reports of epidural electrical stimulation, potentially illustrating similarities in mechanisms of action between the two techniques. However, the problem remains that explicit use and report of preinclusion clinical-neurophysiological measurements is missing in SCI literature. Identifying proper ways to assess these criteria might therefore be unnecessarily difficult, especially for nonestablished neuromodulation techniques.

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For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/WileyCDA/Section/id-301854.html

Source(s) of financial support: The authors have no sources of financial support to report.

Keywords: Clinical neurophysiology, dorsal root ganglion, DRG-stimulation, nonresponder, peripheral nervous system, responder, spinal cord injury

Conflict of Interest: Frank J.P.M. Huygen is a member of the executive advisory board of Abbott and has received unrestricted educational grants from Saluda and Medtronic. In addition, he has received investigator-initiated research grants from Spinal Modulation and St Jude (Abbott). Frank J.P.M. Huygen and Biswadjiet S. Harhangi hold a patent in relation to the present work (WO 2020/101485 A1). Chris I. De Zeeuw has received several research grants from the Medical NeuroDelta, LSH-NWO Cross-over INTENSE, and ZonMW. The other authors report no other financial conflicts of interest.

INTRODUCTION

In recent decades, neuromodulation has gained traction as an experimental approach for treatment of spinal cord injury (SCI)-related problems (1,2) such as loss of motor control (3–5) or spasticity (6,7). Several groups have published on the potential beneficial role of techniques ranging from minimally invasive transcutaneous spinal cord stimulation (6,7) to more invasive techniques such as epidural electrical stimulation (EES), delivered either tonically (4,5) or with spatiotemporal patterns (3). EES especially has recently demonstrated exceptional results in the possibility of restoring volitional movement below the level of injury in patients with motor-complete SCI in the presence of stimulation (8). In some cases of nonmotor complete SCI, this effect could be achieved even in the absence of stimulation, indicating potential for neuroplasticity and reorganization (3).

While the initial reports of neuromodulatory strategies for SCI are very promising, they also present applications in mostly young, male participants carefully selected based on a range of criteria (9–13). A subsection of these criteria seem to focus on ensuring the integrity of spinal cord pathways prior to inclusion of a patient (9–13). However, *how* to best assess the integrity of the pathways conveying the effects of stimulation remains unclear and to the best of our knowledge, unreported. A clear identification of these criteria, however, is vital when wanting to answer questions on generalizability of neuromodulation strategies to a broader SCI population. In other terms, we could question whether a heterogeneous group such as SCI patients will consist of mostly responders to these neuromodulation therapies and more importantly, how we should assess the integrity of the relevant spinal cord structures to predict the responder or nonresponder status of SCI patients prior to stimulation.

In this article, we address this issue by elaborating on a single-institution experience of post hoc assessment of spinal pathway integrity in a series of five motor complete SCI patients included in a neuromodulation study using dorsal root ganglion (DRG)-stimulation. Our group has previously reported on the use of DRG as a novel target for eliciting motor responses in patients with chronic motor complete SCI (14–16). In a different, first case series of a total of five patients we demonstrated how bilateral L4-level DRG-stimulation can evoke both dynamic as well as strong isotonic motor responses in the upper leg muscles of these patients, leading to a potentially weight-bearing extension of the leg around the knee joint (14).

In a second case series of five patients in follow-up to this—which will be the topic of discussion in this article—only two patients presented as ''responders'' to this DRG-stimulation, indicating that they presented with immediate activation of muscles upon DRG-stimulation. Three of these patients were identified as ''nonresponders,'' presenting without immediate muscle activation, unexplained by technical malfunctioning.

To this day, the exact mechanisms of action of DRG-stimulation have not been not reveladed (14). However, based on the regional neuro-anatomy and previous studies using comparable targets (17,18), we would expect one of three candidate neural targets: sensory (afferent) pathways, motor (efferent) pathways, or a combination of both. While we hypothesize now that DRG-stimulation might target *afferent* pathways to recruit spinal circuits leading to motor output similar to EES, it also is reasonable to argue that DRG-stimulation is inherently different than EES. In contrast to EES, we could expect DRG-stimulation to target responsible sensory neurons in the DRG directly and at each spinal level individually, presenting with potential advantages such as spatial selectivity (19). However, scenarios *without* spinal circuit involvement such as direct ventral root-activation also are possible, although less likely (14). With the lack of knowledge on mechanisms of action prior to inclusion for either of the two patient series, our predefined inclusion criteria were not designed to completely reflect those of other neuromodulation applications such as EES (10–13).

The second patient series has brought to light, however, how these predefined inclusion criteria were not able to prevent non-responder recruitment. Post hoc, we are now questioning the possible involvement of spinal circuitry integrity as an explanatory factor.

