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Table of Contents

Fulll Length Papers

Abstracts

Full Length Papers

Jose L. Vargas Luna*, Anna Pataraia, Richard Crevenna, Winfried Mayr and Milan Dimitrijevic

Estimation of the time fluctuation of polysynaptic responses evoked by constant spinal cord stimulation

https://doi.org/10.1515/

Abstract: Polysynaptic activity is necessary to engage the neural circuitry that controls the motor behaviour and is crucial to the recovery after spinal cord injury (SCI) [1]. Polysynaptic responses can be elicited with spinal cord stimulation, and there are few reports on these types of responses in human electrophysiology, most of them describing them as constant to fixed stimuli. However, we have observed that the responses fluctuate in amplitude and time. Amplitude variations can be analysed with statistical methods. However, time fluctuations are more complex due to the multiple parameters involved. This work describes a methodology to analyse the time fluctuation in the responses of each pulse. It is based on the calculation of the signal temporal centroid, representing the whole activity, weighted by its latency, in a single time value. This value is then used to model the temporal fluctuation with linear regression. The methodology was verified with an electromyography dataset from a discomplete spinal cord injured patient with spinal cord stimulation. The parameter is able to follow small changes in the responses' distribution. Examples of how the temporal centroid and linear model identify the fluctuations are presented. Once fitted in a linear model, the fluctuation coefficient describes time fluctuations in the interneuron processing and, together with amplitude metrics, can characterise changes in polysynaptic responses during the application of fixed stimulation parameters.

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Keywords: Spinal Cord Stimulation, Polysynaptic responses, EMG, spinal cord injury, temporal centroid

1 Introduction

Spinal Cord Stimulation (SCS) is getting traction as more and more reports show the potential benefits of motor recovery in spinal cord injured people [2]. In a previous report, we have shown that SCS eliciting long-latency responses facilitates the initiation of rhythmic or sustained activity in muscles [3]. These long-latency responses are projections of the spinal cord's polysynaptic activity to the muscles, *e.g.* lower limb muscles, and are observed in the electromyographic (EMG) activity as polysynaptic responses. They are composed of multiple asynchronous potentials that form discharges or groups. Regardless of their importance, polysynaptic responses are not well characterised in their morphology and spatio-temporal pattern, and the factors of influence are not sufficiently studied and understood in detail with in-vivo models yet.

Electrophysiology of the human body is associated with complex dynamic processes, and while nothing is really constant, it is common practice to presume stable responses to repeated electrical stimuli. Even though all controllable variables are fixed (intensity, frequency, electrode position, posture, anatomy, SCI), changes in the central state of excitability can often induce amplitude and time fluctuations. This static assumption is established in clinical practice and helps to assess electrophysiological behaviour and identify features of pathophysiological mechanisms. However, it fails to describe both monosynaptic and polysynaptic response fluctuations. For monosynaptic responses, at least small latency fluctuations and substantial amplitude changes have been reported earlier [4]. On the other hand, there is less information in polysynaptic responses, which can substantially vary in all their components—latency, amplitude, duration and grouping.

Simple statistical methods can analyse amplitude fluctuations (*e.g.* mean, variance). However, time fluctuations represent a more significant challenge since the polysynaptic part of the response can be constituted by multiple grouped potentials (bursts), varying delays, durations and amplitudes, which can increase or decrease independent of each other. Therefore, just comparing the PS response variables' mean and variability will not accurately reflect the time fluctuations in all the dimensions. This work introduces a methodology to analyse the time fluctuation based on the analogous concept of centre of mass, the temporal centroid. It provides a representation of time fluctuation on polysynaptic responses evoked in a single case exploratory analysis.

2 Methodology

2.1 Estimation of time fluctuation

As mentioned, the polysynaptic responses have more variables than the mono- or oligosynaptic responses. The number of groups, their latency, amplitude, and duration are among the variables of polysynaptic responses. This makes them complex to analyse since the polysynaptic responses of two contiguous pulses are often not comparable. It is crucial to remember that polysynaptic responses are mostly seen at low intensities and reflect the polysynaptic activity on the neural networks of the spinal cord. This differs from mono- and oligosynaptic responses, which have more defined reflex pathways. If we analyse polysynaptic responses under this perspective, a variable representing the time component of the polysynaptic activity becomes useful for characterising temporal features in comparable form. The concept is analogous to the centre of mass of an object, which describes the mass distribution of an object as a standardised interaction point with external forces.

The centre of mass is defined as the equilibrium point where the weighted relative position of the distributed mass of an object sums zero [5]. Figure 1 describes the concept, where different masses m_1 to m_N are distributed along the length of the system with the variable distances of x_1 to x_N. Under these conditions, the centre of mass is calculated with eq 1.

$$\boldsymbol{X_{cm}} = \frac{\sum_{i=1}^{N} \boldsymbol{m_i x_i}}{\sum_{i=1}^{N} \boldsymbol{m_i}} \qquad (1)$$

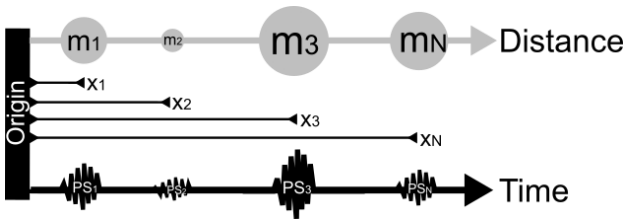

Figure 1: Representation of the mass distribution along with the spatial distribution of an object (grey circles) and the temporal distribution analogy of an EMG signal with multiple polysynaptic responses.

In the case of polysynaptic activity, we want to find a representative point for time distribution instead of a spatial one, the temporal centroid. The mass equivalent is the amplitude of the polysynaptic responses, and the response latencies would represent the distance values.

The polysynaptic bursts are identified as clusters of samples above the noise threshold with at least 10ms duration. Additionally, if two contiguous supra-threshold samples are 5ms apart, then they are considered part of different clusters [3]. This is necessary to calculate individual polysynaptic discharges' amplitude, latency, and duration. It is also useful to visualise how the analysis principle is analogous to the mass problem (Figure 1); however, processing large datasets can become time-consuming.

This additional processing can be avoided if the background noise remains constant for the period between pulses. If this assumption is valid, and mono- and oligosynaptic responses are excluded from the analysis, the whole recorded signal can be used for the calculation. For this report, only samples between 70 and 420ms post-stimulation are considered. With these considerations, eq. 1 can be adapted to eq. 2

$$\boldsymbol{T_c} = \frac{\sum_{i=1}^{N} \boldsymbol{s_i t_i}}{\sum_{i=1}^{N} \boldsymbol{s_i}} \qquad (2)$$

Where T_c is the temporal centroid, and s_i is the sample occurring at time t_i. This form is much more efficient for calculation since it is done with matrix operations. If no responses are detected on the analysed period, T_c will tend to the middle values of the time range, 245ms in this case (the middle between 70 and 420ms).

After calculating the temporal centroid of the responses for each pulse, the data are approximated using a regression for the linear model in eq. 3

$$\boldsymbol{T_f} = \boldsymbol{f} * \boldsymbol{PN} + \boldsymbol{c} \qquad (3)$$

Where *f* is a fluctuation coefficient (slope) indicating how much the temporal centroid changes with each subsequent pulse, *PN* is the pulse number, and *c* is a constant.

For the purpose of this work, all data were processed in MATLAB (The MathWorks Inc., Natick, MA, USA).

2.2 Validation dataset

2.2.1 Subject

The methodology was validated using the electromyographic responses of a discomplete SCI. The subject was a 25-year-old male four years post-SCI. The injury level is C4 and has an AIS A classification. The data from this subject was retrospectively extracted from a database since it exemplifies different fluctuation patterns. The underlying study, from which the data was extracted, was approved by the local ethics committee, conducted in compliance with the Helsinki Declaration, and all participants gave their informed consent before the procedures.

2.2.2 Assessment methodology

The spinal cord stimulation was applied with an implanted quadripolar epidural electrode (3487A, Medtronic, Minneapolis, USA). The electrode was placed in the posterior epidural space, centred over the vertebral levels T11-L1. The final position was such that the contact at the tip of the electrode evoked the largest responses in the quadriceps muscle groups.

The stimulation was applied at 2.1pps (minimum repetition rate of the stimulator). The stimuli consisted of asymmetric biphasic pulses with a stimulating phase of 210µs, and an amplitude range from 1V to 10V or maximum comfortable intensity. The setup allowed the allocation of the cathode (+) and anode (-) to any of the four contacts or the stimulation case, providing multiple electrode configurations. For example, 2-1+, means cathode in contact 2 and anode in contact 1.

The responses evoked by the SCS were monitored on the quadriceps, hamstrings, tibialis anterior and triceps surae bilaterally via surface electromyography (sEMG). In addition, an additional channel was placed on the lower trunk muscles to monitor the stimulus artefact, indicating the stimulation onset. The sEMG was amplified via a Grass 12A5 system (Grass, Quincy, MA, USA), adjusted to a gain of 5000 and a bandwidth of 50–800 Hz, and digitised at 2 kHz with a 12-bit resolution by a CODAS ADC system (DATAQ Instruments, Akron, OH, USA). A more detailed description of the methodology can be found in our previous reports [3].

3 Results

The methodology was applied to the whole dataset; the results are shown in Figure 2. The thin green line represents the temporal centroid at each pulse, while the thick line shows the linear regression of the data. The blue line on the left is proportional to the area under the curve of the polysynaptic discharges. The monosynaptic responses are not clearly shown since the plot focuses on the polysynaptic response.

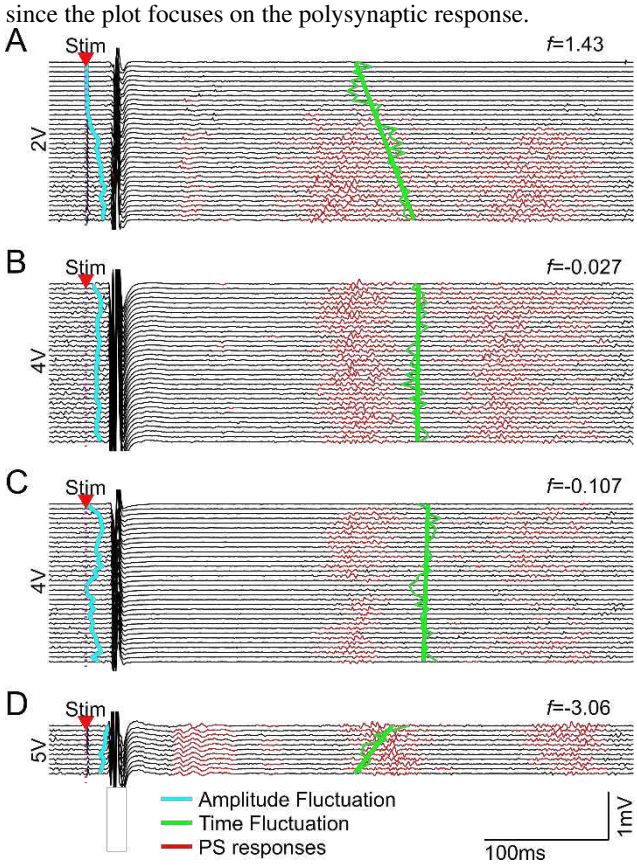

Figure 2. Sequences of responses (first one on top) on the triceps surae evoked by spinal cord stimulation at 2pps using A) 2V and 0-C+; B) 4V and 2-1+; C) 4V with 0-2+; and D) 5V and 3-C+.

Figure 2A shows that on the first pulses, the value is near 245ms, which is the expected behaviour when no polysynaptic responses appear. It can also be seen that after small activity appears around 80ms, it rapidly steers the temporal centroid to the left, showing that the value is quite sensitive. Furthermore, the linear regression correctly follows the signal as stronger activity appears at the end of the pulse, having a final value of

f = 1.43. The overall fluctuation factor (slope) can be used for discriminating the presence of a fluctuation if adequately adjusted to each setup. For this specific setup, deviations larger than 1ms per pulse clearly indicate fluctuation, although half that value could also work.

In the case that polysynaptic discharges are stable, the temporal centroid also performed as expected (figure 2B), having a minimal fluctuation coefficient (f = 0.027) and only negligible variability.

Figure 2D shows the case when fluctuation is not visually apparent. Nevertheless, this methodology can identify a fluctuation caused by the decrease in amplitude of the discharges in the middle and end of the signal, having a strong f = -3.06. It is crucial to notice that, unlike Figure 2A, in Figure 2D the value is negative, indicating the direction of the fluctuation.

Finally, Figure 2C shows a case where there is a fluctuation in amplitude (blue line on the left), which the temporal centroid cannot detect (f = 0.107). This shows that both metrics must be combined to characterise the fluctuation of polysynaptic response.

4 Conclusion

Here, we present a methodology to estimate the time fluctuation of polysynaptic responses evoked by fixed spinal cord stimulation. It was designed to identify signals that fluctuate in time by increasing the magnitude of the f value, and giving a smaller magnitude to signals that are stable over time or have a rhythmic activity (if the entire cycle is included).

It is based on an easily calculated temporal centroid and indicates the action potentials distribution estimated via the EMG area in the studied muscle. This tool has shown to have enough sensibility to detect changes in latency and the distribution of the responses along with the whole pulse. Additionally, the sign indicates the fluctuation direction.

Future developments would include the analysis of the model error, that can could indicate rhythmical activity, which the current model cannot identify if the cycles are complete.

This tool, together with an amplitude-related variable like standard deviation or variance, can identify amplitude and time fluctuations, making it easier to characterise these types of responses and hopefully, helping to understand the mechanisms that govern them.

Author Statement

Research funding: The author state no funding is involved. Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from the individual included in this study. Ethical approval: The research related to human use complies with all the relevant national regulations, and institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the local ethics committee. The participant gave their informed consent before the procedures.

References

[1] Flynn JR, Graham BA, Galea MP, et al. The role of propriospinal interneurons in recovery from spinal cord injury. Neuropharmacology [Internet]. 2011;60:809–822. Available from: http://dx.doi.org/10.1016/j.neuropharm.2011.01.016.

[2] Darrow D, Balser D, Netoff TI, et al. Epidural Spinal Cord Stimulation Facilitates Immediate Restoration of Dormant Motor and Autonomic Supraspinal Pathways after Chronic Neurologically Complete Spinal Cord Injury. J Neurotrauma. 2019;36:2325–2336.

[3] Vargas Luna JL, Brown J, Krenn MJ, et al. Neurophysiology of epidurally evoked spinal cord reflexes in clinically motor-complete posttraumatic spinal cord injury. Exp Brain Res [Internet]. 2021; Available from: https://link.springer.com/10.1007/s00221-021-06153-1.

[4] Minassian K, Jilge B, Rattay F, et al. Stepping-like movements in humans with complete spinal cord injury induced by epidural stimulation of the lumbar cord: electromyographic study of compound muscle action potentials. Spinal Cord [Internet]. 2004 [cited 2014 Dec 22];42:401–416. Available from: http://dx.doi.org/10.1038/sj.sc.3101615.

[5] Wikipedia. Center of Mass [Internet]. [cited 2022 Mar 24]. Available from: https://en.wikipedia.org/wiki/Center_of_mass.

Paul Werginz*, Andrea Corna and Günther Zeck

Avoidance of axonal activation in epiretinal implants using short biphasic pulses

https://doi.org/10.1515/

Abstract: Retinal implants allow patients suffering from degenerative retinal diseases to regain visual percepts. Despite considerable effort in developing and improving retinal neuroprostheses in the last decades, the restored vision in patients does not achieve sufficient quality. The elicited percepts do not accurately match the stimulating pixels and therefore the formation of high acuity vision is hindered. One of the main obstacles in epiretinal implants is the concurrent activation of cells close to a stimulating electrode and cells that have their axons traversing the electrode. In this study, we use computational modeling to examine the effect of pulse duration on the selectivity of focal versus non-focal activation. Our results suggest that biphasic pulses in the range of 10-20 microseconds can prevent axonal activation while still reliably activating target neurons.

Keywords: retinal implant, electrical stimulation, retinal ganglion cells, microelectrode array

1 Introduction

Today, patients suffering from retinal degeneration have the possibility to regain a rudimentary kind of vision by retinal prostheses [1]. Modern neurotechnology allows the remaining, healthy cells in the retina of blind patients to be stimulated electrically and therefore to convey visual information to the brain. Aside from the technical and surgical challenges involved in the development of a retinal implant, many other obstacles related to the specific layout and complex physiology of the retina have to be overcome. The basic idea behind a retinal implant is to focally activate target neurons in the vicinity of a stimulating pixel (electrode) and therefore create a pixelized version of the visual scene. In epiretinal implants, with retinal ganglion cells (RGCs) as target neurons, a problem of particular interest is the concurrent activation of cells close to a stimulating electrode and cells with their cell bodies far distant but axons that traverse below the stimulating electrode. Because of concurrent cell activation, the resulting percept has been reported to be streak-like [2] and therefore an accurate pixelized version of the outer world cannot be created. Several strategies to avoid axonal activation such as long biphasic pulses [3] as well as bi-electrode stimulation [4] have been proposed. Here, we examine the response of RGCs to epiretinal stimulation for short pulse durations using a computational model. In experiments, short pulses in the range of 100 µs have been shown to increase the difference of axonal versus focal thresholds [3] and therefore we sought to study responses for even shorter pulses down to 10 µs. Our results suggest that shorter pulses increase the axonal/focal threshold ratio and therefore may be applicable to generate more focal responses during epiretinal stimulation.

2 Methods

To study the response of RGCs to electrical stimulation *in-silico*, we used morphologically- and biophysically-realistic multicompartment models of mouse ON-alpha RGCs [5]. Extracellular electric stimulation was applied via disk electrodes from the epiretinal side. Extracellular potentials were calculated based on an analytic approach [6]. The modeled retina consisted of 100 RGCs in a rectangle 500x150 μm^2 (Fig. 1A). The z-distance between each cell's soma center and the electrode was 15 µm. We tested rectangular monophasic and biphasic symmetric charge balanced current pulses with durations of 10, 20, 50, 100 and 200 µs (Fig. $1B_1$). Additional simulations were performed with real pulse shapes applied by a CMOS-based Microelectrode array (MEA) [7] and measured as described [8] (Fig. $1B_2$). For the used MEA pulse duration was limited to ≥20 µs. Activation threshold was computed for each cell in the retina and thresholds were compared between cells below the electrode (focal, **1** in Fig. 1) and cells that had their axons passing the stimulating electrode (axonal, **2** in Fig. 1). Threshold ratio for each cell was computed as Thresh / $Thresh_{Min}$ with $Thresh_{Min}$ being the overall minimum threshold across all cells.

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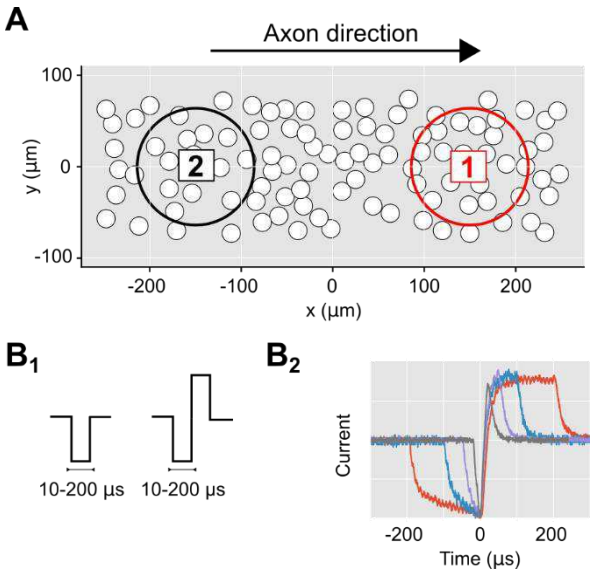

Figure 1: *In-silico* retina model and stimuli used for simulations. **A**) 100 RGCs (white circles) were distributed evenly on the retinal surface. The stimulus electrode (1) was 128 µm in diameter. Threshold ratios were compared between cells below locations 1 and **2**, respectively. RGC axon direction is indicated by the black arrow. **B**) Idealized mono- (left) and biphasic (right) pulses ($\mathbf{B_1}$) as well as measured current output from a CMOS-based Microelectrode Array($\mathbf{B_2}$).

3 Results

This study examines RGC thresholds in response to epiretinal stimulation. Our goal was to investigate the influence of current pulse duration on both, cells close to the stimulating electrode as well as cells far distant that have their axons traversing the stimulating electrode.

3.1 Focal vs. axonal response threshold

We compared focal and non-focal (axonal) activation by computing thresholds for all 100 cells in the model retina and further calculating the ratio between each cell's threshold and the lowest threshold of all RGCs (Fig. 2A). For the 200 µs pulse, thresholds were in the range of 2.2-7.1 µA with threshold ratios rather uniform across the whole retinal surface (Fig. 2A, top). Thus, axonal thresholds were in the same range as thresholds for cells right below the stimulation electrode and focal stimulation of target cells is not achievable. The shortest pulse duration tested (10 µs), on the other hand, resulted in a distinct low-threshold region around the stimulating electrode and higher axonal thresholds by up to a factor of 15 (Fig. 2A, bottom). On average, threshold ratios for cells far distant of the electrode were 4.1 times higher, creating a window of opportunity to activate target cells without activating passing axons. Threshold ratios for all pulses tested can be found in Table 1.

