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Unilateral L2-Level DRG-stimulation evokes bilateral CPG-Like motor response in a patient with chronic pain

Dear Editor,

We present the case of a patient in which we observed bilateral, rhythmic and alternating motor response in the lower extremities driven by unilateral L2-level Dorsal Root Ganglion (DRG)-stimulation.

The patient participated in a study (MEC2015-575) aimed at determining if and under which stimulation parameters motor responses could be elicited in the lower extremities using DRG-stimulation. This study was performed to assess the DRG's potential as a target for motor recovery in Spinal Cord Injury (SCI), as previously reported by our group [1,2]. We included chronic pain patients implanted with a DRG-stimulation device (Axium™, St. Jude Medical, United States) and an intact spinal cord.

The 69-year-old woman was known with a 2-year history of DRG-stimulation for the treatment of intractable chronic neuropathic pain as a result of Pudendal Nerve Entrapment (PNE). Stimulation was performed with two quadripolar DRG-leads, placed on left L1-and L2-level DRGs, connected via extension cables to an Internal Pulse Generator (IPG) placed in the left abdomen (Fig. 1A).

During study measurements, the patient was positioned in a supine position. Responses from the iliopsoas (IL), biceps femoris (BF), vastus medialis (VM), gastrocnemius (GC), tibialis anterior (TA) and abductor hallucis longus (AHL) muscles were recorded bilaterally with BrainRT EEG software (OSG, Belgium) using silver-silverchloride surface electrodes at a sampling frequency of 250 Hz. In addition, paraspinal muscles (PS) were measured to detect stimulation artefact and stimulation onset. Using the clinical programmer with Bluetooth-connection to the IPG, stimulation parameters including Pulse Amplitude (PA), Pulse Frequency (PF) and Pulse Width (PW) were changed according to a predefined protocol with the ultimate aim of evoking muscle responses in the lower extremities. After acquisition, the EMG-data was subjected to high pass filtering to remove cable motion artefact (4th order Butterworth, 50 Hz), notch-filtering (50 Hz), full wave rectification, low-pass filtering (4th order Butterworth, 8 Hz) to create a linear envelope and finally, normalization to the largest value in that specific muscle's EMG-trace [3].

During the experimental measurements, we temporarily adjusted the usual stimulation parameters used by the patient for chronic pain suppression (for both L1 and the L2-lead this was 225 μA and 20 Hz) in order to facilitate motor responses instead. While stimulating the left L2-level DRG-lead at a stimulation range expected to be suitable for elicitation of motor response ($PA = 5.15$ mA, $PF = 8$ Hz, $PW = 200$ μsec), a bilateral motor response was observed in the lower extremities, mostly focusing around upper leg muscles (Supplementary Video 1, Part A). The motor response appeared rhythmic and left-right alternating upon visual inspection, mimicking a bilateral locomotion pattern. The patient reported not being able to 'control' the bilateral movement, experiencing this as laborious and feeling like her legs were 'walking away'. The patient did not report any other sensation during stimulation.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.brs.2020.09.021

In the EMG-traces, responses were observed in mostly the BF and VM muscles in both legs, with highest amplitudes found in the left leg. Interestingly, the BF and VM muscles on both sides appeared to co-contract consistently throughout the recording (Fig. 1B). In line with the visual observation of the patient's response, both the VM- and BF- traces appear to show some left-right alternation (Fig. 1C and D), most clearly observable in the polar plots (Fig. 1F). The alternation, however, did not appear consistently throughout the experiment, making it difficult to pinpoint a cycle duration. When inspecting the frequency spectra of the muscles themselves, the left VM-muscle presented with a clear presence of 8 Hz peaks (and its harmonics) (Fig. 1E), consistent with the pulse characteristics delivered by the IPG.

Asking the patient to perform upper-extremity movements (*fist formation/relaxation, arms up/down*) in order for the patient to relax, modulated the amplitude of the motor response mostly in the left leg, both visually and in the EMG-traces (Supplementary Video 1, Part B).

Discussion

To the best of our knowledge, this is the first report of rhythmic and bilateral motor response in the lower extremities driven by unilateral L2-level DRG-stimulation. The left-right alternating nature of the response resembles a Central Pattern Generator (CPG). CPGs are neuronal networks producing oscillating, rhythmic output through interconnected excitatory and inhibitory neurons [4,5]. In case of the CPG for locomotion, this output entails the rhythmic

Abbreviations: AHL, Abductor Hallucis Longus; CPG, Central Pattern Generator; DRG, Dorsal Root Ganglion; GC, Gastrocnemius; IL, Iliopsoas; IPG, Internal Pulse Generator; NRS, Numeric Rating Scale; PA, Pulse Amplitude; PF, Pulse Frequency; PNE, Pudendal Nerve Entrapment; PS, Paraspinal Muscles; PW, Pulse Width; TA, Tibialis Anterior; VM, Vastus Medialis.