In terms of spinal circuitry, the reason for the lack of response in these three patients should fall in one or more of the following categories: 1) problems with the afferent input entering the spinal cord (facilitated through the dorsal root), 2) problems with internal spinal circuitry, and/or 3) problems with the (L4-specific) motor nerves or muscles.

However, the issue mentioned above returns: how should we assess the integrity of the relevant spinal cord structures to predict the responder or nonresponder status of SCI patients prior to stimulation? In this article, we describe the design and results of a battery of clinical and neurophysiological tests we performed post hoc to potentially identify explanatory factors for the differences in responder status. Additionally, we formulate a set of challenges and recommendations for using neurophysiological tests—focused on the peripheral nervous system (PNS) especially—as a means to ensure effective patient inclusions and treatment in neuromodulatory research.

MATERIAL AND METHODS

Participants

Our case series consists of a group of five patients with chronic motor complete SCI (American Spinal Injury

Table 1. Overview of Outcome Measures as Used in the Current Study.

	Measure	Specifications
Self-reported scales		
1	PSFS	Spasm frequency, spasm severity
2	NRS	Spasm severity
Anamnesis		
1	Provoking factors	-
2	Location spasms	-
3	Current use of antispastic medication	-
4	Development since start of injury	-
Neurological examination		
1	Reflexes*	PTR, ATR, plantar, abdominal, BTR, TTR
2	MAS score†	Knee flexors, knee extensors, ankle dorsal flexors, plantar flexors, hip adductors
3	SCATS	Clonus, flexor spasms, extensor spasm
Neurophysiological measurements¥		
1	CMAP	Soleus muscle (tibial nerve [S1/S2]), vastus medialis muscle (femoral nerve [L2/L3/L4])
2	H-reflex	Soleus muscle (tibial nerve [S1/S2], vastus medialis muscle (femoral nerve [L2/L3/L4])
3	SNAP	Sural nerve (S1/S2)
* Scores used for muscle stretch reflexes		
−4	Absent	
−3	Just elicitable	
−2	Low response	
−1	Moderately low	
0	Normal	
+1	Brisk	
+2	Very brisk	
+3	Exhaustible clonus	
+4	Continuous clonus	
† Scores used for MAS-score		
0	No increase in muscle tone	
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension	
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM	
2	More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved	
3	Considerable increase in muscle tone, passive movement difficult	
4	Affected part(s) rigid in flexion or extension	
¥ Neurophysiological measurements performed		
Test	**Measurement**	**Potential diagnosis when abnormal**
CMAP	Direct activation of second order alpha-motoneuron	Peripheral motoneuron dysfunction/ neuropathy/muscle pathology
H-reflex	Second alpha-motoneuron potential due to activation of Ia sensory fibers. Expression of the monosynaptic reflex pathway.	Decreased excitability of the spinal cord/peripheral nerve/muscle
H/M ratio (max. H-amplitude/max. M amplitude)	Measure of excitability of the spinal cord	Decreased or increased (spasticity) excitability of the spinal cord/peripheral nerve/muscle
SNAP	Sensory nerve conduction assessment	Sensory neuron dysfunction/ neuropathy

ATR, Achilles tendon reflex; BTR, biceps tendon reflex; CMAP, compound muscle action potential; MAS, modified Ashworth scale; NRS, numeric rating scale; PSFS, Penn spasm frequency scale; PTR, patellar tendon reflex; SCATS, spinal cord assessment tool for spasticity; SNAP, sensory nerve action potential; TTR, triceps tendon reflex.

Association [ASIA] impairment scale [AIS] A/B) included in the DRG-motor response study (NL60957.078.17) between March and November 2019.

Patients were included from the investigators' practice at Erasmus MC and the Rijndam Rehabilitation Center in Rotterdam, The Netherlands. Written informed consent was obtained prior to participation.

The level and completeness of injury was confirmed preinclusion using neurological examination in accordance with ASIA guidelines, as performed by a specialist in rehabilitation medicine (*RO*). Patients were included if they suffered from motor complete SCI for greater than two years and were >18 years old at the time of inclusion. Patients were excluded if they were tetraplegic, implanted with an intrathecal baclofen pump, they suffered from anxiety or depression, had pressure ulcers or severe contractures, were pregnant, had known peripheral neuropathies (as reported by the patient or recorded in medical dossier), or had a life expectancy of less than one year.

Responder status

The goal of the DRG-motor response study was to assess the possibility to evoke *dynamic* and *isotonic* motor responses in patients with SCI using DRG-stimulation (15,16) (see more background description in Supporting Information File 1). Previously, our group published a first series of five patients, all responders to the stimulation (16). The currently presented study consists of a second series of five patients in which not all patients responded to the stimulation. Two of the included patients were "responders" (*R1-2*). A responder was defined as a study participant who presented with muscle response in lower extremity electromyography (EMG)-traces as a response to DRG-stimulation. Three participants were "nonresponders" (*NR1–3*). A nonresponder was defined as a participant who showed no muscle response in the EMG-traces, even under the highest pulse amplitude available for DRG-stimulation (6.0 mA, see Supporting Information File 1 for EMG-traces).