We also plotted transmembrane voltage over time for two RGCs at different stimulus amplitudes (Fig. 2B). One cell was located directly below the stimulating electrode whereas the other cell had its soma located approximately 300 µm distant of the electrode center. The threshold for focal cell activation was ~53 µA. Stimulus amplitude was increased to 2, 3 and 4x threshold amplitude to examine the resulting spiking activity in the two cells. Even at 3x threshold focal cell activation was possible (Fig. 2B, red traces), i.e., whereas the cell below the electrode initiated a spike the distant cell stayed silent (Fig. 2B, blue traces). Not until 4x threshold amplitude the distant cell fired an action potential.

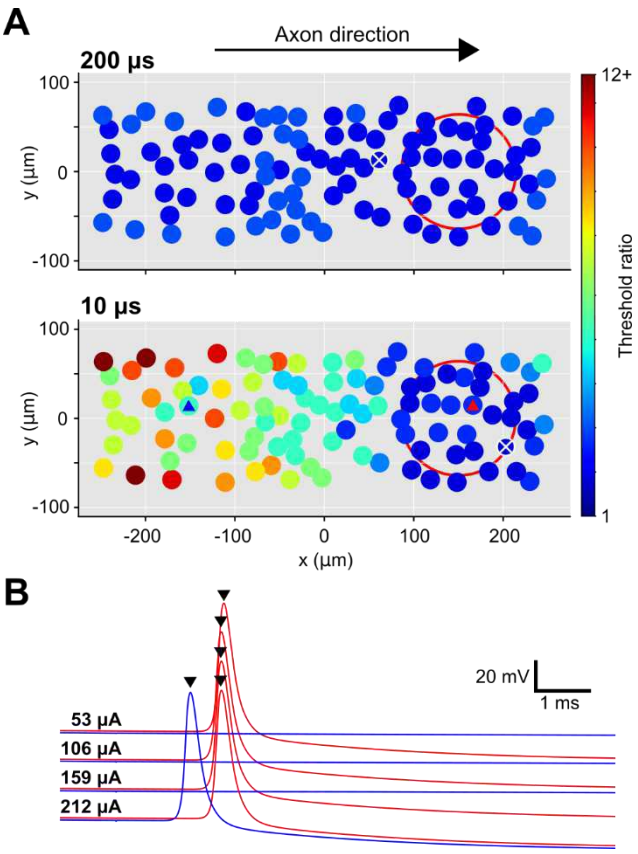

Figure 2: Short biphasic pulses prevent axonal activation. **A**) For each of the 100 simulated RGCs activation threshold was computed in response to the idealized 200 (top) and 10 µs (bottom) pulse. Cells were color-coded by their threshold ratio. The minimum threshold of all RGCs is indicated by the white '**x**'. **B**) Spiking activity in two cells marked by the blue and red arrowheads in A (bottom). Transmembrane voltage is plotted over time for each cell's distal axon for 4 different stimulus amplitudes. Arrowheads indicate action potentials.

3.2 Realistic pulse shape and idealized pulses

Our results using biphasic current pulses suggested that pulses in the range of 10 µs strongly increase axonal vs. focal threshold ratios and are thus useful to create more focal regions of activation. So far, however, only idealized biphasic pulses were applied which may not be easily generated by neurostimulators. Therefore, we measured the current output from a CMOS-based MEA [7,8] for different pulse durations (Fig. 1B$_2$) and used the measurements as inputs for our simulations. Similar to results from the idealized biphasic waveforms also measured waveforms resulted in increased threshold ratios allowing for focal stimulation of RGCs (Table 1). For example, mean threshold ratios for idealized and measured pulses were 5.25 and 4.47, respectively. Monophasic pulses, on the other hand, resulted in substantially lower threshold ratios indicating that the second balancing pulse in the biphasic pulse configuration is key for preventing axonal activation.

Table 1: Threshold ratios for RGC activation. Numbers in red indicate the mean threshold ratio for cells in (1) of Fig. 1A. Numbers in black indicate the mean threshold ratio for cells in (**2**) of Fig. 1A.

Pulse duration (µs)	Mean threshold ratios	
	Monophasic	Biphasic
10	2.79/3.14	1.90/7.80 | -----
20	2.57/2.89	2.77/5.25 | 2.64/4.47
50	2.23/2.42	2.20/3.38 | 2.25/3.25
100	1.88/1.94	1.89/2.44 | 1.93/2.39
200	1.58/1.54	1.54/1.72 | 1.60/1.74

3.3 Stimulation charge with short pulses

Short pulse durations require higher current levels to generate neural activity, and therefore we asked how the stimulation charge scales with decreasing pulse duration. We compared peak current and charge injection for all cells at threshold (Fig. 3). Biphasic pulses required higher peak currents than monophasic pulses for each pulse duration. Measured waveforms resulted in similar peak current as well as slightly lower charge levels when compared to the idealized biphasic pulses. The stimulation charge (calculated during the cathodic phase) increased moderately from 0.80 (200 µs) to 1.22 nC (20 µs) for the idealized pulses and from 0.76 (200 µs) to 0.90 nC (20 µs) for the measured waveforms.

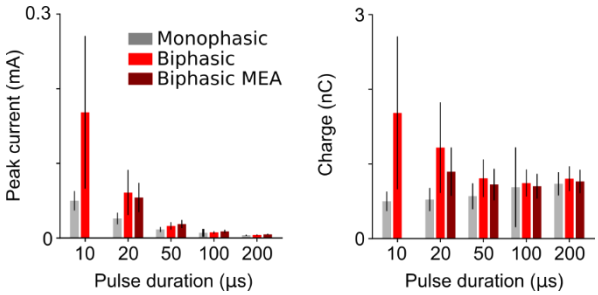

Figure 3: Peak current amplitude (left) and stimulation charge (right) at threshold for all cells.

4 Discussion

We modeled the response of a population of retinal ganglion cells to epiretinal stimulation and found that short biphasic pulses affect the ratio between axonal and focal activation. We did not investigate the underlying mechanisms but one likely factor to contribute to the differential responses for various pulse durations could be the Axon Initial Segment due to its high density of sodium channels [5]. A second potential mechanism could be the much larger somatic capacitance in comparison to the axonal capacitance.

Our results suggest that aside from the previously tested stimulation strategies to avoid axonal activation such as long duration pulses [3] and bi-electrode stimulation [4] also short biphasic pulses <50 µs can focally activate target cells close to the stimulating electrode without activating passing axons. To test the simulation results in experiments will be challenging as generating very short rectangular pulses may be difficult with current MEAs. Especially constraints on power consumption have to be considered when implementing short pulses. The used CMOS-based MEA can apply approximately 1.2 nC of charge/phase for an electrode 128x128 µm^2 in size. In our simulations, thresholds for cells close to the stimulating electrode were in the range of 0.6 nC when 10 µs biphasic pulses were used (Fig. 3, right). Thresholds are strongly dependent on the electrode-to-cell distance which in our study was set to 15 µm; a tight retina-MEA interface could therefore allow for the application of short pulses. Our measured data shows that for pulses shorter than 100 µs the resulting current waveforms can be strongly distorted (Fig. 1B$_2$). However, our simulations indicate that the non-rectangular waveforms have a similar effect on threshold ratios (Table 1) and therefore could still be beneficial to achieve focal cell activation.

Additionally, pulse shape could be optimized by modifying the input voltage waveform.

Author Statement

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References

[1] Palanker D, Le Mer Y, Mohand-Said S, Muqit MMK, Sahel JA. Photovoltaic restoration of central vision in atrophic age-related macular degeneration. Ophthalmology. 2020;127(8):1097-1104.

[2] Nanduri D, Fine I, Horsager A, Boynton GM, Humayun MS, et al. Frequency and amplitude modulation have different effects on the percepts elicited by retinal stimulation. IOVS. 2012;53(1):205-214.

[3] Weitz AC, Nanduri D, Behrend MR, Gonzales-Calle A, Greenberg RJ, et al. Improving the spatial resolution of epiretinal implants by increasing stimulus pulse durations. Sci Transl Med. 2015;7(318):318ra203-318ra203.

[4] Vilkhu RS, Madugula SS, Grosberg LE, Gogliettino AR, Hottowy P, et al. Spatially patterned bi-electrode epiretinal stimulation for axon avoidance at cellular resolution. J Neural Eng. 2021;18(6):066007

[5] Werginz P, Raghuram V, Fried SI. The relationship between morphological properties and thresholds to extracellular electric stimulation in α RGCs. J Neural Eng. 2020;17(4):045015.

[6] Newman J. Resistance for flow of current to a disk. J Electrochem Soc. 1966,

[7] Bertotti G, Velychko D, Dodel N, Wolansky D, Tillak B, et al. A CMOS-based sensor array for in-vitro neural tissue interfacing with 4225 recording sites and 1024 stimulation sites. 2014 IEEE BioCAS Proceedings. 2014.

[8] Corna A, Ramesh P, Jetter F, Lee MJ, Macke JH, et al. Discrimination of simple objects decoded from the output of retinal ganglion cells upon sinusoidal electrical stimulation. J Neural Eng. 2021;18(4):046086

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Hybrid FES-Exoskeleton Control for Walking Gait Correction

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Abstract: Walking gait correction is fundamental to restoring body motion function for patients. Functional Electrical Stimulation (FES) is regarded as a promising method and essential to Neurotherapy, and the exoskeleton is fast becoming a key instrument in rehabilitation. Applying FES or exoskeleton alone, however, has its inherent disadvantages. Therefore, the hybrid exoskeleton combined with FES promoted in recent years overcomes the deficiency of more degree of freedom control. In this paper, a hybrid FES-Exoskeleton for walking gait control was first proposed and evaluated. With the Force Sensing Resistors (FSR) sensor, the exoskeleton actively assists in walking. Simultaneously, it also triggers the FES of the soleus, tibialis anterior, and gastrocnemius muscles for dorsilflexion and plantar flexion. Later, three different control strategies are employed for the pulse-width controlled FES. Eventually, an ILC with a PID controller is applied in the hybrid exoskeleton, following the best foot angle trajectory.

Keywords: Functional Electrical Stimulation (FES), Hybrid Exoskeleton, Walking gait control, ILC control, Force Sensing Resistors (FSR).

1 Introduction

Restoring body motion function, for example, sit-to-stand and walking, after stroke or spinal cord injury (SCI) is regarded as a remarkable goal of rehabilitation. Functional electrical stimulation is a promising method and fundamental to Neurotherapy [1]. Recent research investigates the FES application for body motion rehabilitation on upper limbs or lower limbs [2]. Along with the exoskeleton, the hybrid exoskeleton combined with FES may overcome the limitation of the exoskeleton or FES alone. Previous work has established that the exoskeleton could supply additional power for lower-body movements like walking or sit-to-stand [3]. Most of the exoskeletons provide lower limb assistance, in which the motors are mounted on the hip and knee. It lacks one degree of freedom on the ankle joint. In this work, we utilized the FES on the lower leg for additional joint control (plantar flexion and dorsilflexion).

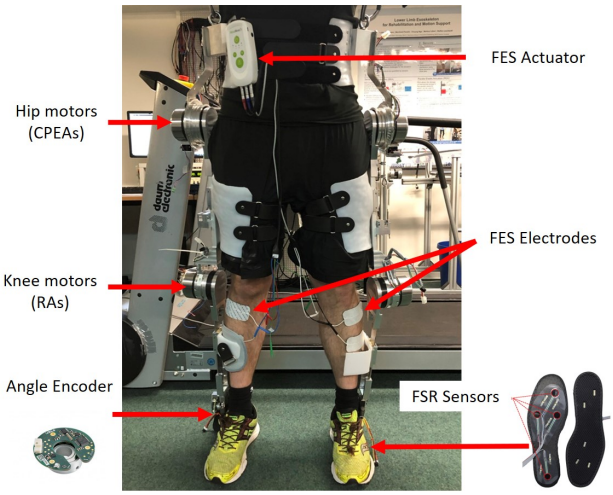

Fig. 1: Lower limb hybrid FES-Exoskeleton with FSR sensor and two channels electrodes.

A hybrid FES-Exoskeleton for walking gait control was first proposed and evaluated. This paper attempts to show the feasibility of the FES application on the exoskeleton for ankle control. The hybrid control system combines the Force Sensing Resistors (FSR), which could detect the gait phase of the patient, and angle encode, which could transfer the real-time degree as feedback for the FES system. Later, three different control strategies are integrated and compared for walking correction. By employing the ILC with PID control, the overall angle RMSE can be controlled under 5.42° during walking.

2 Methods

2.1 Exoskeleton

An active lower limb exoskeleton is applied in the hybrid system. Four motors providing additional torque when walking are mounted on the knee and hip. The whole frame of the exoskeleton is designed to assist lower body motion. Based on the previous work [4], FSR sensors combined with angle encode, which are installed in the shoes, trigger the different legs for further FES control.

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The hybrid exoskeleton is presented in Fig. 1. Stance leg and swing leg shift alternately during the gait. Via custom-designed thin-film FSR, the force data from the sole are measured, from where the exoskeleton is triggered by one side of the FSR. The distinction between these two states is based on implemented threshold values and determines whether the test person is ready for the next step. Based on the motion trajectories of hips and knees, a subordinate cascaded position control strategy is implanted on electric joint actuators. The design of the low-level controller assumes a gait cycle of about 2.8 s with a standstill pause of 0.1 s. The flowchart in Fig. 2 serves as an overview of the FSR-triggered gait phase control.

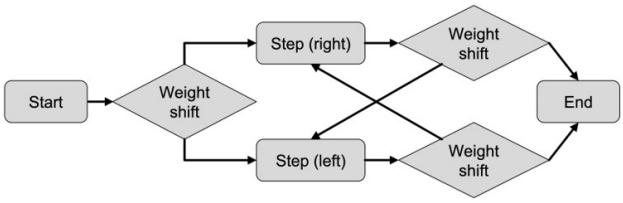

Fig. 2: Flow chart for the FSR-triggered gait phase control.

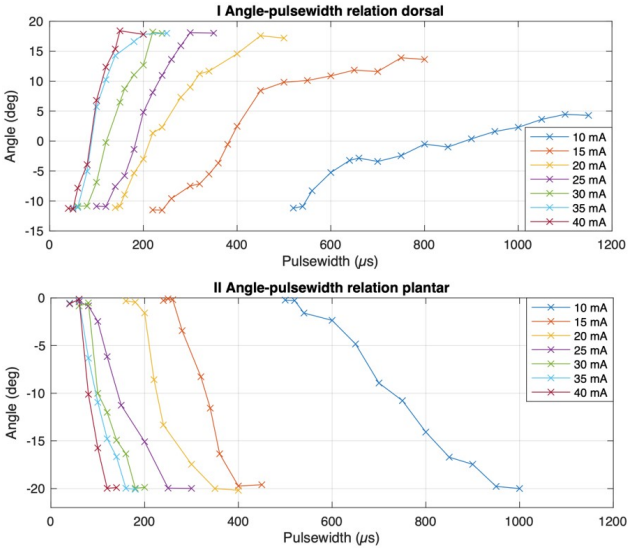

Fig. 3: Angle-Pulse width relation for (I) dorsilflexion and (II) plantar flexion of subject.

2.2 FES

RehaMove3 stimulator (Hasomed GmbH, Magdeburg, Germany) is utilized to combine the hybrid exoskeleton. It can generate rectangular, bi-phasic-shaped impulses. These impulses provide current amplitude from 0 to 150 mA (resolution of 0.5 mA), pulse width from 10 to 4000 μs, and frequency from 1 to 500 Hz. Two pairs of electrodes are attached to the front and back of the leg to stimulate the soleus, tibialis anterior, and gastrocnemius muscles for dorsilflexion and plantar flexion control.

The angle of the footplate ranges from -12° (dorsal) to +18°(plantar). FES-induced muscle contractions are dependent on three parameters, current, frequency, and pulse width. Pulse-width control is applied on FES, and the angle-pulse width relation between dorsal and plantar are evaluated. Fig. 3 describes the angle and FES pulse width relation in dorsilflexion and plantar flexion under the different currents (from 10 mA up to 40 mA) of 30 Hz frequency to find the optimal other parameters in the FES application. In the experiments, the angle is detected by the angle encoder Orbis (RLS Merilna tehnika d.o.o., Zeje pri Komendi, Slovenia), which is a absolute rotary encoder and consists of two components, a diametrically magnetized permanent ring magnet and a printed circuit board.

Except for the constrictions by FES, long-term muscle fatigue in FES control is needed to consider [5, 6]: On the one hand, a higher current covers more pulse width but will make the leg muscle group fatigue sooner, which is not suitable for long-term walking gait rehabilitation. On the other hand, a lower current could prevent fatigue to a certain extent, but it is hard to control. Therefore, the current and frequency of FES are constant with 20 mA 30Hz for dorsilflexion and 25 mA 30 Hz for plantar flexion respectively.

2.3 Hybrid Control

FES and exoskeleton are combined and synchronized to the computer separately via the dSPACE and NI data acquisition. Fig. 4 shows the connection between the two systems, and also illustrates the hardware-in-the-loop test environment for the exoskeleton including the FSR soles and the stimulator. FSR is not only part of the exoskeleton connected to the dSPACE, but also connected to the DAQ system for synchronization and triggering.

Principally, both systems run in parallel. The dSPACE box is programmed in MATLAB/Simulink to control the exoskeleton via the Control Desk. FES stimulator is operated in another user interface to cooperate exoskeleton. Both models are triggered by dSPACE´s Control Desk and an implemented physical voltage change in the connection to the NI USB-6259 integrated into Simulink. This procedure provides an additional safety feature and ensures the user to active stimulation for launch at the desired time. The signals from the FSR soles are also transferred to the FES system via a branch of the cable.

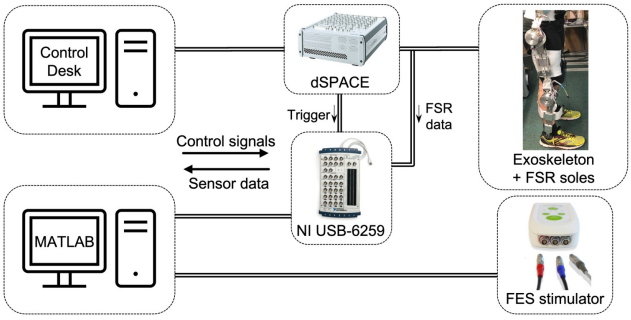

Fig. 4: Hardware in the loop test environment for the exoskeleton and simulator.

3 Results

The exoskeleton is evaluated with the trajectory following. As shown in Fig. 5, the left leg reference and output values of the knee motor M1 (I) and the hip motor (II) are given. The output of two motors reveals that the exoskeleton works well in the walking motion, and it is clear that the errors for the two joints in the control loop are relatively slight.

Furthermore, phases a, b, c, d represent the four walking postures from one sensor on the heel to the two sensors on the side of the middle foot and then to the one sensor on the toe. The chosen starting moment corresponds to the entry into the initialization phase e, which begins 1 s before the actual gait cycle. The gait phase-shifting detected by the threshold value of the FSR is shown in the control panel (III). The gait phase detection implemented for dSPACE confirms that phases a and b last correctly for 1.4 s, while phases c and d exit when the force conditions are satisfied. In addition, the deviation between the detected gait phases of Simulink and the control panel is illustrated (IV). Both parts of the evaluation have been preprocessed to begin at the same moment and display a 60 s gait experiment.

Tab. 1: Comparison of three different control strategies

	Duration	Controller	Parameters	Angle RMSE
1	40 s	ILC	$\Delta t = 0.3s$	$6.24°$
2	40 s	ILC	$\Delta t = 0.4s$	$6.93°$
3	40 s	PID	$PID_{thres} = 0.05$	$5.92°$
4	40 s	PID	$PID_{thres} = 0.025$	$5.46°$
5	40 s	ILC&PID	$\Delta t = 0.3s$ & $PID_{thres} = 0.025$	$5.42°$
6	40 s	ILC&PID	$\Delta t = 0.4s$ & $PID_{thres} = 0.025$	$7.96°$

If we now turn to the FES, we apply the ILC, PID, and PID & ILC combination in the functional electrical stimulation control based on the well-performance exoskeleton for the foot angle control. Table. 1 summarizes the three different strategies and their results in the following experiments in Fig. 6, where the comparison indicates that ILC & PID hybrid presents the best performance in gait control.

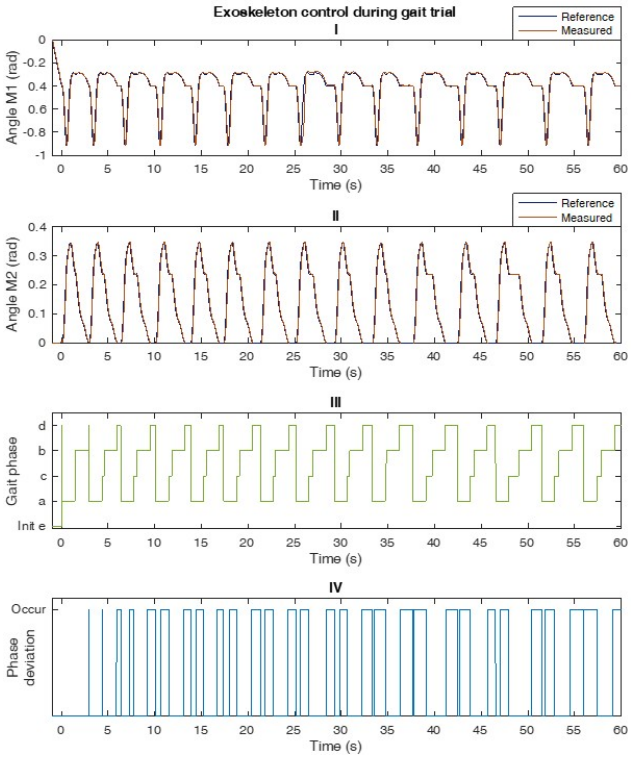

Fig. 5: Evaluation of gait trial, exoskeleton control. (I) Reference and actual angle of the knee motor M1, (II) reference and actual angle of the hip motor M2, (III) detected gait phases, (IV) deviation between detected gait phases between MATLAB and dSPACE.