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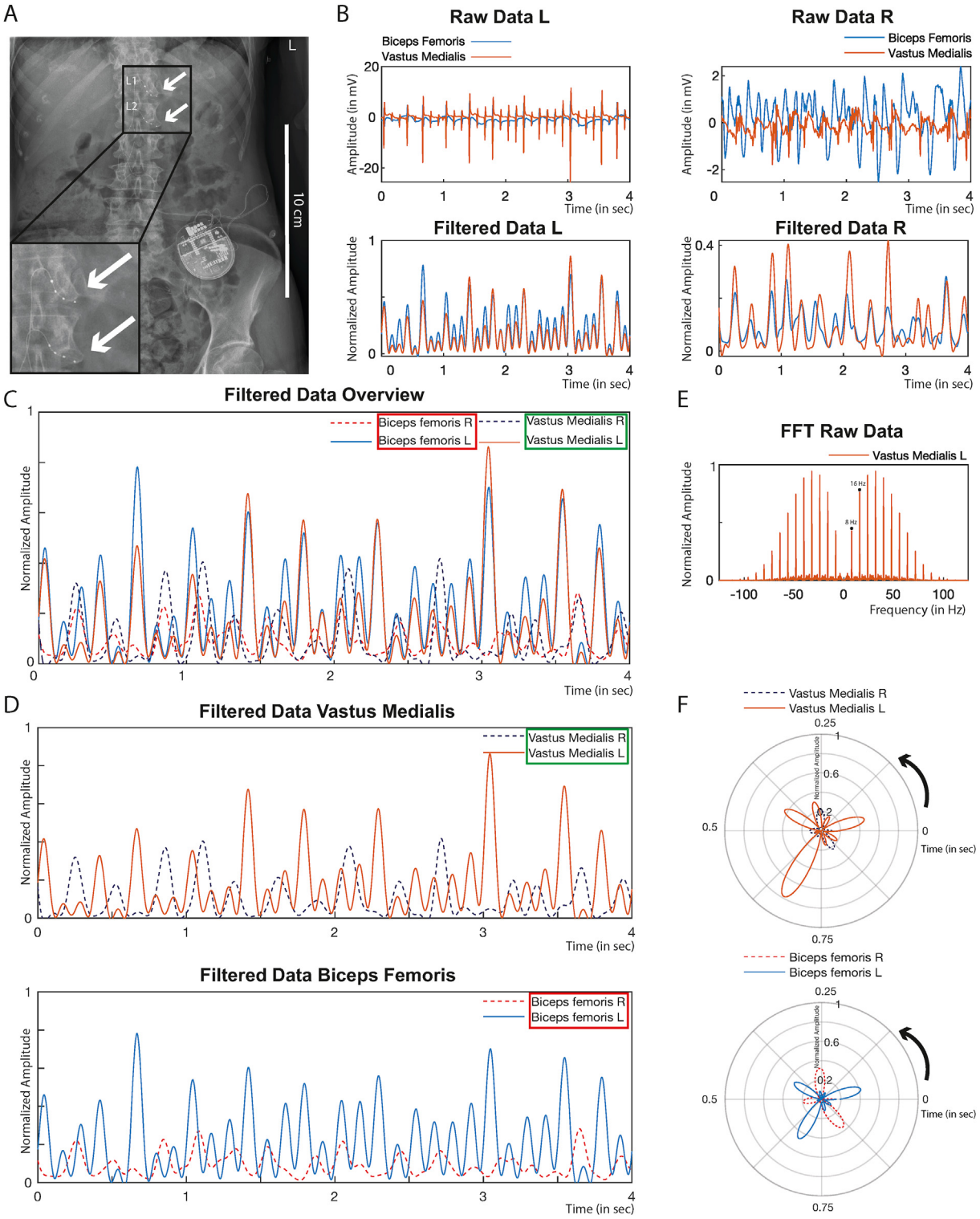