Study design

To assess the underlying mechanisms for the responder or nonresponder status of the patients, a post hoc neurological and neurophysiological test battery was designed consisting of self-reported questionnaires, neurological examination (including anamnesis), and neurophysiological measurements, focused on interrogating the integrity of the potential spinal circuitry involved. This concerned the following anatomical compartments: 1) afferents, 2) spinal circuitry, and 3) efferents (including muscles).

Given category 2, part of the measurements focused on investigating the patient's spinal circuitry by using clinical as well as neurophysiological spasticity-related outcomes. The presence and extent of spasticity can be indicative of the integrity of the spinal neuronal networks involved in, for example, the hyperexcitability of the stretch reflex in spasticity (20,21).

All patients were subjected to this test battery within eight months after their participation in the initial study as part of a follow-up protocol.

Questionnaires

Patients were asked to fill in the Penn spasm frequency scale (PSFS) which consists of domains on spasm severity (1–3) and spasm frequency (0–4), as well as the numeric rating scale (NRS) for the severity of spasms (with "0" being *no spasms at all* and "10" being *the worst spasms imaginable*).

Neurological examination

Reflexes of the leg and arms, as well as the abdominal reflex, were tested by two individual assessors (*RO*, *SS*) and video-taped for later reassessments. Additionally, the modified Ashworth scale (MAS) and the spinal cord assessment tool for spasticity (SCATS) were assessed in a similar fashion.

Neurophysiological outcome measures

Patients were tested on the occurrence of 1) compound muscle action potentials (CMAPs), 2) H-reflexes, and 3) sensory nerve action potentials (SNAPs) after peripheral nerve stimulation of the lower extremities bilaterally. As the initial study involved stimulation on the L4-level DRG (see Supporting Information File 1), we included CMAP-measurements in the vastus medialis (VM) muscle innervated by this spinal level (femoral nerve) (see Table 1). Additionally, one other conventionally measured muscle in neurophysiological practice (soleus muscle, tibial nerve) was added to broaden the protocol. SNAPs were evoked by stimulation of the sural nerve only.

Additionally, we measured the amplitude of the H-reflex in the soleus muscle and VM muscle, which among other things acts as an expression of the monosynaptic reflex pathway (second alpha-motoneuron potential due to activation of Ia sensory fibers). If no CMAP could be elicited in a muscle, the corresponding H-reflex also was not measured.

From the combination of the maximum CMAP-amplitude and the maximum H-reflex amplitude, we determined the H/M-ratio in these two muscles, which is a measure for the excitability of the spinal cord and often used as an indicator for the presence and/or severity of spasticity in mostly experimental settings (22–26). For each of the measurements, we aimed at acquisition of a minimum of five repeated responses, of which the maximum response was considered for further analysis. An overview of all above mentioned outcome measures, as well as the specific nerves and muscles involved, is given in Table 1.

Neurophysiological data acquisition

Data acquisition was performed using the Nicolet EDX system and Viking software (Natus Medical Incorporated, Middleton, WI, USA) under supervision of an experienced clinical neurophysiologist (*JD*). A bipolar stimulation probe (stimulus amplitude range 0–100 mA) was used for stimulation and unipolar silver chloride disk electrodes were used for EMG recording at a sampling frequency of 20–50 kHz. Measurements were performed in an EMI shielded room (Faraday cage) at the Department of Clinical Neurophysiology of the Erasmus MC, to minimize electromagnetic interference.

Neurophysiological data analysis

Presence and amplitudes of CMAPs, H-reflexes, and SNAPs were determined in the Viking software (Viking EDX version 22.3; Natus Medical Incorporated) by an experienced clinical neurophysiologist (*JD*). For the H/M ratio, the maximum CMAP amplitudes and the maximum H-reflex amplitudes were used.

Table 2. Patient Characteristics.

Subject	Age (years)	Sex	Postinjury (years)	Mechanism of injury	Neuro level	AIS			
						AIS-score	Motor (lower extr) (max. 5 per muscle, per side)		
							Level	R	L
NR1	57	M	2	Vascular ischemia	Th10	A	L2| L3| L4| L5| S1	0|0| 0|0|0	0|0| 0|0|0
NR2	27	M	5	HET	Th5	A	L2| L3| L4| L5| S1	0|0| 0|0|0	0|0| 0|0|0
NR3	51	M	15	HET*	Th11	A	L2| L3| L4| L5| S1	0|0| 0|0|0	0|0| 0|0|0
R1	48	M	25	Bullet injury	Th8	A	L2| L3| L4| L5| S1	0|0| 0|0|0	0|0| 0|0|0
R2	46	M	9	HET	C6	B	L2| L3| L4| L5| S1	0|0| 0|0|0	0|0| 0|0|0

NR, nonresponder; R, responder; HET, high energetic trauma; AIS, ASIA impairment scale; R, right; L, left.
*With conus atrophy upon visual inspection of spinal cord integrity based on MRI.