This experiment lasts 40 s long and records dorsilflexion and plantar flexion. Angle trajectories reference and measurement data are contrasted (I), and then the RMSE of the angle per period over the entire experiment can be seen in Fig. 6-(II). The parameters of the ILC are inherited for the learning rate to be fixed at γ = 0.01 while the learn intervals Δtl = 0.3 s and PID_{thres} = 0.025. In addition to the normalized ILC output (III), both aligned PID outputs (IV) and the resulting pulse widths (V) are also plotted. Further analysis shows that in general ILC &PID control strategy follows the reference well and decreases the overall angle RMSE around $5.42°$. The reason why the RMSE fluctuates near the $5.42°$ could be the learning time of ILC at the beginning. Besides, muscle fatigue would also be a factor that affects muscle construction. In summary, the results of this study pave the way for a hybrid exoskeleton with an ILC and PID control on lower limb rehabilitation.

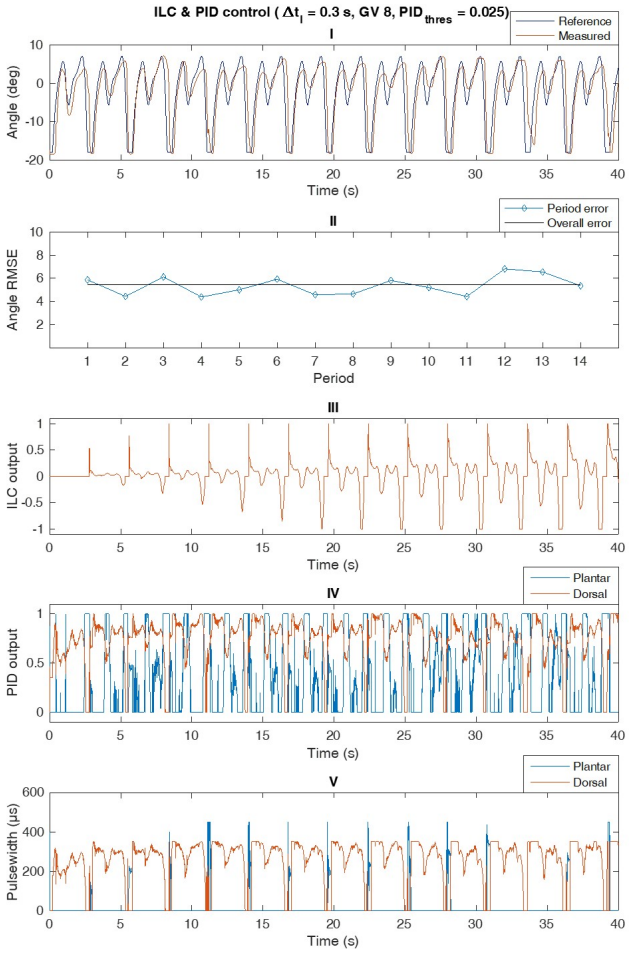

Fig. 6: ILC and PID control with $\Delta tl = 0.3s$ and $PID_{thres} = 0.025$.(I) Reference and actual joint angle, (II) RMSE of the angle per period and overall, (III) ILC output, (IV) PID output, (IV) resulting pulsewidths.

4 Conclusion

This study discussed the combination between FES and exoskeleton application in walking gait. The present research aimed to examine the control possibility of the hybrid exoskeleton, and the second aim of this study was to investigate different control strategies for walking gait correction. These experiments confirmed that FES can be used as rehabilitation and correction tools during walking, and PID with ILC control could better follow the ankle position. In general, therefore, it seems that FES-Exoskeleton could provide a new approach for drop foot and walking correction. Also, this combination of application and control strategies lay the groundwork for future research into lower body motion control. The question raised by this study is the precise angle control and muscle fatigue during the walking trails. Further research might explore the fatigue model of the lower leg and adjust dynamic ILC & PID parameters in control strategies.

Author Statement

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References

[1] Cheung VCK, Niu CM, Li S, Xie Q, Lan N. A Novel FES Strategy for Poststroke Rehabilitation Based on the Natural Organization of Neuromuscular Control. IEEE Rev Biomed Eng. 2019;12:154-167.

[2] I. L. Petersen, W. Nowakowska, C. Ulrich and L. N. S. A. Struijk, "A Novel sEMG Triggered FES-Hybrid Robotic Lower Limb Rehabilitation System for Stroke Patients," in IEEE Transactions on Medical Robotics and Bionics, vol. 2, no. 4, pp. 631-638, Nov. 2020.

[3] Penzlin, B.; Bergmann, L.; Li, Y.; Ji, L.; Leonhardt, S.; Ngo, C. Design and First Operation of an Active Lower Limb Exoskeleton with Parallel Elastic Actuation. Actuators 2021, 10, 75.

[4] Penzlin B, Enes Fincan M, Li Y, et al. Design and analysis of a clutched parallel elastic actuator[C]//Actuators. Multidisciplinary Digital Publishing Institute, 2019, 8(3): 67.

[5] R. Riener, M. Ferrarin, E. E. Pavan and C. A. Frigo, "Patient-driven control of FES-supported standing up and sitting down: experimental results," in IEEE Transactions on Rehabilitation Engineering, vol. 8, no. 4, pp. 523-529, Dec. 2000.

[6] R. Riener and T. Fuhr, "Patient-driven control of FES-supported standing up: a simulation study," in IEEE Transactions on Rehabilitation Engineering, vol. 6, no. 2, pp. 113-124, June 1998.

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The effect of neuromuscular electrical stimulation on skin temperature in individuals with spinal cord injury: A prospective non-controlled intervention study

Neuromuscular electrical stimulation on skin temperature

https://doi.org/10.1515/

Abstract: The research on the effect of neuromuscular electrical stimulation (NMES) protocol on skin temperature (Tsk) in individuals with spinal cord injury (SCI) is a prospective non-controlled intervention study. 47 individuals with SCI were recruited from the outpatient clinic. NMES was applied to the tibial anterior (TA) muscles. Four assessments were performed: baseline, shortly after the end of NMES session (t0), 10 min after the end of NMES (t10) and 20 min after the end of NMES (t20). The intensity used was 1.5 mA RMS (root mean square) depending on the individuals. The variables were Tsk at forehead, dermatome C2 and L5 bilaterally. The dermatome C2 and forehead were measured only at baseline and t20. The measurement device was a non-contact infrared thermometer. Results of this study demonstrated that after NMES the stimulated dermatome (L5), showed an increase in local Tsk. In addition, the t20 showed that the Tsk did not drop to the baseline, being still significant in the analyzed group. The implications for rehabilitation practice and the positive effects of NMES are fundamental to improvement of the blood microcirculation and local metabolism.

Keywords: Neuromuscular Electrical Stimulation, Skin Temperature, Spinal Cord Injury.

1 Introduction

Spinal cord injury (SCI) causes many changes reflected in motor, sensory, and autonomic nervous system damage [1]. Regarding the autonomic nervous system, thermoregulation dysfunction occurs in lesions above sympathetic flow (T4–T6) by interruption of neural transmission of thermoregulatory information, in which the hypothalamus is unable to control cutaneous blood flow [2,3].

Skin temperature (Tsk) is different from the internal temperature, and exhibits variations according to ambient temperature. Compared with central core temperature, Tsk is lower [4]. It is influenced by blood flow to the skin and the microcirculation. In addition, there are variations in temperature in relation to the anatomy, such as tendon regions, ligaments, muscles, and bone [5,6]. Due to limb inactivity or paralysis, individuals with SCI exhibit vascular changes, such as decreases in the diameter of the arterial duct, decreased capillarization, and deficient microcirculation [7-10].

Studies have shown that neuromuscular electrical stimulation (NMES) of paralyzed muscles in individuals with SCI can provide several benefits, such as histochemical changes, activation of paralyzed neuromuscular units, improved muscle hypertrophy and fatigue resistance, increased local blood flow, facilitated venous return and reduced spasticity [8,9,11-13].

We hypothesized that NMES will induce an increase in local blood flow and, in turn, Tsk. An increase in Tsk, even for a short time, improves the condition of the tissue, muscle fiber(s), and cold sensation in the lower limbs reported by many patients. With the application of NMES, the blood circulation of the skin increases and consequently the Tsk, providing beneficial effects for tissue cells and muscle fibers. The literature is comprehensive and reports that the use of NMES in SCI has several beneficial effects in the short and long term, but with regard to Tsk, there are still not many

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studies evaluating precisely how it behaves with NMES. Therefore, the aim of the present study was to observe the effect of NMES protocol on Tsk in SCI patients, which could possibly be a new tool for assessing autonomic dysfunction. The Results reported here support the benefit that NMES protocol applied to the TA muscles for individuals with SCI, as a therapeutic intervention and assessment of autonomic dysfunction induced an increase in local blood flow, leading to consequent increases in Tsk and local metabolism.

2 Methods

A convenience sample of 47 individuals with SCI was recruited. All volunteers presented a good response to NMES, verified by ankle dorsiflexion yielded by the stimulation, always absent in both tetraplegic and paraplegic of our sample. The level of lesions ranged from C4 to T10. Data were collected in the Spinal Cord Injury Rehabilitation Outpatients Clinic of the University Hospital, in a climatized room by only one researcher. Individuals with fever, sun exposure before the test, engaged in strenuous activity, smokers, caffeine < 1 h before the test, autonomic dysreflexia during the test, active urinary tract infection, inflammation or skin lesions were excluded.

To evaluate Tsk, an infrared thermometer (IRT; TG-165, FLIR Systems Inc., Orlando, FL, USA) was used. The IRT, featuring a FLIR Lepton® micro-thermal sensor. Measurement accuracy of the IRT is ±1.5°C, with a measuring range of -25°C to 380°C. This device has been approved by the United States Food and Drug Administration, and is furnished with the appropriate certification document (6, 14,15). The emissivity of the apparatus was adjusted to the skin (0.98).

Room temperature and humidity were controlled using a thermo-hygrometer device (MT-240, Minipa Electronics Inc., Houston, TX, USA). It has an internal sensor (range 0°C to +60°C) with a basic accuracy of ± 5%. The temperature was 23.7 ± 0.25 ◦C (mean ± SD) and Internal humidity was 62.7 ± 6.7%.

For the application of the NMES protocols, a 2-channel electrical stimulator was used at a frequency of 25 Hz, with single-phase rectangular pulses with a duration of 300 μs, and an amplitude ranging from 70–150 V (1 kΩ load), up to 1.5 mA RMS (root mean square), depending on the individuals.

The self-adhesive NMES surface electrodes (Valutrode, Axelgaard Manufacturing Co. Ltd., Fallbrook, CA, USA). For NMES to the tibial anterior (TA) muscle, a self-adhesive electrode, measuring 5 cm × 9 cm, was applied to the distal thigh (QD), and a smaller 3.0 cm diameter circular electrode was used near the head of the fibula (see Figure 1).

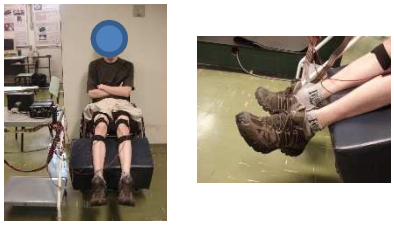

Figure 1: Neuromuscular Electrical Stimulation in TA muscle

The dependent variables measured included forehead, dermatome C2 and L5 bilaterally (see Figure 2).

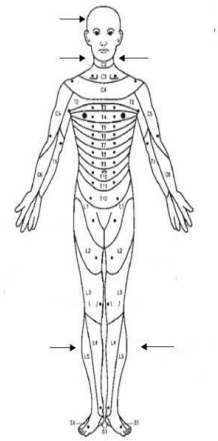

Figure 2: The dependent variables measured: forehead, dermatome C2 and L5 bilaterally.

The dermatome C2 and forehead were measured only at baseline and t20.

Four steps of measurements were used to collect data from the dependent variables. The “outcome measures section”:
Baseline 1: initial data collection.
t0: collection of data shortly after the end of NMES.
t10: collection of data 10 min after the end of NMES.
t20: collection of data 20 min after the end of NMES.

The NMES protocol for the TA muscle was performed for 20 min. In the exercise mode, stimulation is ON for 4 seconds and OFF for 8 seconds, duty cicle of 33%. Dorsiflexion comes on every 4seconds.

3 Statistical analysis

The variables analyzed included Tsk at the forehead and dermatomes C2 and L5. Each variable is expressed as mean, SD, median and corresponding 95% confidence interval (CI). Both paraplegic and tetraplegic individuals presented a good response to NMES, verified by performing ankle dorsiflexion. The normality test of Shapiro-Wilk was done. The Friedman test was used for all analyses. The level of significance adopted in all analyses was 5% (i.e., $p \leq 0.05$).

4 Results

SCI characteristics of the individuals recruited in the research (table 1). The confidence intervals of the mean Tsk difference to forehead and dermatome C2 were presented in table 2. The dermatome C2 and forehead were measured only at baseline and t20.

Table 1: SCI characteristics.

Variables	Mean ± SD
Age, yrs	38.89 ± 9.35
Time of injury, yrs	11.94 ± 6.45
Body Mass Index, kg/m_2	23.37 ± 3.49

Table 2: Confidence interval (95%) of the mean Tsk differences before (baseline) and after the end of NMES (t20) for forehead and dermatome C2 bilaterally and median.

	Side	Median	Confidence interval
Forehead	-	34.3	0.2 ; 0.54
C2	Right	33.73	0.27 ; 0.66
C2	Left	34.13	0.41 ; 0.81

Table 3 shows Tsk for baseline, t0, t10 and t20. In the NMES of the TA muscle, a greater increase was observed in Tsk ($p<0.05$). The highest temperature variation found individually, after NMES, in the sample of recruited individuals was 6.1ºC.

Table 3: Confidence interval of the mean Tsk differences before and after NMES protocol in TA muscle in dermatome L5. Data are reported as mean of differences in Tsk before and after NMES protocol. (95% CI) *p <0.05. Abbreviation: t0, Time soon after the end of the NMES; t10, Time of 10 minutes after the end of the NMES; t20, Time of 20 minutes after the end of the NMES.

Dermatome	Protocol	Median	Confidence interval
L5 Right	Baseline	29.83	0.01 ; 0.4*
L5 Right	t0	33.03	-3.35 ; -2.52*
L5 Right	t10	32.93	-3.11 ; -2.3*
L5 Right	t20	32.05	-2.7 ; -1.81*
L5 Left	Baseline	29.96	0.3 ; 0.57*
L5 Left	t0	33.03	-3.04 ; -2.23*
L5 Left	t10	32.83	-2.94 ; -2.08*
L5 Left	t20	32.4	-2.42 ; -1.55*

After NMES, an increase in Tsk was observed in stimulated L5 dermatomes and, considering t20, a Tsk was still higher than the baseline value.

Figure 3 shows the temperature and color change related to the increase in Tsk in the L5 dermatome.

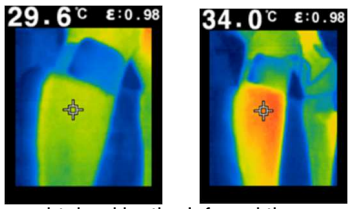

Figure 3: Images obtained by the Infrared thermometer FLIR-TG 165 of the Tsk of the L5 dermatome before and after the NMES protocol.

5 Discussion

The thermoregulatory control reflex causes changes in microcirculation, which may be localized, and/or temperatures throughout the body [16]. Individuals with SCI exhibit microvascular endothelial dysfunction as compromised cutaneous blood flow [17].

The infrared thermometry used in the present study is a technology that detects radiation emitted by a hot surface, and provides an estimate of the measured surface temperature [7]. It allows many benefits to individuals including hygiene, rapid measurement, non-invasiveness, and comfort.

Results of this study have shown no actual changes in the forehead and dermatome C2 Tsk. In contrast, in the stimulated dermatome, an increase in local Tsk occurred. This may have occurred due to increased blood perfusion at the stimulation site, therefore, demonstrating a global metabolic effect due to the deficit in thermoregulation after SCI. In the literature, some studies show the benefits of applying the NMES, as well as in Abram SE. (1980), who evaluated the relationship between Tsk and the use of transcutaneous electrical stimulation in patients with pain. He only observed an increase in Tsk in individuals who had pain relief.

The difference in Tsk after NMES is due to the heat emitted by the joule effect and muscle contraction. Thus, high-frequency broad-pulse NMES interacts with more organized neuronal groups resulting in better muscle contraction response, higher temperature and, consequently, lower metabolic demand.

Tissue damage occurs at temperatures above 44°C, at 51°C it will cause almost immediate destruction of the epidermis [19]. In our study, the highest temperature value found after NMES was 34.2 ºC.

In peripheral regions SCI individuals often have a lower temperature. When the cutaneous circulation when deficient, results in a lower perfusion of the skin and consequently a decrease in the regional temperature due to vasoconstriction [20,21]. Therefore, it was chosen to perform the NMES in the L5 dermatome, which is an extremity region.

The inability of the voluntary contraction caused by SCI reduces the efficiency of the venous pump, located in the calf region [22]. Therefore, considering the results of our study, that due to the inefficiency of the venous pump, the Tsk in the

TA muscle at t10 and t20, was still higher after the protocol. This research main limitation is that the accuracy of the infrared thermometer is estimated in ±1.5°C. To minimized the error, the protocol was realized in a climatized room, with the room temperature controlled, the data collection was done in the same day, by the same researcher and the main results were the comparation of the individuals with themselves.

Results of the current study demonstrated that NMES protocol applied to the TA muscles altered Tsk in individuals with SCI. We observed a significant increase in Tsk in the muscle, which corroborates the hypothesis NMES induces an increase in local blood flow, leading to consequent increases in Tsk and local metabolism, as demonstrated and hypothesized in our study. And according to the literature, every 0.6ºC increase in temperature causes a 10% increase in metabolism [23].

As the Tsk in the L5 dermatome increased, future studies would be interesting evaluating the complete or incomplete SCI, by measuring the sensation of increased temperature in the stimulated dermatome.

Author Statement

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Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

References

[1] Hamid R, Averbeck MA, Chiang H, Garcia A, Al Mousa RT, Oh SJ et al. Epidemiology and pathophysiology of neurogenic bladder after spinal cord injury. World Journal of Urology 2018.

[2] Griggs K.E.; Leicht C.A.; Price M.J.; Goosey-Tolfrey V.L.; Thermoregulation during intermittent exercise in athletes with a spinal cord injury. International Journal of Sports Physiology and Performance 2015; 10(4), pp.469-475.

[3] McAllen, R. M., & McKinley, M. J. (2018). Efferent thermoregulatory pathways regulating cutaneous blood flow and sweating. Thermoregulation: From Basic Neuroscience to Clinical Neurology Part I, 305–316.

[4] Khan S, Plummer M, Martinez-Arizala A, Banovac K. Hypothermia in patients participants with chronic spinal Cord injury. The Journal of Spinal Cord Medicine 2007; 30 (1): 27-30.

[5] van Marken Lichtenbelt WD, Westerterp-Plantenga MS, van Hoydonck P. Individual variation in the relation between body temperature and energy expenditure in response to elevated ambient temperature. Physiology & Behavior 2001; 73. 235-242.

[6] Maniar N, Bach AJE, Stewart IB, Costello JT. The effects of using different regions of interest on local and mean skin temperature. Journal of Thermal Biology 2015; 49-50, 33-38.

[7] Tang YL; He Y, Shao HW, Mizera I. Skin temperature oscillation model for assessing vasomotion of microcirculation. Acta Mechanica Sinica 2015; 31 (1): 132-138.

[8] Bochkezanian V, Newton RU, Trajano GS, Blazevich AJ. Effects of Neuromuscular Electrical Stimulation in People with Spinal Cord Injury. Medicine & Science in Sports & Exercise 2018.

[9] Carvalho DC, Martins CL, Cardoso SD, Cliquet A. Improvement of metabolic and cardiorespiratory responses through treadmill gait training with neuromuscular electrical stimulation in quadriplegic subjects. Artificial Organs 2006; 30:56– 63.

[10] Van Duijnhoven NT, Janssen TW, Green DJ, Minson CT, Hopman MT, Thijssen DH. Effect of functional electrostimulation on impaired skin vasodilator responses to local heating in spinal cord injury. J Appl Physiol (1985) 2009;106(4):1065-71.

[11] Bittar CK and Cliquet A. Effects of quadriceps and anterior tibial muscles electrical stimulation on the feet and ankles of patients participants with spinal cord injuries. Spinal Cord 2010; 48, 881–885.

[12] Tancredo JR, Maria RM, Azevedo ERF, Alonso KC, Varoto R, Cliquet A. Clinical assessment of spasticity in individuals with spinal cord injury. Acta Ortop Bras [online] 2013; 21(6):310-4.

[13] Gorgey AS, Dolbow DR, Dolbow JD, Khalil RK, Gater DR. The effects of electrical stimulation on body composition and metabolic profile after spinal cord injury – Part II. The Journal of Spinal Cord Medicine 2015, 38 (1): 23-37.