Fig. 1. Overview of the case report.
A) Frontal view of the two implanted DRG-leads on level L1 and L2 on the left side (*see white arrows*). Additionally, the Pulse Generator (IPG) implanted in the left lower abdomen is visible, connected to the DRG-leads through lead-extensions. **B)** Overview of the Biceps Femoris (BF) and Vastus Medialis (VM) EMG-traces during the bilateral motor response evoked by unilateral stimulation on the left L2-level DRG-lead (*PA* = 5.15 mA, *PF* =8 Hz, *PW* =200 μsec). As becomes clear from the traces, both muscles on the left and right side are activated during the stimulation. However, the muscle response on the left side (unilateral to stimulation) seems highest in amplitude. After filtering, linear envelopes were created from the data, after which the data was normalized. Especially the filtered traces demonstrate how both legs present with a co-contraction of the BF and VM. This co-contraction appears most clearly in the left leg. **C)** The filtered data of the bilateral upper leg muscles presented in one overview figure. Here, some first hints of left-right alternation can be appreciated. **D**) Separating out the traces in panel C for each of the muscles individually, shows the presence of left-right alternation more clearly, although not always rhythmically consistent. The number of peaks in especially the left traces seems to be consistent with the 8 Hz stimulation delivered by the IPG. However, the peaks clearly differ in amplitude. **E)** Here we display the frequency spectrum of the raw data of the left VM muscle, presented previously in panel B. Especially for this muscle we can confirm the presence of 8 Hz peaks (and its harmonics), in parallel to the stimulation frequency provided by the IPG. **F**) Polar plots created from the first second of the traces depicted in subpanel D, separated out per muscle. Again, the left-right alternation in muscle recruitment can be appreciated.

activation and inhibition of lower extremity muscles in the absence of conscious effort [4,5].

The existence of a spinal locomotor CPG in lower mammals such as rats, cats and rabbits has been well-established for decades starting with T. Graham-Brown in the early 1900s [6]. In humans, however, the presence of the locomotor CPG has been subject of controversy [4,5,7]. In contrast to animal studies, where invasive, decerebrate models can be used and neuronal circuitries manipulated, the human situation is more constrained [5]. Nevertheless, several cases of spontaneous, rhythmic lower limb movements in patients with SCI have been reported in literature [7,8]. Landmark studies have reported locomotor-like movements triggered by epidural stimulation of the midlumbar enlargement in children (near L3-L5) [9] or near L1-L2 in adult patients with mostly thoracic SCI [4]. In vitro studies with murine spinal cord also confirm L2 as a 'hotspot' for this pattern in the lower limbs [10].

In this case report, the patient specifically presented with CPG-like motor response during L2-level DRG-stimulation under high amplitude (4.8–6.0 mA) and low frequency (4–8 Hz) parameters. Neither lower-amplitude (*0.1 mA-4.8* mA, *tested in steps of 0.*1 mA) or higher-frequency (*tested for 10 and* 12 Hz) L2-level stimulation, nor L1-level stimulation (*tested for the range of 0-6.*0 mA, *0*–50 Hz*)*, lead to a similar bilateral CPG-like motor response. Within the vast body of literature studying locomotion in animal models, studies like that of Whelan et al. [11] seem to confirm the possibility of DR- or sensory-evoked rhythmic activity. A surprising observation in our case, was that of the co-contraction of the upper leg muscles. This type of co-contraction has been reported before in the case of a chronic SCI patient presenting with rhythmic alternations of the lower extremities [7]. Here also, the underlying mechanism remained unelucidated.

The patient presented in this report was fully motor intact, which is usually not considered to be the state of the spinal cord in which these patterns can be activated [4,5]. A component of voluntary movement could therefore be present in the EMG-traces. This voluntary component need not just be restricted to the non-stimulated leg but might also be present *unilateral* to stimulation: as visible in Video 1, stimulation-evoked response in the left leg could be modulated when the patient was performing upper-extremity tasks. However, a change in lead-tissue contact due to postural changes cannot be excluded as an explanation. In short, to conclusively report presence of a CPG-driven motor response in our case remains subject to debate. The bilateral, left-right alternating nature of the response under *unilateral* stimulation, however, remains indicative of the involvement of modulating spinal circuitry.

Our ability to recruit CPG-like spinal circuitry using DRG-stimulation is of particular interest in the domain of SCI research, where this spinal circuitry is thought to be a facilitator of neurorehabilitation [12].

Declaration of competing interest

FJPMH 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 (nowadays Abbott). FJPMH and BSH have applied for a patent in relation to the present work. CIDZ has received several research grants from the Medical NeuroDelta, LSH-NWO Crossover INTENSE, and ZonMW. The authors report no other financial conflict of interest.

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