RESULTS

Patient baseline characteristics

Included patients (Table 2) were all male and on average 37 years old (ranging from 27 to 57 years) and presented with on average 11 years since injury (ranging from 2 to 25 years). Most patients were motor and sensory complete (AIS A, $n = 4$), with one patient presenting as only motor complete (AIS B). Most patients suffered the injury due to high energetic trauma (HET) ($n = 3$), while one suffered a bullet injury and one subject vascular ischemia. Only two out of the five patients included in this series presented as responders (R1–2) to DRG-stimulation, meaning that the three nonresponders (NR1–3) did not show any muscle response in the EMG, even during high-amplitude DRG-stimulation (see also Supporting Information File 1).

Self-reported scales and anamnesis

None of the nonresponders reported any signs of spasticity on the PSFS or the NRS. In fact, all nonresponders mentioned no signs of spasticity since the start of their trauma.

Of the responders, both subjects reported complaints of spasticity directly after trauma. R1 scored his spasticity complaints as "infrequent full spasms occurring less than once per hour" on the frequency-axis and "severe" (3) on the severity-axis of the PSFS. On the NRS, R1 scored his complaints with a score of 8 out of 10. For R2, both on the frequency-axis as well as the severity-axis of the PSFS, the patient scored his complaints as "1" (indicating "mild" spasticity and "mild spasms induced by stimulation," respectively). On the NRS, R2 scored his complaints with a score of 6 out of 10 (Table 3).

Neurological examination

All nonresponders presented with completely absent patellar (PTR) and achilles (ATR) tendon reflexes as well as absent abdominal reflexes and indifferent plantar reflexes. All nonresponders scored "0" on all aspects of both the SCATS and MAS, indicating a complete absence of spasticity.

Both responders also presented with completely absent abdominal reflexes and indifferent plantar reflexes. However, in R1, the PTR was elicitable, although low in response. Additionally, R1 presented with overall scores of "0" on the MAS, but with "severe" (3/3) bilateral flexors spasms and mild unilateral extensor spasms (1/3) as scored on the SCATS. In R2, both the PTR and ATR were elicitable, both also low in response. Additionally, R2 also presented with overall scores of "0" on the MAS, but with mild (1/3) bilateral clonus spasms as scored on the SCATS. See Table 3 for the complete overview of the neurological examinations.

Neurophysiological results

In the nonresponders, no CMAPs could be elicited in any of the muscles of interest (soleus muscle, VM muscle) (see Table 3). Consequently, no H-reflexes could be elicited in any of the nonresponders (Table 3) and no H/M ratios could be calculated.

In two of the nonresponders (NR2, NR3) SNAPs of the sural nerve could be measured uni- and bilaterally, respectively, as indicated in Table 3.

In both responders, bilateral CMAPs could be elicited of the soleus muscle, as well as CMAPs in the VM muscle in R1. In R2, an H-reflex of the soleus muscle could be elicited only unilaterally (see Table 3), leading to an H/M-ratio of 0.3. In one of the responders (R2), SNAPs of the sural nerve could be measured only unilaterally as indicated in Table 3.

DISCUSSION

The current study describes the post hoc clinical and neurophysiological assessment of a series of five patients, three of which were nonresponders in a neuromodulation study aimed at evoking motor response in motor complete SCI using bilateral L4-level DRG-stimulation. We as such have attempted to illustrate *how* the responder-status might have been better predicted *prior* to inclusion of these patients.

Our results clearly depict nonresponders separating themselves from the responders in terms of absence of spasticity and absence of leg reflexes. Additionally, the nonresponders presented with no CMAPs or H-reflexes. SNAPs were still present in two of the nonresponders. In contrast, responders presented with clear complaints of spasticity, elicitable leg reflexes, CMAPs, H-reflex, and SNAPs, although not always consistent for all tested muscles.