[14] Alexander J, Richards J, Attah O, Cheema S, Snook J, Wisdell C, May Selfe, J. Delayed effects of a 20-min crushed ice application on knee joint position sense assessed by a functional task during a re-warming period. Gait & Posture 2018; 62, 173–178.

[15] Rossignoli I, Fernández-Cuevas I, Benito PJ, Herrero AJ. Relationship between shoulder pain and skin temperature measured by infrared thermography in a wheelchair propulsion test. Infrared Physics & Technology 2016:76251–258.

[16] Johnson JM, Kellogg DL, Jr. Local thermal control of the human cutaneous circulation. J Appl Physiol 1985; 2010;109(4):1229-38.

[17] Byrne DW, Salzberg CA. Major risk factors for pressure ulcers in the spinal cord disabled: a literature review. Spinal cord 1996;34(5):255-63.

[18] Abram SE, Asiddao CB, and Reynolds AC, Increased Skin Temperature during Transcutaneous Electrical Stimulation. Anesthesia and Analgesia. 1980; 59: 5922-25.

[19] B.B. Ong, Injury, Fatal and Nonfatal | Burns and Scalds,Editor(s): Jason Payne-James,Encyclopedia of Forensic and Legal Medicine,Elsevier,2005,Pages 90-98

[20] Lima A. Bakker J. Noninvasive monitoring of peripheral perfusion. Intensive care Med. 2005; 31: 1316-26.

[21] Tancredo JR, Tambascia RA, Borges M, Fukuchi CA, Cliquet Junior A. Development of a skin temperature map for dermatomes in individuals with spinal cord injury: a cross-sectional study. Spinal Cord. 2020 Oct;58(10):1090-1095. Epub 2020 May 5.

[22] Song YG, Won YH, Park SH, Ko MH, Seo JH. Changes in Body Temperature in Incomplete Spinal Cord Injury by Digital Infrared Thermographic Imaging. Annals of Rehabilitation Medicine 2015;39(5):696-704.

[23] Beutler B, Beutler SM. The pathogenesis of fever. In: Goldman, Bennett and all, editors. Cecil textbook of medicine. W.B. Saunders Company, 21st edition: 1565-1567.

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A feasibility study on the clinical use of non-invasive tibial nerve stimulation towards neurogenic bladder in spinal cord injured individuals

Non- invasive tibial nerve stimulation on urinary incontinence

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Abstract: This research assesses the effect of tibial nerve electrical stimulation on urinary incontinence in individuals with spinal cord injury (SCI) being a prospective non-controlled intervention study. 8 individuals with SCI were recruited from the outpatient clinic. This study demonstrates results of tibial nerve stimulation (TNS) applied to the tibial nerves for 12 weeks. Two questionnaires were applied (Neurogenic Bladder Symptom Score-NBSS and Qualiveen-SF) and presented a tendency to improve symptoms and quality of life, however, without statistical significance. With the urodynamic data: maximum cystometric capacity increased with a mean of 285.6 ml pre, to 314.8 ml post TNS (P-Value: 0.554); compliance increased from 26.38ml/cmH2O pre TNS to 29.88ml/cmH2O post TNS (P-Value: 0.461); detrusor hyperactivity in the filling phase occurred in all patients in the pre TNS assessment; the maximum amplitude of the detrusor pressure in mean detrusor overactivity after TNS increased from 62.0 to 66.6 cmH2 (P-Value: 0.674); urinary leakage pressure during detrusor overactivity pre TNS were mean of 54.0 and 53.2 after (P-Value:1). The implications for rehabilitation practice and the positive effects of TNS are fundamental to improving the quality of life and reducing urinary incontinence on these individuals. Clinical outcomes, i.e., improvement on urinary incontinence can be achieved within a short period of intervention.

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Keywords: Tibial nerve electrical stimulation, Tibial Nerve, Neurogenic Bladder, Spinal Cord Injury.

1 Introduction

Low urinary tract dysfunction (neurogenic bladder) affects individuals with central and peripheral neurological diseases [1,2]. The bladder is innervated by the hypogastric plexus, from T10 to L2-L4, containing only sympathetic fibers, and also by the pelvic plexus from S2 to S4, containing sympathetic (hypogastric plexus) and parasympathetic fibers [2].

In neurogenic bladder (NB) alterations can be: normal voiding pattern (bladder filling and emptying phases), alteration of vesical sensitivity, increased intravesical pressure, incomplete voiding, inability to start or stop voiding and incontinence [2]. In normal bladder physiology, urine storage and emptying are voluntary actions, where the reservoir has an adequate capacity, with low storage pressure and low urethral resistance [3].

In spinal cord injury (SCI), there is an impairment of communication between the brain and the urinary system, where the elimination of urine is no longer controlled [3,4,5]. NB affects quality of life, length of stay, health costs and especially the increased risk of urinary tract infection, which can lead to renal deterioration [6]. The treatment for NB includes several interventions, such as catheterization (internal, intermittent and suprapubic) [7]; assisted bladder emptying; drug therapies; intravesical injection of botulinum toxin; surgery and electrical stimulation (neuromodulation) [8,9].

Regarding the validated questionnaires for spinal cord injury, we have the NBSS (Neurogenic Bladder Symptom Score) [10] and the Qualiveen –SF [11]. One of the therapies used for neurogenic bladder is electrical stimulation of the tibial nerve. In 1983, McGuire et al. [12] described this type

of electrical stimulation as a minimally invasive treatment for urge urinary incontinence. Stampas et al. (2019) reported in the preliminary study performed that transcutaneous electrical stimulation in individuals with acute spinal cord injury is able to achieve bladder neuromodulation.

The study verified the effect of TNS on the tibial nerve in relation to urinary incontinence. The main objective was primarily for research, since there are few works of this nature in the scientific literature, proving or not the effectiveness of the use of TNS; and second, to provide greater security for the applicability of the TNS technique, aiming at a better quality of life for these individuals and reducing the risk of urological complications.

2 Methods

A convenience sample of 8 individuals with SCI was recruited. All evaluations were performed Spinal Cord Injury Rehabilitation Outpatient Clinic of the University Hospital. The study was approved by the local ethics committee (CAAE: 40799720.1.0000.5404).

The inclusion criteria were individuals with SCI, diagnosed with paraplegia or tetraplegia (complete or incomplete), with frequent urine leakage and recurrent urinary tract infection. In addition, individuals had to be young adults (over 18 years of age), with a diagnosis of SCI for more than 1 year and not present any pathology that contraindicates participation in the study.

Individuals with urinary tract infection or any other type of infection, those with urinary insufficiency in any other way, recent urological surgery, normal control of voluntary urination, malignant tumors, skin pathologies, patients using medication with antimuscarinics and mirabegron, women who are menstruating or being pregnant, participation in other investigational drug or product research within the 30 days prior to and during the present study, neuromodulation treatment for urological or intestinal indication within the last 6 months or in progress, botulinum toxin injection in the last 6 months, bilateral absence of the tibial nerve were excluded.

For the application of the TNS protocols, a two-channel custom made electrical stimulator was used at a frequency of 25 Hz, single-phase, with single-phase rectangular pulses with a duration of 300 μs, and an amplitude ranging from 70–150 V (1 kΩ load), up to 0.9 mA RMS, depending upon the individuals. Such intensity goes through skin fat tissue impedance (capacitive) thus becoming a bipolare one.

The self-adhesive surface electrodes (Valutrode, Axelgaard Manufacturing Co. Ltd., Fallbrook, CA, USA). NMES were applied to the tibial nerve (L4 dermatome). The exact locations of the electrodes were: one electrode (3 cm) at the height of the medial malleolus (negative electrode) and another electrode (5x5cm) at a distance of 10 cm (positive electrode) [14,15], also in the medial region of the leg (see Figure 1).

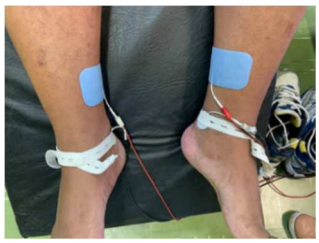

Figure 1: Non- Invasive Tibial nerve stimulation (TNS)

Two validated questionnaires were applied to this population: the NBSS and the Qualiveen –SF. These questionnaires are commonly used for urinary incontinence and to verify the quality of life of these individuals.

Therefore, the developed protocol consisted of:

1) Urodynamic assessment for all recruited individuals (see Figure 2). All individuals stared TNS within 5 days of being through the urodynamic assessment.

2) Application of 2 questionnaires validated for this population and specific for NB (NBSS and Qualiveen -SF) before starting treatment with the TNS protocol and after 12 sessions of it.

3) Application of the TNS protocol on the tibial nerve for 12 sessions [16], once a week, for 30 minutes. The TNS application to the lower limbs bilateraly. The intensity was adjusted until the beginning of muscle contraction (just above motor threshold).

4) Re-ordering the Urodynamic assessment for all recruited individuals.

At the end of the 12 weeks, a question was asked to the recruited individuals if they noticed an improvement or not in the symptoms of incontinence.

In the last application, the two questionnaires were also applied again. After 12 weeks [16], the urodynamics assessment was performed again.

3 Statistical analysis

For the comparison between before and after TNS, for the continuous variables, the paired nonparametric Mann-Whitney tests were used, because they did not follow a normal distribution, verified by means of the Anderson-Darling test, and were homogeneous, verified by the Bartlett test. For categorical variables, the McNemar test was used. In the analysis of correlations between the variables, simple linear regression was used. The significance level adopted in the tests was 0.05. Two-tailed hypotheses were considered. In addition, the confidence intervals constructed are 95%. R software version 4.0.2 was used to perform all analyses.

4 Results

SCI characteristics of the individuals recruited (table 1).

Table 1: SCI characteristics.

Variables	Individuals							
	1	2	3	4	5	6	7	8
Level of injury	T6-7	T6-7	T9-10	C6	C5	T6-7	T9-12	T1-2
AIS	T5B	T5B	T8A	C6B	C6B	T5A	T8A	T4 D
Bladder control	No	No	No	No	No	No	No	Yes
Time post injury (yrs)	4	15	13	16	17	19	4	8

All recruited individuals were initially submitted to urinalysis and urine culture. Five (62.5%) had bacterial growth before the first procedure and six (75%) before the second procedure. These findings of asymptomatic bacteriuria are very common in individuals who undergo clean intermittent catheterization. All of them used antibiotic therapy guided by the antibiogram result, at least 7 days before the urodynamic evaluation. In addition, no individual developed urinary infection during the stimulation protocol.

At the end of the 12 weeks of the TNS protocol, a question was asked on the observation of the recruited individuals about the effect of the applied protocol. Five subjects (62.5%) reported improvement, one (12.5%) mild improvement and two (25%) did not notice improvement.

After the application of the TNS protocol, none of the individuals reported side effects and complications, such as discomfort at the electrode application site, or skin changes.

Regarding the questionnaires applied, the NBSS, seven individuals performed clean intermittent catheterization (87.5%) and only one individual used a collection bag/permanent catheter (12.5%). In all spheres of the questionnaire, there was an improvement to the mean before and after the protocol; only in the storage that there was no improvement.

In the Qualiveen-SF questionnaire, all questions showed improvement, with the exception of the question about Worrying about Limitations, where five individuals (62.5%) showed improvement, two individuals (25%) showed no improvement and one (12.5%) remained the same answer on this question. Regarding the results found in this questionnaire, there was a tendency towards quality of life improvement, however, without statistical significance (P-Value >0.05).

Regarding the urodynamic data analyzed and compared pre and post TNS were: maximum cystometric capacity (MCC), compliance, detrusor overactivity (DO) in the bladder filling phase (FP), leakage pressure (LP) during DO, maximum DO amplitude (MA).

Table 2 shows individuals' outcomes.

Table 2: Urodynamic data of individuals. Outcomes Before and after the TNS protocol. Maximum cystometric capacity (MCC), compliance, detrusor overactivity (DO) in the bladder filling phase (FP), leakage pressure (LP) during DO, maximum DO amplitude (MA).

Individuals		Variables				
		MCC	Compliance	LP	FP	MA
1	Before	184	20	101	present	116
	After	341	42	27	present	69
2	Before	303	23	78	present	98
	After	400	36	absent	absent	absent
3	Before	246	15	42	present	87
	After	231	19	54	present	69
4	Before	521	40	absent	present	22
	After	471	30	absent	absent	absent
5	Before	219	18	present	present	18
	After	394	32	58	present	32
6	Before	362	21	absent	present	42
	After	200	33	absent	present	71
7	Before	150	37	14	present	38
	After	182	30	80	present	86
8	Before	300	37	18	present	18
	After	300	17	47	present	47

In the Maximum Cystometric Capacity (MCC) there was an increase with a mean of 285.6 ml pre, to 314.8 ml post TNS, without statistical significance (P-Value: 0.554). Analyzing the MCC in each patient separately, four (50%) had an increase and one (12.5%) had no change.

Compliance showed an increase pre TNS from 26.38ml/cmH2O to 29.88ml/cmH2O post TNS (P-Value: 0.461) without statistical significance. Likewise, when analyzed separately, five individuals (62.5%) show an increase. In the filling phase, DO can occur, and it occurred in all patients in the pre TNS evaluation. In the post TNS evaluation, two (25%) of the eight individuals no longer presented this hyperactivity. Urinary leakage pressure during DO pre TNS was a mean of 54.0 and 53.2 after (P-Value:1).

In the maximum amplitude of the detrusor pressure, the mean post TNS increased from 62.0 to 66.6 cmH2 (P-Value: 0.674). Analyzing this variable separately, three (37.5%) had reduced amplitude and two (25%) had no more DO. With this finding, it indicates an improvement of 62.5% in relation to the pre TNS assessment.

5 Discussion

Currently, it is believed that the stimulation of peripheral sensory afferent fibers block the lumbar and somatic sacral afferent signals, responsible for the anomalous activity of the bladder, preventing the efferent reflexive motor response, which would result in detrusor hyperactivity and dyssynergia. [17]. McGuire et al (1983) was the first to report the

effectiveness of applying direct electrical stimulation of the tibial nerve in individuals with urge incontinence. Randomized clinical trials have evaluated the effect of electrical stimulation of the tibial nerve in individuals with neurogenic bladder secondary to SCI.

In our study, we noticed a trend towards improvement in cystometric parameters. At initial cystometry, the individuals in our study showed a decrease in the number of detrusor contractions, as well as an increase in the volume needed to trigger them. In addition, in the initial cystometry, two recruited individuals presented detrusor hyperactivity, but after application of the protocol they did not present hyperactivity. We also verified that 75% of the individuals noticed a subjective improvement with the treatment, and both the NBSS questionnaire and the Qualiveen-SF had a tendency to improve the total score.

Therefore, with all these findings, transcutaneous tibial electrostimulation might be an option as a form of treatment for these individuals, but further studies are needed with a larger sample and/or with the possibility of increasing the number of applications.

Author Statement

Research funding: The author state no funding involved.
Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

References

[1] Diniz MSC. Neurological Diseases and the Urinary Tract.In: Girão, et al. Treatise on Urogynecology and Pelvic Floor Disorders. 1st ed. São Paulo: Manole, 2015. p. 673-692.

[2] Wheat , FE. Gomes, RCM. Neurogenic bladder. In: Zaretti Filho, M. Nardozza Junior, A. Reis, RB. Fundamental Urology. 1st ed. São Paulo: Phanmarc, 2010. 240-249

[3] Walsh , Retik, Vaughan, Wein: Campbell's Urology. Philadelphi Saunders. 2002; vol. 2: 1305-06.

[4] Gimenez MM, Fontes SV, Fukujima MM: Physiotherapeutic procedures for vesical sphincter disorder in patients with spinal cord trauma – a narrative bibliographic review. 2005; 13:34-38.

[5] Chartier -Kastler E, Ayoub N, Even-Schneider A, Richard F, Soler JM, Denys P. Neurogenic bladder: pathophysiology of the disorder of compliance. Prog Urol 2004;14(4):472-8.

[6] Adams J, Watts R, Yearwood M, Watts A, Hartshorn C, Simpson S, et al. Strategies to promote intermittent self-catheterization in adults with neurogenic bladder: a comprehensive systematic review. JBI Libr System Rev. 2011; 9: 1392–446.

[7] Goetz LL, Cardenas DD, Kennelly M, Lee BSB, Linsenmeyer T, Moser C, et al. International spinal cord injury urinary tract infection basic data set. Spinal Cord. 2013; 51:700-4.

[8] Blok B, Pannek Castro-Diaz JD, del Popolo G, Groen J, Hamid R, Karsenty G, et al. EAU guidelines on neuro-urology. Eur Urol. 2015; 69: 324–33.

[9] Groen J, Pannek J, Castro Diaz D, Del Popolo G, Gross T, Hamid R, Karsenty G, Kessler TM, Schneider M, t Hoen L, Blok B. Summary of European Association of Urology (EAU) Guidelines on Neuro-Urology. Eur Urol. 2016; 69(2):324–333.

[10] Welk B, Lenherr S, Elliott S, Stoffel J, Presson AP, Zhang C, Myers JB. The neurogenic bladder Symptom Score (NBSS): a secondary assessment of its validity, reliability among with a spinal cord injury. Spinal Cord. 2018; 56:259-264.

[11] Cintra LKL, de Bessa J, Kawahara VI, Ferreira TPA, Srougi M, Battistella LR, et al. Cross-cultural adaptation and validation of the neurogenic bladder symptom scoring questionnaire into Brazilian Portuguese. Int braz j urol. May 2, 2019; 45.

[12] McGuire EJ, Shi-chun Z, Horwinski ER, Lytton B. Treatment of motor and sensory detrusor instability by electrical stimulation. J Urol. 1983;129(1):78-79.

[13] Stampas A, Gustafson K, Korupolu R, Smith C, Zhu L, Li S. Bladder Neuromodulation in Acute Spinal Cord Injury via Transcutaneous Tibial Nerve Stimulatio: cystometrogram and Autonomic Nervous System Evidence From a Randomized Control Pilot Trial. Front. Neurosci.2019; 13: 119.

[14] Bride AA, Tailor V, Fernando R, Khullar V, Digesu GA. Posteriortibial nerve stimulation for overactive bladder-techniques and efficacy. International Urogynecology Journal, 2020; 31:865-870.

[15] Welk B, Mckibbon M. A randomized, controlled trial of transcutaneous tibial nerve stimulation to treat overactive bladder and neurogenic bladder patients. Can Urol Assoc J. 2020; 4(7): E297-303.

[16] Seth JH, Gonzales G, Haslam C, Pakzad M, Vashisht A, Sahai A, Knowles C, Tucker A, Panicker J. Feasibility of using a novel non-invasive ambulatory tibial nerve stimulation device for the home-based treatment of overactive bladder symptoms. Transl Androl Urol 2018;7(6):912-919.

[17] Vodusek DB, Light JK, Libby JM. Detrusor inhibition induced by stimulation of pudendal nerve afferents. Neurourol Urodyn 1986;5:381–389

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Exploring methods for targeted activation of the sympathetic nervous system without exercise

Finding solutions to enhance FES-cycling performance for individuals with SCI

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Abstract: When using functional electrical stimulation (FES) for cycling in individuals with spinal cord injury (SCI) during FES-cycling, a rapid onset of muscular fatigue can be observed. Among other reasons, missing neural feedback from the lower extremities might be responsible for a reduced sympathetic response during stimulation. Therefore, this project explores different methods to activate the sympathetic nervous system to increase the heart rate to allow better blood circulation and oxygenation in the working muscles. Six techniques were selected to be tested on 10 healthy participants in the context of pilot measurements. Those were the cold pressor test with both hands, a virtual reality rollercoaster ride, the hot water immersion test with two hands, the Wim Hof breathing method, the Valsalva manoeuvre and the ingestion of Capsaicin through Prik Jinda chilli peppers. The results showed a significant increase in average as well as peak heart rate during all methods performed. From baselines of around 68±1.3 bpm, the strongest increases in both parameters were found for the Valsalva manoeuvre (to 118±20.9 bpm peak, 91±14.2 bpm average), the Wim Hof breathing method (to 112±13.5 bpm peak, 86±11.8 bpm average) and Capsaicin ingestion (to 103±18.9 bpm peak, 80±16.7 bpm average). The methods as they were performed in this project, are not all directly applicable to FES-Cycling but rather serve as exploration how efficiently which stimuli can increase the heart rate. In future research, adaptation or combination of techniques might help to increase performance during FES-Cycling.

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Keywords: FES-cycling, heart rate, sympathetic nervous system, stress reaction, cold pressor test, Capsaicin, hot water immersion test, Wim Hof method, virtual reality

1 Introduction

Functional electrical stimulation (FES) is often used to train paralysed muscles in individuals with spinal cord injury (SCI). The technique allows to regain certain strength and functionality, even though patients are unable to voluntarily contract affected muscles or feel any sensory stimuli. After a dedicated training of the muscles, some patients are eligible for advanced training modalities such as FES-Cycling on an instrumented trike. Besides the maximal power output, a rapid onset of muscular fatigue remains an open challenge in any functional application of FES. This might be linked to a rather crude motor-control and missing neural feedback leading to an inappropriate response of the cardiovascular system not fully compensating for the increased blood oxygen. [1], [2] A potential solution to that problem is the targeted activation of the sympathetic nervous system (SNS) to enhance blood circulation and therefore oxygen supply in the muscles. Existing studies that already present methods to increase the heart rate, which is an indicator for an increased SNS activity, were evaluated and the strategies adapted or replicated, while analysing the heart rate of the subjects.