Table 3. Overview of All Outcomes as Used in This Study. [Color table can be viewed at wileyonlinelibrary.com]

Measure	NR1		NR2		NR3		R1		R2	
Self-reported scales										
1 PSFS										
Spasm frequency	0		0		0		2		1	
Spasm severity	NA		NA		NA		3		1	
2 NRS	0		0		0		8		6	
Anamnesis										
1 Provoking factors	None		None		None		Transfers		Transfers	
2 Location spasms	NA		NA		NA		R: flexion hip and extension knee + adduction hip L: flexion hip and flexion knee		L/R: full leg extension spasms (L > R) Back and abdominal spasms	
3 Current use of antispastic medication	NA		NA		NA		NA (baclofen seven years prior, [20 mg, 3/day])		Baclofen (20 mg, 3/day)	
4 Development since start of injury	Flaccid since trauma		Flaccid since trauma		Flaccid since trauma		Spastic directly after trauma		Spastic directly after trauma	
Neurological examination										
1 Reflexes*	***R***	***L***	***R***	***L***	***R***	***L***	***R***	***L***	***R***	***L***
PTR	−4	−4	−4	−4	−4	-4	−1	−3	−4	−3
ATR	−4	−4	−4	−4	−4	−4	−4	−4	−1	+1
Plantar	Ind	Ind	Ind	Ind	Ind	Ind	Ind	Ind	Ind	Ind
Abdominal	−4	−4	−4	−4	−4	−4	−4	−4	−4	−4
BTR	0	+1	+1	0	−1	−2	−1	−1	−4	−4
TTR	0	0	+1	0	−1	−2	−3	−3	−4	−4
2 MAS score†										
Knee flexors	0	0	0	0	0	0	0	0	0	0
Knee extensors	0	0	0	0	0	0	0	0	0	0
Ankle dorsal flexors	0	0	0	0	0	0	0	0	0	0
Plantar flexors	0	0	0	0	0	0	0	0	0	0
Hip adductors	0	0	0	0	0	0	0	0	0	0
3 SCATS										
Clonus	0	0	0	0	0	0	0	0	1	1
Flexor spasm	0	0	0	0	0	0	3	3	0	0
Extensor spasm	0	0	0	0	0	0	0	1	0	0
Neurophysiological measurements										
1 CMAPs (amplitude in mV)										
	R	***L***	***R***	***L***	***R***	***L***	***R***	***L***	***R***	***L***
Soleus muscle	NP	NP	NP	NP	NP	NP	0.2	0.3	1.7	3.0
Vastus medialis muscle	NP	NP	NP	NP	NP	NP	1.1	2.3	NP	NP
2 H-reflex (amplitude in mV)										
Soleus muscle	NA	NA	NA	NA	NA	NA	NP	NP	NP	0.3
Vastus medialis muscle	NA	NA	NA	NA	NA	NA	NP	NP	NA	NA
3 H/M ratio										
Soleus muscle	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.1
Vastus medialis muscle	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
4 SNAP (amplitude in μV)										
Sural nerve	NP	NP	15.2	NP	4.4	9.8	NP	NP	11	10

ATR, Achilles tendon reflex; BTR, biceps tendon reflex; CMAP, compound muscle action potential; MAS, modified Ashworth scale; NA, not applicable; NP, not present; NRS, numeric rating scale; PSFS, Penn spasm frequency scale; PTR, patellar tendon reflex; SCATS, spinal cord assessment tool for spasticity; SNAP, sensory nerve action potential; TTR, triceps tendon reflex.

From the above, we can conclude that neurophysiologically, all our nonresponders had signs of peripheral motor neuropathies (*category 3—problems with the [L4-specific] motor nerves or muscles—as mentioned in the introduction*), with no motor responses being evoked after peripheral nerve stimulation of the tibial nerve and femoral nerve. One patient (NR1) also presented with signs of sensory neuropathy (*category 1—problems with the afferent input entering the spinal cord—as mentioned in the* introduction). However, the SNAPs of the sural nerve were measurable in the two other nonresponders. Additionally, none of the nonresponders presented with clinical or neurophysiological signs of spasticity (*category 2 and/or 3 as mentioned in the introduction*). Both responders, however, presented with intact peripheral motor nerves, although with at times abnormal response amplitudes (see Table 3).

Electrophysiological changes post-SCI

The electrophysiological changes following chronic SCI have puzzled the field for decades, with still a lack of consensus in literature on the exact mechanisms underlying this process (27–33). Small sample sizes, heterogeneity in patient population as well as technical difficulties have been brought forward as explaining factors for the discrepancies found across electrophysiological studies (32). However, the neurophysiological results displayed in the current study seem to mirror some similar results found in literature.

One of the main assumptions in the field is that an upper motor neuron lesion such as SCI should leave the lower motor neuron anatomically intact, with a normal axon extending to the periphery (33,34). However, studies like that of Kirshblum et al. (32), Riley et al. (28), and Van De Meent et al. (29) present reduction in or even absence of SNAPs and CMAPs in some patients with SCI as compared to for example healthy controls, similar to our results. The hypothesis is that these types of developments are secondary plastic changes in the PNS (28–30,34), in one or more of the anatomical compartments mentioned in the introduction. These changes include motoneuron degeneration distal to the lesion or changes to primary sensory neurons in the dorsal column tracts. Additionally, central axotomy and retrograde degeneration may affect the neuron soma in the DRG and can lead to degeneration of the peripheral axon branch (35).

Concerning the reduction of the CMAPs specifically, it is often questioned whether this is a result of the muscle atrophy found in the chronic phase postinjury. In fact, upon visual feedback, responders as well as nonresponders in this study also presented with the typical reduction in muscle bulk seen in SCI (see also Fig. 1b, Supporting Information File 1). However, research has shown that muscle atrophy due to disuse alone (i.e., muscle atrophy *without* actual muscle fiber *loss*) has close to no effect of CMAP amplitudes (36). Rather, it is thought that disuse can lead to nerve compression in paralyzed limbs—and that as a consequence axonal degeneration post-SCI causes the decline of CMAP amplitudes. Other causes for reduced CMAP amplitudes may include edema in the lower extremities caused by inactivity and reduced blood flow following SCI (28,29). In one of our patients (NR1), edema around the lower leg, ankle, and foot was clearly observed, which might also explain the absent sural nerve SNAPs in this patient, in contrast to R2.

Another potential scenario left undiscussed until now concerns a more critical review of the *integrity* of the lumbosacral spinal cord in our responders versus nonresponders (*category 2—problems with internal spinal circuitry*). Normally, this can be best assessed using MRI, which unfortunately was only available for NR1 and NR3. For NR1, who has suffered SCI as a result of vascular ischemia (Table 2), obvious signs of ischemia were reported after clinical-radiological assessment at time of injury (*data not shown*). Here, potential mechanisms such as motoneuron and subsequent peripheral axonal degradation (37) might have had an important influence in our neurophysiological findings. For NR3, signs of

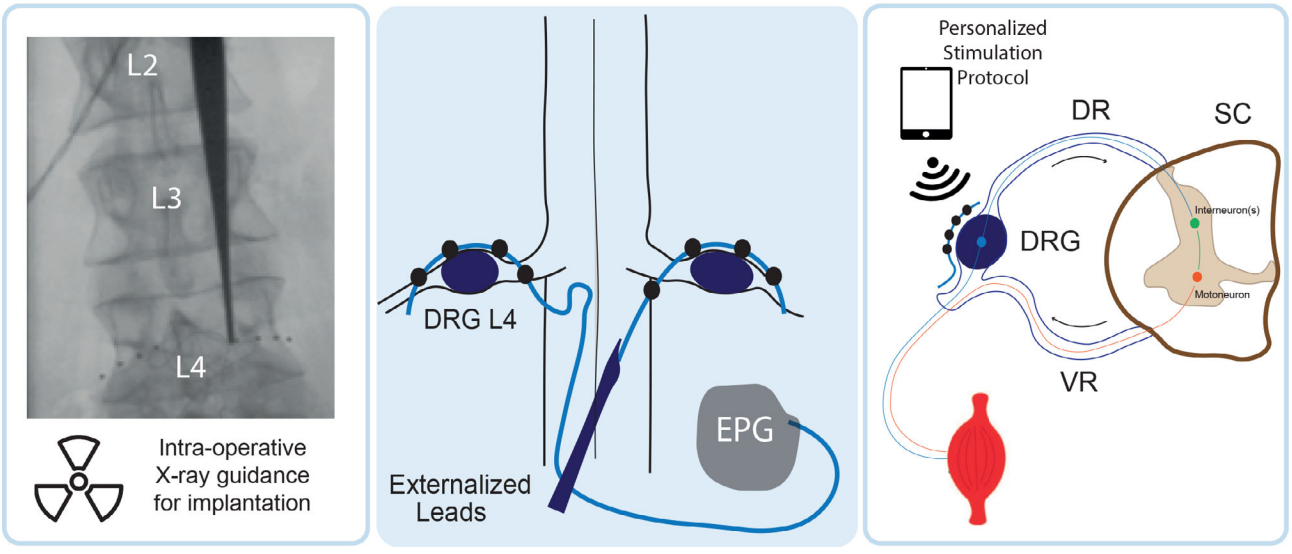

Figure 1. Overview of the implanted DRG-electrodes and potential circuitry involved. DRG-leads were placed bilaterally over the L4-level DRGs with the help of intraoperative fluoroscopy guidance and a percutaneous implantation technique (left panel). Each DRG-lead consisted of a total of four electrode points. Leads were externalized through the skin due to the temporary nature of the implantation and connected to an externalized pulse generator (EPG) (middle panel). The EPG was responsible for driving each DRG-lead through a Bluetooth-connection to facilitate personalized stimulation protocols. It could be hypothesized that DRG-stimulation is in fact afferent pathway activation (similar to EES), facilitating 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 (44–46), resulting in recruitment of both monosynaptic as well as polysynaptic spinal reflex pathways (14), and as such, motor output (right panel). [Color figure can be viewed at wileyonlinelibrary.com]