In previous studies, an increased heart rate (HR) has been used as a marker to assess the activity of the SNS [3]–[6]. A popular breathing technique known as the Wim Hof method (WHM), is composed of phases of hyperventilation and breath holds to increase the heart rate to well over 100 bpm compared to a resting heart rate of about 60 bpm. The heart rate is mainly elevated during hyperventilation phases. [3] Another method related to breathing is the Valsalva manoeuvre, which induces complex effects in heart rate and blood pressure. Through a strong build-up of

pressure in the airways a previous study reported an up to 44 bpm increase in HR [6]. Other techniques such as the cold pressor test (CPT) and hot water immersion test (HIT) are typically performed by putting one hand in water with temperatures of 0 – 4 °C and 46 – 48 °C, respectively. When immersed in such extreme tempered water, thermo-sensors in the skin recognize the demand to regulate the skin temperature and blood circulation, while pain receptors are responsible for the additional stress. While the CPT showed relatively small peak increases in heart rate of maximum 16 bpm [4], whole body heat stress can cause the HR go up to 130 bpm compared to a baseline of 82 bpm [5]. Further, virtual reality (VR) immersion seems to increase heart rate especially in individuals susceptible to motion sickness or when having other negative experiences with VR [7]. Motion sickness itself has also proven to increase heart rate [8] and therefore might be the main cause to elevate HR, since during VR a mismatch between visual and vestibular information exists [9]. When Capsaicin containing substances are ingested, Capsaicin binds to the receptor Transient Receptor Potential Vanilloid 1 (TRPV1), usually activated by painful stimuli [10]. Therefore, the central nervous system is receiving a nociceptive stimulus, causing the SNS to be activated [11].

The aim of our project was to explore and compare different strategies for increasing the sympathetic activity without exercise, by analysing the heart rate of a group of healthy volunteers. These pilot measurements are intended to serve as basis for future measurements in the SCI population with the goal of increasing the performance during FES-Cycling.

2 Materials and Methods

2.1 Measurement equipment

To determine the heart rate, an ECG was recorded. Three Ag/AgCl surface electrodes (Skintact, Leonhard Lang GmbH, Innsbruck, Austria) were placed on the skin in a lead II configuration. A bio signal amplifier (Bio Amp FE231, ADInstruments Inc, Colorado Springs, USA) recorded the data, which was received by a Powerlab (Powerlab 16/35, ADInstruments Inc, Colorado Springs, USA). The digital signal was transferred to a PC so that in the LabChart 8.0 software (ADInstruments Inc, Colorado Springs, USA) the data could be analysed in real-time.

2.2 Preliminary measurements

Prior to the pilot experiments, the author herself thoroughly explored various existing methods (CPT, HIT, WHM, CAP, VM, VR, whole body heat stress in an infrared heat chamber, musical stimuli, creepy scenarios and caffeine ingestion) during preliminary measurements. Based on the outcome of these measurements, previous achievements found in literature and necessary equipment, six methods were selected to be further investigated in pilot measurements.

2.3 Pilot measurements

2.3.1 Participants

10 healthy participants (8 male, 2 female) were voluntarily taking part in the pilot measurements. They received a thorough explanation of all processes and potential side effects. Everyone gave their informed written consent before start of the measurements. Table 1 shows the subject demographics of the participants of the pilot measurements.

Table 1: Subject demographics of the 10 subjects (8 male, 2 female) taking part in the pilot measurements

	Age [years]	Height [cm]	Weight [kg]
Mean ± SD	26.3 ± 3.9	179.2 ± 11.5	73.7 ± 12.3

2.3.2 Measurement protocol

All measurements were performed in the Vienna general hospital at the Centre for Medical Physics and Biomedical Engineering of the Medical University of Vienna. The total time required for all procedures was about 2.5 h. After detailed information, the ECG electrodes were placed and the measurement devices tested. All tests were performed in the trike (ICE VTX, ICE, Cornwall, United Kingdom) to simulate the position during FES-Cycling. Before each stressor was applied, a baseline measurement at rest was done for 3 min. After every procedure, the participant was given a few minutes to rest in order to minimize influences from the previous method. Test 1 (CPT): The cold pressor test was carried out two hands immersed in 0 °C water for 5 min, or as long as tolerable for the participant. Test 2 (VR): The subjects experienced three rounds on a virtual tropical island rollercoaster (“Epic Roller Coasters”, B4T Games) through the VR headset “Oculus Go” (Facebook

technologies, Menlo Park, CA, United States) and headphones. Test 3 (HIT): The hot water immersion test was conducted the same way as the CPT, only the water had a temperature of 48 °C. Test 4 (WHM): The Wim Hof method was executed guided by the interactive training in the WHM app (Innerfire B.V., Stroe, Netherlands). For 35 breaths, it was necessary to inhale as deeply as possible, followed by exhaling passively. This is called hyperventilation phase, which is followed by the retention phase, where the breath is held after fully exhaling. In a third phase, one single deep breath is held for 15 s before the first phase starts again. In total, three cycles of the method were performed. Test 5 (VM): The Valsalva manoeuvre begins by taking one deep inhale. After closing mouth and nose, the participant strongly presses the enclosed air against the hands to create pressure, which is held for 15 – 20 s. Test 6 (CAP): To realize the ingestion of Capsaicin, a teaspoon of chopped up fresh Prik Jinda peppers (75 000 Scoville Heat Units [12]) was chewed for 2 min or as long as tolerable. Swallowing was not recommended and after spitting out the chilli, measurement continued for 8 mins to record aftereffects.

2.3.3 Data analysis

The LabChart 8.0 software allows visualization and analysis of the received data. By applying an automatic R-peak detection algorithm to the ECG data, the heart rate was calculated and presented in real-time. The HR data was imported into MATLAB (R2021b, The MathWorks Inc., Natick, MA, USA), where the mean and peak HR values of the baseline measurements and the methods are computed.

2.3.4 Statistical analysis

It was not possible to demonstrate normal distribution in all tests by using the Shapiro-Wilk test. Thus, the Wilcoxon-signed-rank-test was conducted with a significance level of $\alpha = 0.05$ to test the hypothesis that there is a difference between the applied method and their respective baseline measurement. The data of the baseline measurements was found to be normally distributed by using the Shapiro-Wilk test, so that a one way repeated measures ANOVA was performed to test the hypothesis that the baselines are not different from each other.

3 Results

Two subjects tolerated the 0 °C water in the CPT for only 1 min and one person endured the HIT for only 1 min. Further, one participant endured the chilli chewing for only 1 min instead of 2 min. One subject was not able to do the Capsaicin ingestion at all, due to a wound on the lip.

Figure 1 presents the mean values of average, peak and baseline heart rate for all the performed tests.

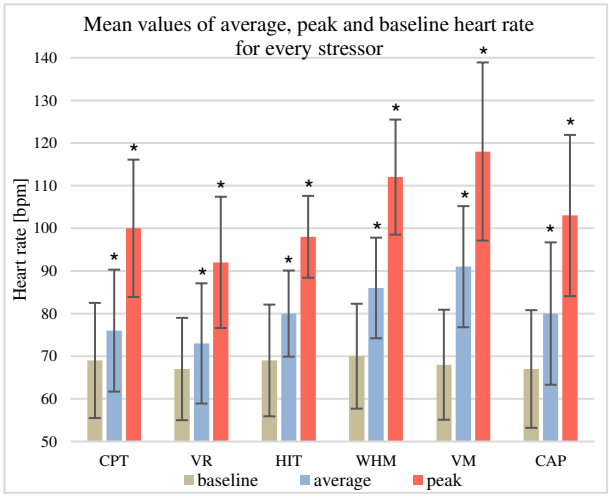

Figure 1: Values (mean ± SD) of all participants are displayed for average heart rate at rest (baseline, grey), average heartrate during stressor (blue), peak heart rate during stressor (red). Stressors: CPT = cold pressor test, VR = Virtual reality, HIT = Hot water immersion test, WHM = Wim Hof method, VM = Valsalva maneouvre, CAP = Capsaicin ingestion, '*' marks values significantly different from the previous baseline value

The VM showed the highest increase in peak heart rate (118±20.9 bpm), followed by the WHM (112±13.5 bpm), CAP (103±18.9 bpm), CPT (100±16.1 bpm), HIT (98±9.6 bpm) and lastly VR immersion (92±15.4 bpm). Throughout the entire duration of applying the stressor, the HR was increased to an average of 91±14.2 bpm in the VM, 86±11.8 bpm in the WHM, 80±16.7 bpm during CAP, 80±10.1 bpm during the HIT, 76±14.3 bpm during the CPT and 73±14.1 bpm in the VR experience. Therefore, almost the same order was found for the average and peak HR values, only the HIT had a higher average heart rate than the CPT. For all methods, average as well as peak values were significantly different from the respective baseline at $\alpha = 0.05$. Comparing the baselines of the individual stressors did not reveal a significant difference.

4 Discussion

The Valsalva manoeuvre achieved the highest heart rates but its effect was only short-term. While the VM with its

short duration can elevate the heart rate for about a minute, the hyperventilation phase of the WHM could be performed for much longer, creating a long-lasting elevation of the heart rate. Thinking about the application in FES-Cycling, the WHM could probably be adapted so that the breath hold phases are left out, since they let the heart rate decrease and don't oxygenate the blood.

The result that the peak HR is higher during the CPT than the HIT, but for the average HR the HIT reached a higher value than the CPT, suggests that the cold water induces a slightly higher pain stimulus than hot water. This was confirmed by the subjective feeling of the participant. Over the course of the CPT, the heart rate tended to decrease after the initial peak response while it increased or remained rather stable during the HIT. This might explain the higher values in average heart rate. The rising tendency of the heart rate during whole body heat exposure could be confirmed in preliminary tests using an infrared heat chamber. Those measurements were going on for up to an hour or longer, which would not have been feasible in the pilot testing. For Virtual reality it was observed that especially in subjects that reported motion sickness and nausea, or even ended the test early, the heart rate was increased while other subjects appeared completely relaxed and showed only little rise in heart rate. Thus, the increase in HR might depend a lot on the subjective susceptibility to motion sickness or other factors like fear of hight.

The results of these pilot experiments demonstrate clear beneficial effects for the investigated breathing methods. A combination of performing the WHM and the VM in alternation might be able to effectively increase heart rate and muscular oxygenation, potentially useful to achieve higher performances in FES-Cycling

Author Statement

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Personal information and data of the participants were anonymized and used for purposes of this work only.

References

[1] T. J. Demchak, J. K. Linderman, W. J. Mysiw, R. Jackson, J. Suun, and S. T. Devor, "Effects of Functional Electric Stimulation Cycle Ergometry Training on Lower Limb Musculature in Acute Sci Individuals," *J Sports Sci Med*, vol. 4, no. 3, pp. 263–271, Sep. 2005.

[2] E. H. Estigoni, C. Fornusek, R. M. Smith, and G. M. Davis, "Evoked EMG and Muscle Fatigue During Isokinetic FES-Cycling in Individuals With SCI," *Neuromodulation: Technology at the Neural Interface*, vol. 14, no. 4, pp. 349–355, Aug. 2011, doi: 10.1111/j.1525-1403.2011.00354.x.

[3] M. Kox *et al.*, "Voluntary activation of the sympathetic nervous system and attenuation of the innate immune response in humans," *Proc Natl Acad Sci U S A*, vol. 111, no. 20, pp. 7379–7384, May 2014, doi: 10.1073/pnas.1322174111.

[4] B. D. Johnson, J. R. Sackett, Z. J. Schlader, and J. J. Leddy, "Attenuated Cardiovascular Responses to the Cold Pressor Test in Concussed Collegiate Athletes," *J Athl Train*, vol. 55, no. 2, pp. 124–131, Feb. 2020, doi: 10.4085/1062-6050-573-18.

[5] M. Iguchi, A. E. Littmann, S.-H. Chang, L. A. Wester, J. S. Knipper, and R. K. Shields, "Heat Stress and Cardiovascular, Hormonal, and Heat Shock Proteins in Humans," *J Athl Train*, vol. 47, no. 2, pp. 184–190, 2012.

[6] V. Minatel *et al.*, "Maximal expiratory pressure and Valsalva manoeuvre do not produce similar cardiovascular responses in healthy men," *Experimental Physiology*, vol. 101, no. 5, pp. 599–611, 2016, doi: 10.1113/EP085203.

[7] K. A. Fadeev, A. S. Smirnov, O. P. Zhigalova, P. S. Bazhina, A. V. Tumialis, and K. S. Golokhvast, "Too Real to Be Virtual: Autonomic and EEG Responses to Extreme Stress Scenarios in Virtual Reality," *Behav Neurol*, vol. 2020, p. 5758038, Mar. 2020, doi: 10.1155/2020/5758038.

[8] J. Dahlman, A. Sjörs, J. Lindström, T. Ledin, and T. Falkmer, "Performance and Autonomic Responses During Motion Sickness," *Hum Factors*, vol. 51, no. 1, pp. 56–66, Feb. 2009, doi: 10.1177/0018720809332848.

[9] S. Ohyama *et al.*, "Autonomic responses during motion sickness induced by virtual reality," *Auris Nasus Larynx*, vol. 34, no. 3, pp. 303–306, Sep. 2007, doi: 10.1016/j.anl.2007.01.002.

[10] J. Vriens, G. Appendino, and B. Nilius, "Pharmacology of Vanilloid Transient Receptor Potential Cation Channels," *Mol Pharmacol*, vol. 75, no. 6, pp. 1262–1279, Jun. 2009, doi: 10.1124/mol.109.055624.

[11] S. Michlig *et al.*, "Effects of TRP channel agonist ingestion on metabolism and autonomic nervous system in a randomized clinical trial of healthy subjects," *Sci Rep*, vol. 6, p. 20795, Feb. 2016, doi: 10.1038/srep20795.

[12] "Thai Chillies Heat Levels - Scoville Scale," *Thai Food Online*. https://www.thai-food-online.co.uk/blogs/thai-food-online-blog/thai-chillies-scoville-scale (accessed Apr. 09, 2022).

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Clinical outcomes of neuromuscular electrical stimulation applied to different neurological levels of spinal cord injuries: a pilot study.

https://doi.org/10.1515/

Abstract: Electrical stimulation is a tool that has been used in various ways in the rehabilitation of spinal cord injuries. Surface i.e. electromyography is an effective method for assessing the many conditions in which the patient is. **Objective:** To evaluate the benefits through neuromuscular electrostimulation in patients with spinal cord injury and possible neuroplasticity gain observed in electromyography. **Method:** This is a pilot study on the evolution of clinical cases of different neurological levels of spinal cord injury. **Conclusion:** It was observed that the spinal cord injured patients analyzed in this preliminary study showed possible gain in neuroplasticity.

Keywords: Electrical Stimulation; Electromyography; Spinal cord injury.

1. Introduction

It has been sought to improve the quality of life of people with spinal cord injury suffering from physical and psychological difficulties, one of which is Neuromuscular Electrical Stimulation (NMES). According to Varoto & Cliquet[1], the NMES is a device that projects electrical impulses into the muscle, reproducing nerve impulses[1]. Its function is a possible neural restoration; and it has been used as a therapeutic resource for the rehabilitation of spinal cord injuries, showing relevant clinical results of possible gains in walking ability [2].

It is important to note that the nervous system has neuroplasticity. Neuroplasticity is the ability to adapt and mold at the structural and functional level when exposed to an environmental modification[3]. NMES has contributed to functional and neurological gains during rehabilitation. Neuroplasticity is the ability to adapt and shape at a structural and functional level when exposed to a modification of the medium[3]. NMES has been contributing to functional and neurological gains during rehabilitation.

Some methods have been used to assist in the diagnosis and analysis of some functions and disorders in people with spinal cord injury. A neurological examination that examines the level of injury through sensory and painful pathways and motor strength is an international standard protocol required by the American Spinal Injury Association[4].

Another way to evaluate patients with spinal cord injury is through electromyography (EMG). It is a painless and non-invasive examination that has electrodes capable of monitoring the electrical activity of the muscle to be evaluated. Thus, the clinical evolution of patients with spinal cord injury can be evaluated after NMES. For Clancy et al[5], electromyography is the record of muscle activity. According to Cacho[6], EMG is used to evaluate the action potential of muscle fiber. Electromyography produces a visual analysis of the pattern of neuromuscular activity. Thus, the main questions of this study were: "What are the benefits and efficacy generated by NMES in the rehabilitation of people with spinal cord injury?" and "What are the changes in the variables caused by the use of NMES presented through EMG?

2. Objective

Evaluate the benefits through neuromuscular electrostimulation in patients with spinal cord injury and possible neuroplasticity gain observed in EMG .

3. Materials and Methods

The sample consisted of four patients, named A, B, C and D. The patients in the sample underwent stimulation protocol in the quadriceps and fibular muscles in the pilot study of 6 months of NMES treatment. A sitting NMES protocol was first performed with duration of 20 minutes in the quadriceps and 10 minutes in the fibula, totaling 30 minutes.

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After 30 days of treatment of sitting NMES, an orthostatism protocol was initiated for each minute standing, at the same time of pause for sitting rest.

Subsequently, a gait protocol was performed, in which the following method was used, the five-minute gait test in the hospital corridor and rest pauses until completing the total 30 minutes of NMES. The quadriceps and fibular nerves were stimulated in the gait with NMES and assist of the walker. It is emphasized that no physical activity was performed during NMES, only knee extension and back flexion when the patient performed the NMES seated , due to the reaction of electrical impulses in the stimulated nerves.

Patient A underwent treatment with NMES at home every day, because of the RISE[7] project and once a week performed gait treatment at the Unicamp clinical hospital in an orthostatic position. Patient D performed a sitting NMES protocol, and only performed knee extension due to electrical impulse generated in the quadriceps.

It is important to highlight that the NMES protocol was established once a week following a protocol established by the outpatient clinic.

Electromyography (EMG) was performed separately from NMES. Another point, EMG was performed in the pre- and post-treatment period of NMES. During the evaluation of EMG, it was requested by means of a verbal command for the patient s to perform the movements of the hip and flexion of the hip and knee extension, with signs of muscle activation during EMG.

3.1 Neuromuscular electrical stimulation (NMES)

A four-channel electric stimulator was used, generating a 25Hzpulse train with rectangular pulses of 300μ duration, with intensity of 70-150 V and another stimulator that has a pulse train with 10 and 2 milliseconds; 1 kΩ of charge, is the impedance of skin fat, measuring not the stimulator of treatment or oscilloscope for resorption, i.e. it is not safe to measure in the patient.

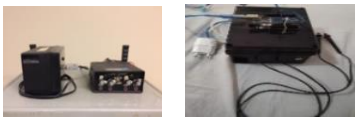

Figure 1. 4-channel electric stimulator, and another 2-channel stimulator with 2 milliseconds. source: photos of the devices used in the outpatient clinic.

3.2 Electromyography (EMG)

Electromyography is a technique for monitoring the electrical activity of excitable membranes of muscle cells and patients were analyzed following the recommendations of SENIAM[8]. The device used in this study to perform the surface EMG examination was the Electromyography-NORAXON®. Surface EMG was measured in anterior fascia late, rectus femoris pre and pos NMES. The signals were filtered by smoothing with an RMS algorithm. During the EMG examination, it was requested by verbal command that all patients perform hip flexion and knee extension movements, which was performed within one minute of each requested movement.

3.3 Scale ASIA - (AIS)

A neurological examination that examines the level of injury through sensory and painful pathways and motor strength is an international standard protocol mandated by the American Spinal Injury Association (AIS)[4].

Table 1. Characteristics of the subjects and the Control Individual

Patient	Gender	Age	Injury	Injury Time (years)	AIS
A	Male	28	Flaccid Paraplegia	4	Level A, T12
B	Male	43	Spastic paraplegia	2	Level C, T11
C	Male	40	Spastic paraplegia	16	Level C, T 6
D	female	62	Spastic paraplegia	20	Level D, T 8
Individual control 1	Male	20-29	-	-	-
Individual Control 2	Male	40-49	-	-	-
Individual Control 3	female	60-69	-	-	-

4. Results

Patients A, B, C and D were evaluated by EMG examination, the results are described in table 2 and 3.

Table 2. Hip Flexion-Electromyography results.

Patient	Phases	Muscle	Average	Minimum	Maximum	Standard Deviation
A	Pre treatment	Tensor fl. Lt	22,8	12	33,6	15,27
		Tensor fl. Rt	64,25	35,9	92,6	40,09
		Rectus fem. Rt	154,75*	54,5*	255*	141,77*
		Rectus fem. Lt	5,9	4,8	7	1,55
	After treatment	Tensor fl. Lt	110,6	47,2	174	89,66
		Tensor fl. Rt	106,45	52,9	160	75,73
		Rectus fem. Rt	15,1	8,9	21,3	8,76
		Rectus fem. Lt	12,95	7,2	18,7	8,13
	Control 1	Tensor fl. Lt	325,9	98,8	553	321,16
		Tensor fl. Rt	168	62	274	149,9
		Rectus fem. Rt	68,55	22,1	115	65,69
		Rectus fem. Lt	61,75	16,5	107	63,99
B	Pre treatment	Tensor fl. Lt	23,95	13,5	34,4	14,77
		Tensor fl. Rt	31,3	16,4	46,2	21,07
		Rectus fem. Rt	111,7	95,4	128	23,05
		Rectus fem. Lt	69,05	37,1	101	45,18
	After treatment	Tensor fl. Lt	127,6	48,2	207	112,28
		Tensor fl. Rt	17,95	6,3	29,6	16,47
		Rectus fem. Rt	22,2	6,5	37,9	22,2
		Rectus fem. Lt	55,5	23,8	87,2	44,83
	Control 2	Tensor fl. Lt	88	38	138	70,71
		Tensor fl. Rt	159,75	71,5	248	124,8
		Rectus fem. Rt	21,3	11,3	31,3	14,14
		Rectus fem. Lt	18	10,3	25,7	10,88
C	Pre treatment	Tensor fl. Lt	3,7	3,1	4,3	0,84
		Tensor fl. Rt	55,55*	22,6*	88,5*	46,59*
		Rectus fem. Rt	1,67	1,4	1,95	0,38
		Rectus fem. Lt	8,4	5,2	11,6	4,52
	After treatment	Tensor fl. Lt	20,15	4,6	35,7	21,99
		Tensor fl. Rt	7,7	2,5	12,9	7,35
		Rectus fem. Rt	5,25	1,8	8,7	4,87
		Rectus fem. Lt	8,85	2,6	15,1	8,83
	Control 2	Tensor fl. Lt	88	38	138	70,71
		Tensor fl. Rt	159,75	71,5	248	124,8
		Rectus fem. Rt	21,3	11,3	31,3	14,14
		Rectus fem. Lt	18	10,3	25,7	10,88
D	Pre treatment	Tensor fl. Lt	9,4	6,6	12,2	3,95
		Tensor fl. Rt	27,65	17,8	37,5	13,93
		Rectus fem. Rt	30,85	18,2	43,5	17,88
		Rectus fem. Lt	7,45	5,4	9,5	2,89
	After treatment	Tensor fl. Lt	27,85	12,5	43,2	21,7

Table 3. Knee Extension-Electromyography results.

Patient	Phases	Muscle	Average	Minimum	Maximum	Standard Deviation
A	Pre treatment	Tensor fl. Lt	6,4	4,2	8,6	3,11
		Tensor fl. Rt	15,7	9,4	22	8,9
		Rectus fem. Rt	8,6	6,3	10,9	3,25
		Rectus fem. Lt	1,32	1,1	1,54	0,31
	Pos treatment	Tensor fl. Lt	27,75	15,3	40,2	17,6
		Tensor fl. Rt	19,65	11,5	27,8	11,52
		Rectus fem. Rt	6	4,2	7,8	1,8
		Rectus fem. Lt	7,4	4,9	9,9	3,53
	Control 1	Tensor fl. Lt	220,15	74,3	366	206,26
		Tensor fl. Rt	131,35	52,7	210	111,22
		Rectus fem. Rt	170,85	59,7	282	157,18
		Rectus fem. Lt	85,6	30,2	141	78,34
B	Pre treatment	Tensor fl. Lt	1291*	974*	1608*	448,3*
		Tensor fl. Rt	38,05	20,4	55,7	24,96
		Rectus fem. Rt	60,85	45,3	76,4	21,99
		Rectus fem. Lt	14,26	8,03	20,5	8,81
	Pos treatment	Tensor fl. Lt	46,8	20,6	73	37,05
		Tensor fl. Rt	51,85	15,6	88,1	51,25
		Rectus fem. Rt	118,1	30,2	206	124
		Rectus fem. Lt	94,8	26,6	163	96,44
	Control 2	Tensor fl. Lt	112,2	33,4	191	111,44
		Tensor fl. Rt	161,95	281	42,9	168,36
		Rectus fem. Rt	36,65	25,3	145	82,51
		Rectus fem. Lt	78,5	132	25	75,66
C	Pre treatment	Tensor fl. Lt	10,15	5,31	15	6,85
		Tensor fl. Rt	87,65*	74,3*	101*	18,8*
		Rectus fem. Rt	2,29	1,9	2,69	0,55
		Rectus fem. Lt	18,65	11,7	25,6	9,82
	Pos treatment	Tensor fl. Lt	8,95	5,1	12,8	5,44
		Tensor fl. Rt	3,85	2	5,7	2,61
		Rectus fem. Rt	2,05	1,6	2,5	0,63
		Rectus fem. Lt	6,95	3,8	10,1	4,45
	Control 2	Tensor fl. Lt	112,2	33,4	191	111,44
		Tensor fl. Rt	161,95	281	42,9	168,36
		Rectus fem. Rt	36,65	25,3	145	82,51
		Rectus fem. Lt	78,5	132	25	75,66

Legend: In table 2 and 3 the values with asterisks* indicate noises that may have been caused by external interference such as electronic devices or spasticity, depending on the patient. Source: Software Excel® of Microsoft version 2019.

It is important to highlight that patient D, when she entered the treatment in the outpatient clinic, was classified as AIS A, however, when she entered this pilot study , her classification was AIS D and remained so; Patient D presents voluntary movements and walks with the help of a walking. Therefore, it was observed that the clinical results of EMG, which were extremely significant, showing the efficacy of NMES treatment.

Patient A has a lower motor neuron lesion. After treatment with NMES, it was expected that there would be greater recruitment of the hip flexion muscles with a possible innervation of the muscles, resulting in the presence of voluntary movement.

The figures below represent a sample of the EMG results of post-treatment patient B patients compared with individual control 2.

Patient B **Control 2**

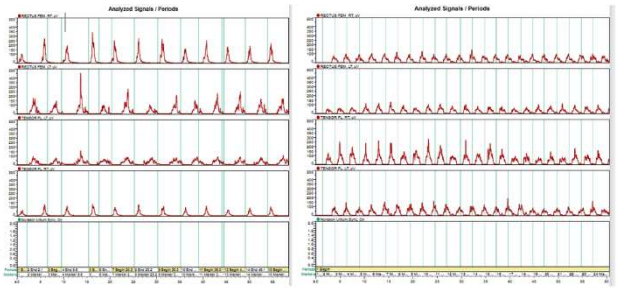

Figure 2. Images of the electromyography chart result for patient 2 and control individual. Source: Electromyography-NORAXON ®.

The figure above is a result of the EMG examination that shows signs of action potential in knee extension movement after six months of NMES treatment and compared to one control individual.

5. Discussion

The data presented in the tables above show EMG signs after the application of NMES protocols for patients with spinal cord injury at different neurological levels of injury. When comparing patients with control subjects, he showed significant results in the EMG examination, showing that the action potential showed that the signals evolved in the amount of frequency of muscle activation. During this preliminary pilot study, there was also a considerable approximation of the results of patients "A, B and D" in relation to their control subjects. Patient "C" did not present significant results due to his absence from treatment for two months. It is important to highlight that, although EMG has relevant results in patient "A, B and D". The AIS does not change or, however, a functional gain of voluntary movements was observed in all patients, as shown in tab. 2 and 3. These results corroborate some studies, which show that NMES is a rehabilitation method that generates several benefits and leads to a possible gain of movements, generating nervous system adaptations and that this is possible to be observed through EMG [9,10]. The limitation of this study was a small number of cases due to a pilot study and future studies will be conducted with a larger sample to confirm this data.

6. Conclusion

It was observed in this study that there was according to the parameters of EMG, a possible improvement in neuroplasticity and gains of voluntary movements in patients.

References

[1] Varoto, R., & Cliquet Jr, A. (2015). Experiencing roots of functional electrical stimulation in education, and clinical developments in paraplegia and tetraplegia with technological innovation. Artificial Organs, 39(10), E187-E201.

[2] Ck Bittar, Cliquet A Jr. Effects of electrical stimulation of the quadriceps and previous tibial muscles on the feet and ankles of patients with spinal cord injury. Spinal Cord. 2010; 48 (12): 881-885. doi: 10.1038 / sc.2010.50.

[3] Araújo TS, Brandão A, Didier T, Bracco B, Gamboa HF, Cliquet A. Analysis of descriptive electrophysiological parameters in contralateral interlimb reflexes on tetraplegic patients. Spinal Cord. 2014 Dec;52(12):894-900. doi: 10.1038/sc.2014.169. Epub 2014 Oct 7. PMID: 25288037.

[4] ASIA American Spinal Injury Association - AIS, http://asia-spinalinjury.org.

[5] Clancy, E.A., Morin, E. L., & Merletti, R. (2002). Sample problems, noise reduction and amplitude estimation in superficial electromyography. Journal of Electromyography and Kinesiology, 12(1), 1-16.

[6] Cacho, E. W. A., de Oliveira, R., Ortolan, R. L., Varoto, R., & Cliquet, A. (2011). Evaluation of the upper limb in tetraplegia: clinical, functional and kinematic correlations. International Journal of Rehabilitation Research, 34(1), 65-72.

[7] Carraro, U., Edmunds, K. J., & Gargiulo, P. (2015). 3D false color computed tomography for diagnosis and follow-up of permanent denervated human muscles submitted to home-based Functional Electrical Stimulation. *European Journal of Translational Myology*, *25*(2).

[8] SENIAM, www.seniam.org.

[9] Jo, H. J., & Perez, M. A. (2020). Corticospinal-motor neuronal plasticity promotes exercise-mediated recovery in humans with spinal cord injury. Brain, 143(5), 1368-1382.

[10] Castro de Medeiros, R., Jaccard, A. P.B., & Cliquet, A. (2010). Sagittarius alignment of the spine in paraplegics: a new paradigm for rehabilitation under neuromuscular electrical stimulation. Balm C, 48(3), 251-25.

Andrea Corna*, Timo Lausen, Roland Thewes, and Günther Zeck

Electrical imaging of axonal stimulation in the retina

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Abstract: Stimulation of axons or its avoidance plays a central role for neuroprosthetics and neural-interfaces research. One peculiar example constitutes retinal implants. Retinal implants aim to artificially activate retinal ganglion cells (RGCs) via electrical stimulation. Such stimulation, however, often generates undesired stimulation of RGC axon bundles, which leads to distorted visual percepts. In order to establish stimulation strategies avoiding axonal stimulation it is necessary to image the evoked activity in single axons. In this work we electrically imaged axonal stimulation in *ex vivo* mouse retina using a high-density CMOS-based microelectrode array. We demonstrate signal propagation tracking via stimulus triggered average during high frequency (100 Hz) sinusoidal electrical stimulation.

Keywords: electrical stimulation, electrical imaging, retinal implant, microelectrode array, MEA.

1 Introduction

Axons are considered stable neuronal transmission cables, which convey information from the site of initiation to synaptically connected cells. In neuroprosthetic applications axon stimulation is of general interest, predominantly in peripheral nerve interfaces. For retinal prostheses, which aim to replace lost photoreceptor input[1, 2], axonal stimulation causes a distorted visual percept in blind patients and therefore needs to be avoided [3]. Stimulation at one spatial location may activate axons of passage, which originate from remote locations. The development of stimulus protocols avoiding axonal stimulation requires techniques allowing imaging of the stimulated action potentials (AP). High-density CMOS-based microelectrode arrays have been used to image spontaneously occurring axonal signals in the retina [4] and axonal and potentially dendritic signals in elaborate neurites of dissociated neurons [5]. In general extracellular axonal signals have a much lower amplitude compared to the somatic one, and strategies to enhance the signal to noise ratio are required. This is especially true for tissue or possibly *in vivo* application, where an optimal interface is challenging to achieve. The most common approach to electrically image signal propagation relies on spike triggered average (STA) algorithms. STA consists in aligning multiple snippets of extracellular recording on the somatic spike. Averaging of snippets reduces the noise and visualizes the axonal AP. This is a very effective technique as shown previously also by us [6]. The main limitation of the technique is the necessary detection of somatic spikes and consequent spike sorting to perform the STA. More recently imaging of axons has been demonstrated with stimulus triggered average (StiTA) in cell culture with pulsatile stimulation [7]. In this work we utilized a HD CMOS based MEA comprising 4225 recording electrodes and 1024 stimulation electrodes [8] to investigate axonal propagation during electrical stimulation of the *ex vivo* mouse retina. We first localized high adhesion areas of the retina sample on the sensor array analyzing the standard deviation (SD) of the recorded extracellular voltage. As a proof-of-concept we electrically imaged axonal activation and signal propagation during sinusoidal stimulation at 100 Hz.

2 Methods

2.1 Retina preparation and extracellular recording using CMOS-based MEAs

Experiments were performed using *ex vivo* retinae from either adult wild-type (C57BL6/J) or from photoreceptor-degenerated mice (rd10). The experimental procedures for preparation of the *ex vivo* retina were reported and approved by the Center for Biomedical Research, Medical University Vienna, Austria. Retina preparation and recording were done using carbogenated (95% O2, 5% CO2) Ames' medium (Ames A 1420, Sigma Aldrich + $NaHCO_3$). The preparation was performed at room temperature while for the recording the temperature was adjusted to 32-35°C . The retina preparation was previously described here [6]. In detail: a portion of the retina is separated from the enucleated eye using a scalpel, detached from the pigment epithelium and the vitreous is removed; Finally the sample is placed on the MEA sensor with the RGC layer directly facing the electrodes. Retina samples were dark adapted for 30-45 min before recording. Recordings involv-

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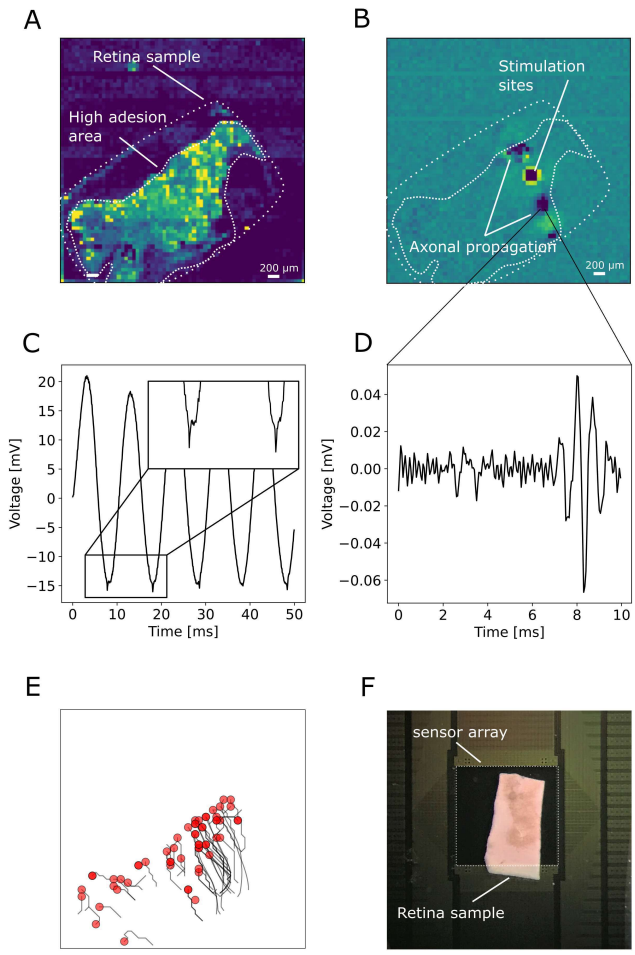

Fig. 1: A) Heat-map of the standard deviation (SD) of the extracellular voltage recorded by an array of 65x65 electrodes of the HD CMOS MEA, showing the adhesion of a retina sample during spontaneous activity. Yellow-green color marks higher SD as compared to the surround, which indicates better tissue adhesion. B) Stimulus Triggered Average (StiTA) for a 100 Hz sinusoidal stimulation, for the sample shown in A. At the center of the heatmap the artifact generated by the stimulating electrodes is visible as well as two branches of signal propagation in the axon. Yellow indicates positive extracellular voltage, blue negative. C) Sinusoidal Stimulation artifact in a recording electrode in proximity of the stimulation. The insert shows the evoked activity (spikes) of a retinal ganglion cell (RGC) in phase with the stimulus. D) Electrode voltage computed with StiTA for a single electrode located under the axon showing the axonal extracellular action potential, with a tri-phasic waveform. The duration of one stimulation cycle (10 ms) is shown. E) Single cells and axon computed via spike sorting and spike triggered average (STA) from the sample shown in A. Red dots indicate the soma locations and black lines the axons. F) Picture of an exemplary retina sample placed in epiretinal configuration over the 5.3 mm^2 CMOS sensor array.

ing electrical stimulation were performed in dark, while light stimuli were presented during the spontaneous activity recording (Figure C,D). A CMOS-MEA comprising 4225 recording electrodes was used for the recording (CMOS-MEA 5000, Multi Channel Systems MCS GmbH), with an electrode pitch of 16 or 36 µm (65 × 65 pixels and a total area: 1 or 5.3 mm^2) and 1024 stimulation electrodes. The chip surface was cleaned with detergent (Tickopur R60, 5%, Stamm/Berlin, 80 °C), rinsed with bi-distilled water and coated with ≈ 100 μl (1 mg/ ml) poly-L-lysine (P1399, MW 150–300 kDa, Sigma, Germany) before the recording. Recordings were performed at 20 kHz using CMOS-MEA Control software (Multi Channel Systems MCS GmbH).

2.2 Retina stimulation, data analysis and stimulus triggered average

The signal was high-pass filtered at 1 kHz (butterworth 4th order). Adhesion was computed as the SD of the filtered electrode voltage and visualized as a heat-map. The HD MEA allows arbitrary selection of the stimulation pattern and waveform. We tested different stimulation protocols to find the optimal parameters. For the sample shown in Figure 1B we stimulated with a 100Hz sinus for 100 ms, and repeated the stimuli for 30 repetitions with a 500 ms pause between repetition. For the stimulation we used 4 adjacent stimulating electrodes for a total area of 0.02 mm^2. To compute the Stimulus triggered average we high-pass filtered the signal at 1 kHz. We then cut 10 ms snippets aligned with the start and the end of the sinus cycle. We average between the 300 snippets for each channel to obtain the final stimulus triggered average. Sorting and STA analysis was done with the CMOS-MEA Tool software (Multi Channel Systems MCS GmbH).

3 Results

This work demonstrates signal propagation imaging in the retina upon sinusoidal high frequency stimulation. This project had two main goals: first, to image the axonal signals propagation from the extracellular recording without additional knowledge of single cell location or activity; second, we wanted to investigate the characteristic, antidromic or orthodromic, of the elicited signal. In order to track the axons and study signal propagation it is necessary to know the location and the adhesion of the tissue on the MEA sensor array. To calculate the area of high adhesion of the retina sample, we computed the SD of the filtered signal of each electrode. The results are visualized as a heat-map in Figure 1A. Strong adhesion means

high cleft resistance (the resistance of the electrolyte between the electrode and the tissue), which translates in an increased SD of the recorded voltage signal [9, 10]. In Figure 1A the green-yellow areas indicate good sample adhesion. The validity of the results is confirmed when comparing the adhesion map with the results of the spike sorter spontaneous activity (Figure 1E). All the detected cells are located in the area with computed high adhesion. Once the position of the tissue was identified, we proceeded to deliver a stimulation in a central area of the sample (Figure 1B). We applied a 100 Hz sinusoidal stimulation as shown in the artifact generated in the recording electrode (Figure 1C). High frequency sinusoidal stimulation causes the excitation of APs in RGC that are in phase-lock with the stimulation waveform. This is shown in the insert of Figure 1C, where it is possible to see a stimulated spike in concomitance with the cathodic phase of the sinus. The stimulus triggered average (StiTA) is computed averaging between the recording snippets of a stimulation cycle aligned with the stimulation phase. The result is a mean response to the stimulation characterized by a lower electrical noise. A single frame of the StiTA is shown in Figure 1B as a heat-map of the voltage. The image shows the artifact of the stimulation in the center and the axonal signal propagating both antidromically or orthodromically to the edges of the sample. The StiTA detected axonal propagation follows the same path of the STA calculated axons (Figure 1E). In figure 1D we show the StiTA computed signal of a single electrode located under the axon. The image shows the electrode voltage during the total duration (10ms) of a 100Hz sinusoidal stimuli. The analysis was repeated at different frequencies: 20, 40, 60, 80 and 100 Hz, with constant charge. It was possible to detect signal propagation along single axons exclusively with 80 and 100 Hz stimulation. For the stimulation we used 4 adjacent stimulation electrodes with a total stimulation area of 0.02 mm^2. The displacement charge per sinusoidal half-cycle was 1.3 nC with a fully charge-balanced stimulus cycle.

4 Discussion

In this work we demonstrate electrical imaging of axonal signals upon electrical stimulation using stimulus triggered averaging. A similar approach, however using shorter pulsatile stimuli (100-200 μsec) has been demonstrated in neural networks grown on a HD CMOS MEA [7]. In the retina, axonal signals identification upon epiretinal activation with such short pulsatile stimuli has been reported recently [11]. The approach presented here takes advantage of the physically separated stimulation and recording arrays which, however, are in close proximity of a few micrometers. This avoids saturation of the recording sensor at a distance of 72 μm from the stimulation electrode (Figure 1B) for the 5.3 mm^2 sensor or no saturation for the 1 mm^2 sensor (Figure 1C). An open question is if sinusoidal stimulation can, and in which regimes, avoid axonal stimulation. While the axonal activation upon 100 - 80 Hz sinusoidal stimuli (1.3 nC, stimulation electrode area: 0.02 mm^2) could be imaged electrically, lower stimulation frequencies (i.e. 40 Hz) did not show axonal propagation with this approach. A possibility is that phase-lock for 40 Hz is not precise enough to allow StiTA, and the StiTA cannot provide a definitive answer for low frequency stimulation. In our previous studies, comprising thousands of cells, we did not detect axonal stimulation with 40 Hz stimulation via somatic activation [6]. In the result shown here the propagation proceeds both in antidromic or orthodromic direction. Therefore another possibility is that elicited axonal AP propagates antidromically (towards the soma), but without activating the soma. Antidromic propagation, however, should lead to somatic activation, as previously reported by different groups [7, 12, 13]. The underlying mechanism is currently investigated and should be clarified in future experiments.