conus atrophy were reported postinjury, which also brings into question the potential influence of spinal cord integrity on our neurophysiological results (38). In fact, NR3 was the subject presenting with the most caudal neurological level of injury (Th11) of all tested individuals (see Table 2 and Supporting Information File 2). Similarly, NR1 also presented with a relatively caudal neurological level of injury (Th10), especially compared to the responders in the first study, where the most caudal level of injury was Th5 (see Supporting Information File 2). This observation might indicate that there should be a minimum intact distance between level of lesion and the lumbar spinal cord. In comparison, other EES-based groups (9,10) do accept Th10 as the most caudal level of lesion.

Future studies will be necessary to determine 1) to what extent the MRI analyses can already distinguish between responders and nonresponders, with or without additional neurological and neurophysiological assessments and 2) to what extent there should be a minimum intact distance between the most caudal lesion site and the lumbosacral spinal cord.

The importance of the PNS in neuromodulation for SCI

Although the above tells us there is still a lacuna in our understanding of the post-SCI changes in the PNS, it confirms the undoubtedly important nature of the PNS for neuromodulation in SCI. Especially so, when considering how the status of the PNS postinjury can effect neuromodulatory treatment success, in an experimental and eventually clinical setting.

Especially neuromodulatory interventions in SCI, aimed at harnessing the remaining anatomy below injury, have to rely on this intactness. EES relies on recruiting afferent feedback circuits which directly activate motor neuron pools and their respective muscles (3,39–41). Therefore, an intact efferent pathway and the ability to evoke CMAPs is essential when applying EES. However, the intactness of the afferent pathway is as vital. In fact, EES research has shown that propagation of *natural* proprioceptive signals back to the brain and/or spinal cord is essential for natural modulation of reciprocal inhibitory networks producing alternating recruitment of antagonist motor pools during locomotion (39). Without intact afferents, the modulation of spinal circuits with EES or DRG-stimulation may be compromised, as well as the reorganization of residual descending pathways during rehabilitation enabled by EES (1,39). In fact, keeping this remaining anatomy as intact as possible postinjury might be essential to increase the likelihood of treatment success through neuromodulation. Therefore, researchers are arguing for the importance of studying interventions in the *acute* postinjury stage (42).

Using neurophysiological measurements as a predictor for responder-status

Our single institution experience of including patients—which post hoc could be identified as suffering potential PNS-damage—warrants the explicit and structural consideration of the PNS in SCI-neuromodulation research.

Online clinical trial protocols of other ongoing SCI projects (9,10) do not make explicit mention of *specific* neurophysiological measurements prior to inclusion. However, several studies mention the need for segmental reflexes to be intact below the injury (10–13) as an inclusion criterion, while another names peripheral nerve damage which *limits* walking function—as an exclusion criterion (9). The question that remains is, what suffices as a protocol prior to inclusion to predict responder-status?

Our responders and nonresponders clearly divided themselves based on the presence of spasticity, and to a certain extent, the presence of reflexes. In a different, earlier series of patients with chronic motor complete SCI stimulated using DRG-stimulation to evoke motor response (n = 5, responders) (16), all patients also presented with self-reported complaints of spasticity (see Supporting Information File 2). Unfortunately, no neurophysiological measurements were performed here.

Based on these results, the illustration of our responder and nonresponder series could further support the idea that that EES and DRG-stimulation are indeed similar in mechanisms of action: they both recruit reflex-like spinal circuitries for locomotion. Therefore, it would be expected that those patients with intact (hyperexcitable) reflex pathways, will also be responders to neuromodulation. As said, the assessment of segmental reflexes prior to inclusion of a patient for EES-studies is not new (10–13).

What remains, however, is that spasticity is a notoriously difficult phenomenon to capture objectively within a single outcome measure. As our results demonstrate: the responders with self-reported spasticity who did not score on the MAS-scale, did score on one or more domains of the SCATS. Reflex-measurements can be considered as more straight-forward. However, Table 3 displays how also our responders presented with uni- or bilaterally absent reflexes.

Is there any place for neurophysiological measurements preinclusion? As Table 3 shows us, in contrast to the neurological examination, CMAPs, SNAPs, and H-reflexes do not separate our responders and nonresponders as clearly. Rather, we saw the nonresponders showed close to complete absence of the neurophysiological measures (except for the SNAPs in n = 2). The responders, however, displayed some degree of response, although not in all measures and not always at physiological levels (43). We could wonder, for example, if we would have excluded R1 based on the absence of the SNAPS preinclusion, even though now in hindsight, R1 presented as a responder. What is more, the absence of the SNAPs in R1 might just also have been the consequence of the edema seen in the patient's lower extremities, a technical-skill issue during measurements, or both (28,29).