Author Statement

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References

[1] Zrenner E. Fighting blindness with microelectronics. Science translational medicine. 2013 Nov 6;5(210):210ps16-.

[2] Palanker D, Le Mer Y, Mohand-Said S, Muqit M, Sahel JA. Photovoltaic restoration of central vision in atrophic age-related macular degeneration. Ophthalmology. 2020 Aug 1;127(8):1097-104.

[3] Nanduri D, Fine I, Horsager A, Boynton GM, Humayun MS, Greenberg RJ, Weiland JD. Frequency and amplitude modulation have different effects on the percepts elicited by retinal stimulation. Investigative ophthalmology visual science. 2012 Jan 1;53(1):205-14.

[4] Zeck G, Lambacher A, Fromherz P. Axonal transmission in the retina introduces a small dispersion of relative timing in the ganglion cell population response. PLoS one. 2011 Jun 2;6(6):e20810.

[5] Buccino AP, Yuan X, Emmenegger V, Xue X, Gänswein T, Hierlemann A. An automated method for precise axon reconstruction from recordings of high-density microelectrode arrays. Journal of Neural Engineering. 2022 Mar 31;19(2):026026.

[6] Corna A, Ramesh P, Jetter F, Lee MJ, Macke JH, Zeck G. Discrimination of simple objects decoded from the output of

retinal ganglion cells upon sinusoidal electrical stimulation. Journal of Neural Engineering. 2021 Jun 17;18(4):046086.

[7] Bakkum DJ, Frey U, Radivojevic M, Russell TL, Müller J, Fiscella M, Takahashi H, Hierlemann A. Tracking axonal action potential propagation on a high-density microelectrode array across hundreds of sites. Nature communications. 2013 Jul 19;4(1):1-2.

[8] Bertotti, G., Velychko, D., Dodel, N., Keil, S., Wolansky, D., Tillak, B., ... Thewes, R. (2014, October). A CMOS-based sensor array for in-vitro neural tissue interfacing with 4225 recording sites and 1024 stimulation sites. In 2014 IEEE Biomedical Circuits and Systems Conference (BioCAS) Proceedings (pp. 304-307). IEEE.

[9] Voelker M, Fromherz P. Nyquist noise of cell adhesion detected in a neuron-silicon transistor. Physical Review Letters. 2006 Jun 6;96(22):228102.

[10] Zeitler R, Fromherz P, Zeck G. Extracellular voltage noise probes the interface between retina and silicon chip. Applied Physics Letters. 2011 Dec 26;99(26):263702.

[11] Tandon P, Bhaskhar N, Shah N, Madugula S, Grosberg L, Fan VH, Hottowy P, Sher A, Litke AM, Chichilnisky EJ, Mitra S. Automatic Identification of Axon Bundle Activation for Epiretinal Prosthesis. IEEE Transactions on Neural Systems and Rehabilitation Engineering. 2021 Nov 16;29:2496-502.

[12] Lipski J. Antidromic activation of neurones as an analytic tool in the study of the central nervous system. Journal of neuroscience methods. 1981 Jun 1;4(1):1-32.

[13] Eccles JC. The central action of antidromic impulses in motor nerve fibres. Pflüger's Archiv für die gesamte Physiologie des Menschen und der Tiere. 1955 Mar;260(5):385-415.

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The evoked compound nerve action potential is shaped by the electrical pulse-width

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Abstract: Introduction: Despite its central role in medicine electrical stimulation (ES) is still limited by its selectivity. Different reports did assess effects of different waveforms, intensities, and frequency on the activation threshold of nerve fibres with different diameters. We aimed to extend this knowledge by investigating the effect of short monophasic rectangular pulses (1, 2, 5, 10, 50, 100 and 200 µs) on the recruitment order. **Methods:** The sciatic nerve of rats was stimulated, and the evoked compound nerve action potential (CNAP) measured at two sites on the tibialis nerve, using epineural electrodes. Changes in delay, amplitude, and the shape of the CNAP were analyzed. **Results:** The amplitude and delay of the CNAP were significantly affected by the pulse-width (PW). The delay and duration of the compound nerve action potential increased with longer PW, while the amplitude decreased. **Discussion:** Found changes are likely caused by changes in the time point of excitation of individual neuron fibres, depending on electrical field strength and exposure time. This might be of particular interest when selecting PWs for design and validation of stimulation patterns and analysis of experimental and clinical observations.

Keywords: electric stimulation (ES), compound nerve action potential (CNAP), pulse-width (PW), epineural electrodes

Introduction

One of the fundamental principles of ES is the observation that the excitation threshold of a nerve fibre is inversely proportional to the PW. This was already described by Weiss and Lapicque more than 100 years ago [1], and yet, the significance of the PW in practical applications is often underestimated. Grill and Mortimer [2] tested rectangular PW of 500, 100, 50, and 10 µs in computer simulations and validated the results with in-vitro and in-vivo measurements. They concluded that a PW below 100µs allows for more spatially selective activation of neurons and increases the threshold differences between fibre types. Gorman and Mortimer [3] concluded that PW below 10µs would increase the threshold differences even more, but suggested 10µs as a reasonable limit for neural stimulation [3]. On the other hand, longer PWs produce stronger muscle contractions and deeper penetration below the skin [4].

This study aims to provide more in-depth knowledge of the effect of PW under 10µs and to compare them with more typical durations in terms of their effects on the recruitment of nerve fibres. With this purpose, an exploratory proof of principle study in an in-vivo model was performed at the Department for *Sport and Exercise Sciences* of the *John Moores University* in Liverpool.

Methods

All experiments were carried out under strict adherence to the Animals (Scientific Procedures) Act of 1986. The procedures were approved by the Home Office (PPL 40/3743) and were conducted in four non-recovery experiments in adult Wistar rats.

Anaesthesia was induced using 3% isoflurane in oxygen. To maintain stable, deep anaesthesia, the respiration rate was monitored, and the isoflurane concentration was adjusted between 1% and 2%. The body temperature was kept between 37-38°C with an adjustable heat pad (E-Z Systems Corporation, Pennsylvania, USA), and the core temperature was monitored using a rectal temperature probe. 0.05 mg kg−1 of Buprenorphine (Temgesic, Indivior, Slough, UK) was administered intramuscularly in the contralateral leg for analgesia. For stimulation, a 1.2mm diameter tripolar cuff electrode (Micro Cuffe Tunnel, Cortec, Germany) was placed proximal to the tibialis branch on the sciatic nerve. For monitoring, two 0.6mm diameter bipolar cuff electrodes (Micro Cuffe Tunnel, Cortec, Germany) were placed on the tibialis nerve with a 1mm distance between them (see Figure 1).

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Stimulation pulses were generated at a resolution of 1MS/s using LabVIEW 2016 (National Instruments Corporation, Austin, USA). Voltage-controlled stimulation was applied using the analogue output of a NI PCIe 6351 Data Acquisition Card (National Instruments Corporation, Austin, Texas, USA) with ±10V output range, 5mA output current drive, 20V/µs slew rate and 16bit DAC resolution. The stimulation artefact was minimised by applying the stimulation via tripolar cuff electrodes using the middle electrode as cathode and interconnected proximal and distal electrode surfaces as anodes.

Stimulation sets with PWs of 100, 50, 20, 10, 5, 2, and 1µs were tested. All pulses were monophasic. After an initial trial with 50 repetitions per duration, the subsequent assessments were done with 100 repetitions to increase the resolution. Amplitudes ranged from sub-threshold to full nerve activation. The threshold and supramaximal intensity for each set and subject were determined by single test stimulations. At least 40 or 85 different intensities were then tested within the selected range. The different stimulation PW and amplitudes were applied in a randomised order. The data were normalised by applying a supramaximal pulse – monophasic with 100µs PW – every 20th stimulation. The electroneurogram (ENG) signals were recorded using a PowerLab 16/35 (ADINSTRUMENTS Ltd, New Zealand) acquisition unit controlled with LabChart (ADINSTRUMENTS Ltd, New Zealand) at a sampling frequency of 200kHz.

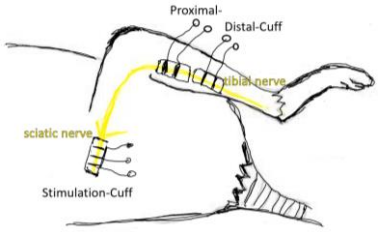

Figure 1: Measurement setup with the tripolar stimulation cuff at the sciatic nerve and the two bipolar measurement cuffs at the tibial nerve.

The ENG was differentially amplified, using the proximal electrode as anode and the distal electrode of the same cuff as cathode for both recording cuffs. Shielded copper wire cables with two conductors were used to connect the cuff electrodes to the before mentioned amplifier for the ENG recording. All shields were connected to a metallic rectal probe which served as reference ground for the differential amplifier.

Data processing, analyses, and visualisation were done using MATLAB R2019b (The Mathworks, Inc., US).

Three points of interest (POI), P1, N1, and P2, according to the expected waveform of an evoked ENG response described by Parker [5], were determined in the recorded traces (see Figure 2a).

The response amplitude was defined as the difference between P1 and N1, similar definitions can be found in [5], and it was normalised relative to the nearest control response. The normalisation responses were checked over time to see if there was a time-dependent effect of the stimulation or the prolonged anaesthesia.

The delay between the stimulation onset and P1 was calculated. For each subject and PW the difference between the appearance of P1 in the proximal and distal channel was calculated. Three-way ANOVAs were conducted to evaluate the effect of stimulation amplitude, PW, and subject on the delay between stimulation and P1, the time difference between the appearance of P1 in the proximal and distal channels (proportional to the conduction velocity), as well as on the duration and amplitude of the CNAP. The duration of the CNAP was defined as the time difference between P1 and P2.

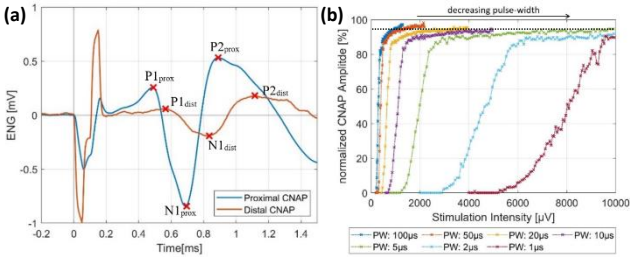

Figure 2: (a) Example of a measured response with the marked points of interest (P1, N1, and P2) in the proximal and distal cuff electrode (stimulation parameters: PW=100µs; Amplitude=1.289mV) **(b)** Normalized recruitment curve of the proximal cuff of the CNAP responses of a single subject for different PW. The black dotted line visualizes that for this subject PW 20µs and 5µs saturate at nearly at the same level

Results

The delay of the neural responses was between 280µs and 535µs ($\bar{x}$=414±38µs n=2114), after the stimulation and lasted between 140µs and 570µs ($\bar{x}$=369±74µs n=2114) depending on the subject, PW, and stimulation amplitude. Both the mean duration of the CNAP and the mean delay of the response decreased with decreasing PW. The latencies of P1, N1 and P2 were always longer in the distal channel (see example in Figure 2a).

Delays between stimulation onset and P1 got shorter with decreasing PW. However, this effect becomes undetectable for PW smaller or equal to 10µs. Furthermore, this effect decreases with higher recruitment (supra-threshold intensity).

The calculated conduction speed varied between ~35 and ~87m/s. The intersubject variability accounted for most of the difference in the speed. This might be due to physiological differences and differences in the distance between the electrodes. Due to poor detection of P1 in the distal cuff within one subject, the data of this subject was not used to calculated conduction speed. The influence of the PW and of the stimulation amplitde were not significant. On the other hand, the delay of P1 was significantly influenced by the PW and the subject, but

not by the stimulation amplitude (see Table 1). The normalised CNAP amplitude and its duration was significantly affected by all three factors (see Table 1).

Table 1: Three-way ANOVAs conducted on the effect of PW, amplitude and subject on P1 conduction velocity and latency, and the CNAP amplitude. DF=degrees of freedom. * DF=2

	PW DF= 6	**stim. amplitude DF=1**	**Subject DF=3**
Conduction P1 Error=1378	F=0.23 p=0.97	F=1.48 p=0.22	F=6839.39 p<<0.01*
delay P1 Error= 2096	F=379.97 p<<0.01	F=0.15 p=0.70	F=4614.11 p<<0.01
CNAP amplitude Error= 2103	F=276.81 p<<0.01	F=1188.52 p<<0.01	F=25.83 p<<0.01

Longer PWs tend to cause a longer delay of P1. With higher recruitment, the duration of the CNAP response increased for all subjects.

Figure 2b shows the normalised recruitment curve (RC) for all different stimulation PW in one subject. As results were similar in both distal and proximal positions, only the normalised CNAP amplitudes from the proximal cuff are reported. In both cases, the response amplitude of the control pulses did not change significantly with time, showing that there was no time-dependent bias of the results.

Stimulation amplitude ranges for each PW to reach certain response levels are remarkably similar in all subjects. The saturation of longer PW is steeper compared with shorter PW. This can be seen in a high asymmetry of the recruitment curve, especially for longer PW, caused by a more linear rise, after the recruitment starts to saturate. Hence, PW do seem to finally saturate at nearly the same level (see black dotted line in Figure 2b). However, none of the responses reaches 100%. This is due to supramaximal stimulation used as normalisation pulses. The stimulation step size increases with shorter PW, as the difference between below threshold to "full activation" increases with decreasing PW.

Discussion

Estimation of recruitment of neurons of different type, size and conduction velocity in a mixed nerve by applying specific electrical stimuli is a complex task and, despite the long history of electrical stimulation, not resolved to a sufficient extent. Here we present an in-vivo model with cuff electrodes placed along a rat's sciatic nerve for stimulation and ENG-recording, to explore the influence of unusually short PW (1 to 100µs) on neuron recruitment characteristic by amplitude variation, in 4 animal subjects.

All recorded ENGs in the 4 subjects in the proximal as well as the distal channel had a similar shape, consistent with published results on CNAP shape and the descriptive parameters amplitude, latency, and duration [5-7]. Assessed conduction velocities were within the expected range for sciatic nerves of rats [8]. Differences in delay of evoked CNAPs, attributed to variations in anatomical distances were verified and considered in calculations and interpretations.

Since neither the PW nor the stimulus amplitude affected the conduction velocity, we assume that differences in the delay of P1 are mainly due to changes in the time point of excitation between different PW. Hence, the duration of the CNAP, calculated via the time difference of P1 and P2 in the proximal channel, and the time difference between P1 and N1, are comparable across subjects.

The shape of a CNAP is influenced by several factors, as it is a projection of multiple single fibre action potentials (APs) with different conduction speed and sagittal distance to the recording electrode. The longer the distance from starting point to recording site the broader the variance of arrival time of contributing APs, with immediate consequences for P1-latency, -amplitude, and the CNAP duration. Another influence on CNAP shape is contributed by the range of distances from individual fibres to the recording electrode. An additional factor is variation in the time from the stimulus leading edge to the start of a propagating AP, which depends on fibre size and local field strength (see Figure 3b).

The saturation level in Figure 2b shows a gradual increase of maximum CNAP amplitude with increasing PWs. This might originate from exciting less small unmyelinated and distant fibres with lower PW due to extremely increased amplitude threshold.

Figure 2b also illustrates a significant effect of PW on fibre threshold and gradient of the RC slope; shortening of PW strongly increases threshold amplitude. Although a similar relation can be found in classical strength duration curves, obtained via sensory perception feedback or neuromuscular reactions [9], the results from direct neural response recording suggest that more pronounced changes in selectivity neuron types occurs with lower PWs.

For a certain pulse amplitude, an "excitation window" EW can be defined, showing the range of pulse durations for which, this amplitude will excite different quality fibres. It starts at the threshold of the most sensitive, nearest-to-electrode, large axons and extends to the threshold of the most distant, small size and/or non-myelinated axons. Two examples are labeled in red and blue (red with 2 different amplitude levels) in the threshold curves in Figure 3b.

Within an EW a stimulus of a certain length and amplitude activates action potentials in each reachable neuron. Taking

this into account, the observed differences in recruitment and CNAP shape, elicited by variation of PW, are most likely not only due to size-dependent fibre involvement, but also by a distance-to-electrode component. This is probably a specific feature of epineural electrode placements. Although not evaluated here, we expect that the distance-to-electrode influence gradually disappears with greater distance.

A further influence on CNAP is associated with asynchrony of arrival of contributing single fibre APs, elicited in synchrony but traveling with different velocities. This effect is also specific for epineural electrodes and gets more diffused with larger neuron-to electrode-distance and higher desynchronization of fibre APs.

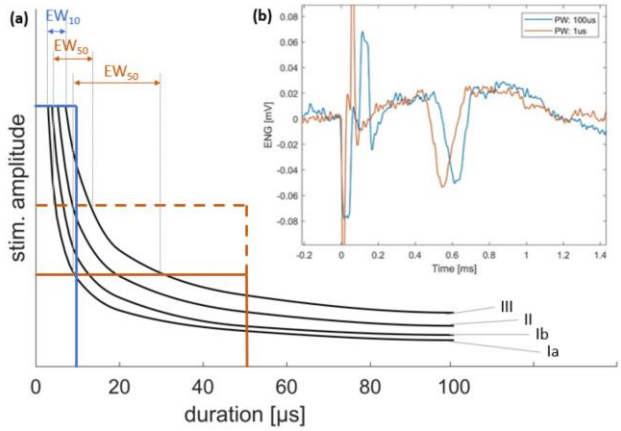

Figure 3: (a) 5: Illustration of strength-duration curves with thresholds for different types of nerve fibres (Ia, Ib, II & III). Two different stimulation PW (blue 10µs and orange 50µs) have different windows of excitation (EW). **(b)** Exemplary recording of responses for two different PW in the proximal cuff electrode.

Figure 3a represents strength-duration curves for different fibre types and helps to identify the excitation windows of PW different intensities (EW20, EW100). The activation window is defined as the time where the first fibre is triggered (e.g. fibre Ia) until the last fibre is activated (Fibre III), and it is implied in the strength-duration curve described by Lapique more than a century ago.

The presence of the excitation window can already be seen in strength-duration behaviour for different sized fibres (see Figure 3a). Higher amplitudes (blue rectangle) decrease the delay between stimulation stimulus onset and threshold (in this example Ia fibres) and decrease the length of the excitation window (e.g. time between reaching the threshold for fibres type Ia and III). Higher synchronisation leads to an additional increase of CNAP amplitude.

In conclusion, CNAP amplitude alone is not specific enough to reliably infer the recruited fibre pool when responses to different stimulus parameters are investigated. Other parameters in the CNAP shape can provide additional meaningful information for better estimation of recruited neurons in a specific setup and parameter set. Here we demonstrated that latency and duration of the response complement information based on changes in amplitude. The findings are most relevant for electrodes directly attached to the epineurium. Other more distant electrode configurations require specific studies for better understanding of anatomical and physiological interaction with artificially induced ES fields.

As suitable methods for selective in-vivo activation of single neurons and recording from single nerve fibres are not in sight for the foreseeable future, critical analysis of bio signal recordings in meticulously target-oriented experimental setups seem currently most promising approaches for gaining more detailed insight in mechanisms of ES of neural structures.

Author Statement

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References

[1] Grill, W.M., *Nerve Stimulation*, in *Wiley Encyclopedia of Biomedical Engineering*, M. Akay, Editor. 2006, John Wiley & Sons, Inc: New Jersey.

[2] Grill, W.M. and J.T. Mortimer, *The effect of stimulus pulse duration on selectivity of neural stimulation.* IEEE Trans Biomed Eng, 1996. **43**(2): p. 161-6.

[3] Gorman, P.H. and J.T. Mortimer, *The Effect of Stimulus Parameters on the Recruitment Characteristics of Direct Nerve Stimulation.* IEEE Transactions on Biomedical Engineering, 1983. **BME-30**(7): p. 407-414.

[4] Milosevic, M., et al., *Why brain-controlled neuroprosthetics matter: mechanisms underlying electrical stimulation of muscles and nerves in rehabilitation.* Biomedical engineering online, 2020. **19**(1): p. 81-81.

[5] Parker, J.L., et al., *Evoked Compound Action Potentials Reveal Spinal Cord Dorsal Column Neuroanatomy.* Neuromodulation, 2020. **23**(1): p. 82-95.

[6] Chapin, J. and K. Moxon, *How to Use Nerve Cuffs to Stimulate, Record or Modulate Neural Activity*, in *Neural Prostheses for Restoration of Sensory and Motor Function*. 2000, CRC Press: Boca Raton.

[7] Sabetian, P., M.R. Popovic, and P.B. Yoo, *Optimising the design of bipolar nerve cuff electrodes for improved recording of peripheral nerve activity*. J Neural Eng, 2017. **14**(3): p. 036015.

[8] Birren, J.E. and P.D. Wall, *Age changes in conduction velocity, refractory period, number of fibers, connective tissue space and blood vessels in sciatic nerve of rats.* J Comp Neurol, 1956. **104**(1): p. 1-16.

[9] Tyler, D.J., *Peripheral Nerve Stimulation*, in *Neuroprosthetics*, K. Horch and D. Kipke, Editors. 2017. p. 300-347.