The results presented here are too preliminary to use for determining an all-encompassing PNS screening method for future SCI research. However, we do think that the real-life single-institution scenario presented in this article gives a clear example of the need for PNS assessment in SCI research. The field as a whole would benefit from post hoc analyses of the PNS of previously included successful and nonsuccessful SCI study subjects, to increase the numbers for comparative purposes. Ultimately, the prospective use of preinclusion neurophysiological test batteries should be assessed to determine the actual predictive power. As experimental SCI treatments are moving from bench to bedside, the real-life patient heterogeneity becomes a reality. Being able to navigate treatment allocation within that heterogeneity is of vital importance for treatment efficiency, treatment success, as well as patient satisfaction.

Study limitations

The current study was performed post hoc in a series of five patients that divided themselves in responders and nonresponders in a clinical neuromodulation study targeting the DRG

post-SCI. The number of patients studied is very limited. What is more, to get a complete picture of the status of the PNS of our responders versus nonresponders, a more elaborate set of neurophysiological measurements involving more muscle groups, would be valuable in an experimental setting. Additionally, in some patients the measurements were performed up to eight months postcompletion of the initial study. Although highly unlikely given the fact that all patients were chronic SCI patients, this delay in measurements may have led to an inaccurate assumption of the status of our patients' PNS during the initial study period.

Finally, because our initial focus was on spinal pathway integrity, we have interpreted our results mainly in light of the anatomical three-compartment division described in the introduction. However, it is important to note that this does not cover all potential explanations for the responders and nonresponders. One important potential explanation would concern technical malfunctioning of our devices, although Supporting Information File 1 shows us that even in the nonresponders, stimulation artifacts could still be recorded in the absence of muscle recruitment.

CONCLUSIONS

In this study, we describe a single-institution's experience with responders and nonresponders to DRG-stimulation, a novel target for neuromodulation in motor complete SCI. With a series of post-hoc tests and measurements, we have attempted to illustrate *how* the responder-status might have been better predicted *prior* to inclusion of these patients.

The set of post hoc neurophysiological measurements we described were limited in clearly separating responders from nonresponders. Clinically, the complete absence of spasticity-related complaints in nonresponders was a distinguishing factor between responders and nonresponders in this institutional case series, which mimics prior reports of EES, and perhaps warrants similar inclusion criteria for DRG-stimulation as EES. It also illustrates potential similarities in mechanisms of action between the two techniques.

However, the problem remains that explicit use and report of such preinclusion clinical or neurophysiological measurements is missing in SCI literature in general. Identifying proper ways to assess these criteria might therefore be unnecessarily difficult, especially for nonestablished neuromodulatory applications such as ours. A clear identification of these criteria is vital to prevent (recurrence of) nonresponder recruitment in currently available as well as future neuromodulation techniques. Future studies will need to determine the best set of assessment tools to distinguish between responders and nonresponders for DRG-stimulation, including options such as MRI-analyses with or without neurological or neurophysiological assessments.

Acknowledgements

The authors would like to express great gratitude to Marjan Scheltens-de Boer, Venny Pires, and Karla Biesheuvel at the Department of Clinical Neurophysiology of the Erasmus MC, for their role in the EMG-data acquisition. The authors would also like to thank Siri van der Meijden for her valuable support during measurements and initial data analysis.

Authorship Statement

Sadaf Soloukey, Judith Drenthen, Rutger Osterthun, and Cecile C. de Vos were involved in the study design. Sadaf Soloukey and Rutger Osterthun were involved in the data collection. Sadaf Soloukey and Judith Drenthen were involved in the data analysis. Sadaf Soloukey and Biswadjiet 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.

How to Cite this Article:

Soloukey S., Drenthen J., Osterthun R., Vos C.C., De Zeeuw C.I., Huygen F.J.P.M., Harhangi B.S. 2021. How to Identify Responders and Nonresponders to Dorsal Root Ganglion-Stimulation Aimed at Eliciting Motor Responses in Chronic Spinal Cord Injury: Post Hoc Clinical and Neurophysiological Tests in a Case Series of Five Patients. Neuromodulation 2021; 24: 719–728

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SUPPORTING INFORMATION

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

COMMENT

The authors have presented a follow-up manuscript to their earlier work regarding DRG stimulation for motor complete SCI. Specifically, this manuscript attempts to elucidate potential pre-stimulation predictors of responder status. Combined with the work of other physicians looking at restoring volitional movement using dorsal column SCS, medicine may potentially have answers and new options to dramatically improve function in SCI patients. This is remarkable and inspiring, and I'll be eagerly following the work of these dedicated physicians.

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