Varshini Nandakumar*, Ian Swain, Paul Taylor, Earl Merson and Marcin Budka

SmartStim: A Recurrent Neural Network Assisted Adaptive Functional Electrical Stimulation for Walking

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Abstract: According to the Neuro Patience report of the Neurological Alliance, 1 in 6 people in the UK has a neurological condition. With the growth in technology, rehabilitation for neurological problems is one of the fast-growing fields. Functional Electrical Stimulation (FES) is one of those neuro-rehabilitation methods that uses electrical nerve stimulation to restore functional muscle movements that are lost due to neurological problems such as stroke and multiple sclerosis. This neuroprosthetic device is frequently used to assist walking by treating a condition called Drop Foot, a result of paralysis of the pretibial muscles. This study proposes a two-channel FES device called the SmartStim, which has the ability to modulate its stimulation levels according to various obstacles such as stairs and ramps. This system employs a sensor-based module with a Recurrent Neural Network to classify these different walking scenarios. The module is built with Inertial Measurement sensors embedded in a pair of shoes, and the Recurrent Neural Network uses data from these sensors to predict various obstacles as the user is walking. These predictions are then used by a Fuzzy Logic Controller to control and regulate the stimulation current in two channels of the SmartStim system.
In the two channels of the system, one channel will help aid with drop foot, while the other will be used to stimulate another muscle group to help access stairs and ramps by the user. The Recurrent Neural Network module in this system has been trained and tested using the k-fold cross-validation. The evaluation of this trained model shows that it can predict obstacles from sensor data at 97 percent accuracy. Currently, further testing is being performed to assess the workings of the fuzzy logic controller in combination with the Recurrent Neural Network in healthy individuals. It is expected that the SmartStim system may aid users in accessing various walking scenarios more efficiently.

Keywords: Functional Electrical Stimulation, Drop Foot, Machine Learning, Recurrent Neural Network, Fuzzy Logic Controller

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1 Introduction

Functional Electrical Stimulation (FES) is a neuro-rehabilitation technique used to aid muscle movement in people with neurological disorders such as stroke, multiple sclerosis, or incomplete spinal cord injury. Most individuals affected by a neurological condition suffer from limited ability to control their ankle dorsiflexion through voluntary muscle activation. This condition is commonly known as Drop Foot (DF) and leads the individual to drag or scuff their foot while walking. DF mainly arises due to the weakness or paralysis of the dorsiflexor muscle. FES devices such as the Odstock Drop Foot Stimulator (ODFS) [1], Walkaide stimulators [2], or the Actigait system [3] treat DF by stimulating the common peroneal nerve or the tibialis anterior muscle to enable ankle dorsiflexion. All the commercially available Drop Foot Stimulators (DFS) have assisted walking in people with DF for many years. Yet literature reviews show that further developments can improve the working of these present devices [4].
A questionnaire was administered to the patients at the National Clinical FES centre, UK, which helped us identify some of the concerns each individual has while using the DFS in their routine life. Mainly, results [5] of the questionnaire showed that despite using the DFS, many participants required great effort to access different obstacles such as stairs and ramps. Some participants reported they followed special gait patterns to do so, such as descending the stairs by coming down backward or sideways, initially progressing with the unaffected leg, circumduction of the hip, dragging their foot, and other abnormal ground clearing methods.
A literature review taking into account past studies based on FES and terrains [1], [6], [7] showed that terrains played a vital role in DFS users. As a result, the goal of this study was

to design a new FES system that uses machine learning to detect terrains and regulate the stimulation parameters in the device.

2 SmartStim System

In this study, we present the SmartStim system, a two-channel terrain-adaptive FES device that can modify stimulation intensity in response to obstacles such as steps and ramps. Primarily, this system uses two 6-axes MetaMotionC (Mbientlab Inc., San Francisco) Inertial Measurement Units (IMUs) embedded in a pair of shoes to collect data points on the terrain the user is walking. Each of the IMUs consists of 3-axis accelerometers (BMI160) and 3-axis gyroscopes (BMI160).

Walking data was collected from the accelerometers at ±8 g and gyroscopes at ±500 °/s with a sampling frequency of 100 Hz. The data collected from the IMUs were analysed and further noise filtering was done using the Savitzky-Golay filter at 10 Hz. This processed data was then fed into a machine learning algorithm to predict the various obstacles. Three obstacles have been chosen for classification in this study namely ascending steps/ramp, descending steps/ ramps, and level ground. A Recurrent Neural Network (RNN) was programmed using the PyTorch framework and was used for this application. Due to its ability to maintain internal memory and execute classifications based on previous computations, a bidirectional Long-Short Term Memory (LSTM) RNN model was chosen for this project. The RNN model was trained and tested with the IMU data using k-fold cross-validation method, in which the dataset is randomly divided into k subsets and k-1 subsets are used for training and one subset is used to evaluate the model. As shown in the figure, a panel of LEDs with three colours shows the detected obstacles from the output of the RNN model in this system.

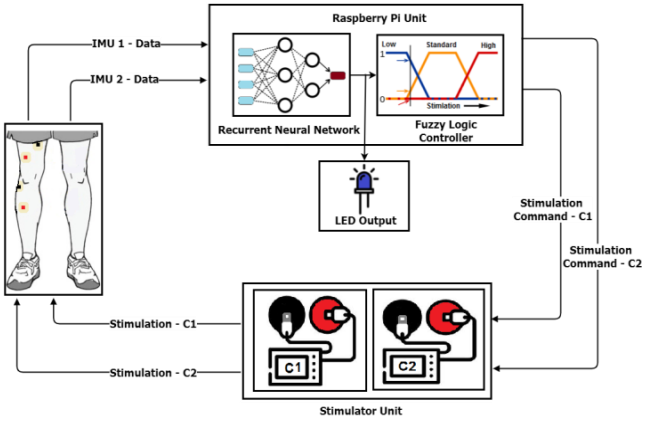

Figure: SmartStim System Layout

The classifications from the RNN were then fed into the Fuzzy Logic Controller (FLC) to control the stimulation current of the devices to provide sufficient stimulation, enabling the user to lift their leg as required to overcome each obstacle.

The main participant group involved in this project will be people with hemiplegia due to stroke and multiple sclerosis. This specific group of people were chosen for this study because the sensor on the unaffected leg helps detects the obstacles before the affected leg touches the ground. The working of the system is programmed as such that the sensors can detect the terrain with enough time to change the stimulation for the affected leg to clear the specific obstacle with more ease.

Three alternative settings are available on the stimulation controller, one for each obstacle. The stimulation controls for level ground in these settings will be equivalent to the participant's standard settings used regularly by them in their device. Similarly, the stimulation control for ramps and stairs will be tailored to the specific needs of each individual.

A questionnaire was administered to FES clinicians to get opinions about a two-channel stimulator to be used in different walking scenarios by people with unilateral drop foot. The two main results obtained from questionnaire was to introduce a second channel of stilmuation to a different muscle group and alter the stimualtion parameters to allow efficient walking in various obstacels. Hence, the SmartStim system design involves stimulation controls being delivered to two channels of the FES device. In order to control dorsiflexion, channel-1 (C1) will control the common peroneal nerve and the tibialis anterior muscle. While, channel-2 (C2) will be utilised to control a second muscle group, such as the quadriceps for knee extension or hip flexion or the hamstrings for knee flexion or decrease knee hyperextension, according to each users.

3 SmartStim System Testing

Initial testing of the SmartStim system has been planned and the study includes three sessions including five people affected by Multiple Sclerosis and five people with Stroke, with 10 participants in total. The study will take place in an outdoor area consisting of slopes, steps, and flat ground on a set course. In Session A participants will walk around the set area at their own pace with their normal FES device in its usual settings with required walking aids for support. The ODFS used by the participant everyday will be setup with a single channel for this session.

Then in Session B all the participants will walk with the SmartStim system with two stimulation channels setup as required for each participant. During both session A and B all the necessary data including walking distance, speed, heart rate, and videos for validation. Finally in session C, after finishing both the walking tests the researcher will administer a usability questionnaire to the participants.

4 Preliminary Results

In evaluating the initial data from the LSTM-RNN model, it shows that this model can classify all the various obstacles with 97 percent accuracy. Similarly, the Receiver Operating Characteristic Curve (ROC-AUC) score for this model was calculated to be 0.99. The ROC-AUC allows the model to create true prediction thresholds that are ideally between 0.5 and 1. Currently, the SmartStim model is being tested with ten healthy participants and further studies involving FES users are planned.

5 Conclusion

In conclusion, a basic design for an FES device that can adapt to various walking scenarios is presented in this article. The design proposes using IMU sensors with an RNN-LSTM model to detect terrains and an FLC control system to modify stimulation parameters in response to the terrain variations. The preliminary findings demonstrate that a terrain adaptive FES system can be constructed to help people with neurological disorders move more easily. The stimulation controls previously done manually by the patient as needed for each terrain, can now be automated with the help of the SmartStim system. This may allow users to access steps and ramps without requiring external adjustments to the FES device. This also serves to pave the way for future research including more terrains and changes to DFS stimulation parameters.

Author Statement

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References

[1] Burridge J, Taylor P, Hagan S, Swain I. Experience of clinical use of the Odstock dropped foot stimulator. Artif Organs 1997; 21(3): 254-260.

[2] Martin KD, et al., ActiGait implantable drop foot stimulator in multiple sclerosis: A new indication. J Neurosurg. 2017; *126*(5): 1685-1690.

[3] Schauer T. Sensing motion and muscle activity for feedback control of functional electrical stimulation: Ten years of experience in Berlin. Annual Reviews in Control. 2017; 44: 355-374.

[4] Nandakumar V, Swain I, Taylor P, Merson E. Initial Design Consideration for an Adaptive Functional Electrical Stimulation System. SSNR, Baiona. 2019: 30-32.

[5] Ma L, Yang Y, Chen N, Song R, Li L. Effect of different terrains on onset timing, duration and amplitude of tibialis anterior activation. Biomedical Signal Processing and Control. 2015; 19: 115-121.

[6] Jung J, Chung Y. The effects of functional electrical stimulation applied to the gluteus medius and tibialis anterior on stair climbing ability in persons with stroke. Physical Therapy Rehabilitation Science. 2018; 7(3): 134-138.

Abstracts

Electrical stimulation of patterned neural networks in vitro at high spatial resolution

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Introduction

Understanding information processing and memory formation of neural networks in the brain poses one of the greatest challenges in neuroscience. In vivo studies on the brain attempt to answer these questions by either monitoring subsets of neurons embedded in a complex network or by whole-brain imaging at low spatiotemporal resolution. The fundamentals of neural processing are difficult to study in such environments. Therefore, we are following the approach of bottom-up neuroscience, in which small engineered neural networks are studied in vitro.

Methods

Primary cortical neurons are seeded into polydimethylsiloxane (PDMS) microstructures to spatially confine the location of their soma and guide neurite growth with the goal of minimising the network complexity [1,2]. In order to study the neural information encoding and processing, the microstructures are placed on high-density microelectrode arrays (HD-MEAs), where network interaction is enabled by means of stimulation and recording from the network [3,4].

Results

Electrical stimulation on individual network electrodes is used to elicit network responses. Exploiting the electrode pitch of only 17.5 µm, we are able to detect the information flow in the network at a much higher spatial resolution compared to previous studies on 60-electrode glass MEAs [5].

Conclusion

The combination of microstructures with HD-MEAs enables analysis of network responses with respect to stimulus location. With these tools we aim to describe the complex input-output relationship of small neural networks. We believe that this could validate fundamental neuroscience postulates, inform the design of in silico models and one day enable performing computational tasks.

References

1. Forro, C., et al. (2018) Biosensors & Bioelectronics, 122
2. Mateus, J. C., et al. (2021) bioRxiv
3. Muller, J., et al. (2015) Lab Chip, 15(13), 2767-2780
4. Duru, et al. (2022) Frontiers in Neuroscience: 16.
5. Ihle, S. J., et al. (2021) Biosensors and Bioelectronics: 113896.

Design of a multi-sensor FES-cycling device

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Introduction

Mortality in people with spinal cord injury is three times higher than in the rest of the population. Cardiovascular diseases are some of the most relevant among the health conditions that affect them, for whom physical inactivity is one of the main risk factors. Due to lower voluntary muscle recruitment levels, therapeutic interventions that provide cardiorespiratory conditioning are limited. Among the existing alternatives is functional electrical stimulation-enabled cycling (FES-cycling). FES-cycling is a method of coordinated transcutaneous muscle stimulation capable of producing the sequenced contraction of lower limbs muscles, reproducing the activity of pedaling a stationary bicycle even in people with spinal cord injury. With the course of training and the emergence of an adaptive response, the pedals resistance can be modified, generating greater aerobic overload and better cardiovascular conditioning.

Methods

The study proposes the development and use of FES-cycling with constant monitoring of heart rates, blood pressure, body temperature, and oxygen saturation. The reduction in cycling speed and variations in biological signals throughout the exercise sessions (such as a reduction in blood oxygen levels) are indicators of early muscle fatigue.

Results

Preliminary results from people with spinal cord injury who are treated with FES-cycling and are constantly monitored suggest a relationship between fatigue (characterized by reduced cycling speed), increased heart rate and negative variations in oxygen saturation.

Conclusion

There is no clear evidence of the relatinship between fatigue and other biological variables during FES cycling sessions. More studies are needed to verify the correlation between the variables in order to predict early fatigue.

Remote electrical stimulation monitoring system: design and proofs of concept

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Introduction

Functional electrical stimulation (FES) uses the controlled application of electricity to stimulate the neuromuscular system. For spinal cord injury cases, FES can be used to stimulate various muscle groups and systems, such as the respiratory muscles, bowels and bladder, in addition to the upper and lower limbs. Misuse and incorrect setup of the equipment are risks to the safe and effective use of this therapeutic intervention, demanding continuous monitoring by health professionals. The evolution of remote monitoring technologies favors the development of electrotherapy medical devices that allow remote guidance and monitoring of the operation by end users themselves.

Methods

The proposed system consists of a portable device associated with an electronic platform that allows remote monitoring and management of its operation, with the possibility of prescribing, creating and applying different therapeutic protocols. The solution comprises a portable embedded system controlled by an interface that can be operated via Bluetooth from a mobile application connected to the internet, in addition to a web-based interface for monitoring the use and history of multiple users. The application contains friendly instructions addressing the end user on all the procedures necessary to setup the device and carry out stimulation sessions in a simple and safe way.

Results

The advantages observed in the proof of concept carried out by the therapists in the team were the simplicity, versatility and potential for managing multiple patients. However, so far, all tests have been carried out by experienced professionals, and should be extended to other groups in the next phases.

Conclusion

As this is a preliminary assessment for the development of a medical equipment, further studies are needed to validate the system.

Reducing spine curvature with functional electrical stimulation (FES): a scoliosis case study

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Introduction

Scoliosis is a change in body structure characterized by the rotation and tilting of the vertebral body. The rotation of the vertebral body is related to how convex or concave is the curve. There are several conservative treatments to prevent or reduce the resulting deformity, including the use of Neuromuscular Electrical Stimulation (NMES). A parameter established by the Scoliosis Research Society, known as the Cobb angle, indicates that curve angles greater than 50° in children can augment during adulthood, causing health problems and worst quality of life.

Methods

We used NMES to treat a 7-year-old male child with incomplete flaccid quadriplegia and S-shaped thoracolumbar scoliosis. By analyzing the forces produced by the musculature originating at the apex of the scoliosis curves, our hypothesis indicated that the convex side was hypertonic, producing traction and rotation of the vertebral body, and that the concave side was hypotonic. The stimulation protocol used consisted of a one-hour daily application of NMES (frequency of 20 Hz and pulse width of 500 μs) on the quadratus lumborum and latissimus dorsi muscles in the region of the thoracolumbar concavity. Case evolution was measured by the changes in the Cobb angle over the months.

Results

Initially, measures have shown Cobb angles of 50° in the lumbar region, and of 56° in the thoracic region. After 6 months, the angle in the lumbar region was 38°, and 55° in the thoracic region. Two years after the first assessment, it reached 30° in the lumbar region, and 56° in the thoracic region.

Conclusion

This case study reports the use of NMES in a child with thoracolumbar scoliosis at high risk of complications in adulthood. The results demonstrate that, after treatment, we observed a reduction in the Cobb angle in lumbar scoliosis and a stabilization of the progression of thoracic scoliosis.

Estimation of the time fluctuation of polysynaptic responses evoked by constant spinal cord stimulation

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Introduction

Polysynaptic activity is necessary to engage the neural circuitry that controls the motor behaviour and is crucial to the recovery after spinal cord injury (SCI) [1]. Polysynaptic responses can be elicited with spinal cord stimulation, and there are few reports on these types of responses in human electrophysiology, most of them describing them as constant to fixed stimuli. However, we have observed that the responses fluctuate in amplitude and time. Amplitude variations can be analysed with statistical methods. However, time fluctuations are more complex due to the multiple parameters involved.

Methods

This work describes a methodology to analyse the time fluctuation in the responses of each pulse. It is based on the calculation of the signal temporal centroid, representing the whole activity, weighted by its latency, in a single time value. This value is then used to model the temporal fluctuation with linear regression. The methodology was verified with an electromyography dataset from a discomplete spinal cord injured patient with spinal cord stimulation.

Results

The parameter is able to follow small changes in the responses' distribution. Examples of how the temporal centroid and linear model identify the fluctuations are presented.

Conclusion

Once fitted in a linear model, the fluctuation coefficient describes time fluctuations in the interneuron processing and, together with amplitude metrics, can characterise changes in polysynaptic responses during the application of fixed stimulation parameters.

Standardised FES-induced fatigue-testing of paralysed human quadriceps muscles during a dynamic movement task

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Introduction

Muscular fatigue remains a persistent problem during functional electrical stimulation (FES). One technique known as spatially distributed sequential stimulation (SDSS), uses multiple electrodes to stimulate distinct pools of motor-units at a lower frequency to decrease fatigue. Although literature claims clear benefits, interpretation of the results and applicability proves difficult due to heterogeneous testing strategies. Thus, we present a standardized method for fatigue testing in individuals with spinal cord injury (SCI), tailored to the requirements of a practical application (e.g. FES-Cycling).

Methods

The fatigue-development of 6 paralysed quadriceps muscles of 3 different participants with complete paraplegia was assessed via a fatigue-index during 180 dynamic contractions, comparing different SDSS electrode-configurations against conventional single-channel stimulation. For standardisation, testing was conducted at 40% of the peak-torque during a maximal evoked contraction (MEC), in previously trained individuals with SCI.

Results

Our results were unable to detect a significant difference in the fatigue-development comparing SDSS against conventional stimulation. Indifferent results regarding the potential benefits of SDSS in a practical setting are widely reported across various international research groups. We hypothesise that the positive effects of SDSS diminish with increasing stimulation amplitudes (required to elicit strong contractions), due to a loss of selectivity.

Conclusion

Assessing muscular fatigue is not a trivial task. To allow for a successful practical translation of a technique, it is crucial to perform fatigue-testing tailored to the requirements of a potential use-case. In practical applications, FES is often used to elicit forceful dynamic contraction in individuals with SCI who already conducted a dedicated FES-training program. Therefore, we recommend to assess fatigue-development at higher forces (e.g. 40% MEC) in pre-trained individuals with SCI to better reflect the practical demands of FES-applications.

Avoidance of axonal activation in epiretinal implants using short biphasic pulses

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Introduction

Retinal implants allow patients suffering from degenerative retinal diseases to regain visual percepts. Despite considerable effort in developing and improving retinal neuroprostheses in the last decades, the restored vision in patients does not achieve sufficient quality. One of the main obstacles in epiretinal implants is the concurrent activation of cells close to a stimulating electrode and cells that have their axons traversing the electrode.

Methods

In this study, we employ computational modeling to examine the effect of pulse duration on the selectivity of focal versus non-focal activation. We used morphologically- and biophysically-realistic multicompartment models of mouse RGCs. Extracellular electric stimulation was applied via disk electrodes from the epiretinal side.

Results

Our results suggest that biphasic pulses in the range of 10-20 microseconds can prevent axonal activation while still reliably activating target neurons. This was the case for idealized biphasic rectangular pulses as well as for measured waveforms generated by an CMOS-based Microelectrode array (MEA). Despite the short pulse duration charge levels to induce activity were in a range well below the limit for safe stimulation.

Conclusion

Shorter pulses increase the axonal/focal threshold ratio and therefore may be applicable to generate more focal responses during epiretinal stimulation. This may improve the clinical outcome in patients with retinal implants.

The effect of neuromuscular electrical stimulation on bowel management in people with spinal cord injury - preliminary results

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Introduction

Spinal cord injury (SCI) causes a disruption of the autonomic nervous system affecting gastrointestinal function amongst many others. More than one hour is spent for defaecation in 14% of this population (Coggrave et al., 2009) and people are limited in their participation in social life activities.

Methods

We included five participants with chronic SCI (>2 years) in the analysis of the preliminary results. They applied electrical stimulation onto their abdominal musculature for 16 weeks for 30 minutes before their regular defaecation times. At each of the five study visits, participants' bladder, bowel and sexual function have been evaluated using the Qualiveen SF, Neurogenic Bowel Dysfunction Score (NBDS) and the ISAFSCI respectively. They documented the stimulation and defaecation time in an online database. Transit time was evaluated using the Corn test.

Results

NBDS varied amongst participants without recognizable pattern in regards to the stimulation. The NBDS increased in some, which indicates a worsening of the magnitude of bowel dysfunction. This is in contrast with the remaining results of the present study. Satisfaction of bowel function increased by 2.6 points (Likert scale: 0-10) on average in all participants after starting the stimulation. Furthermore, two out of five participants could successfully decrease their bowel transit time (33.8% and 85.2%). Finally, defaecation frequency and defaecation duration could be reduced in three out of five participants. The bladder function decreased by 0.45 points on average after stimulation as measured by the Qualiveen SF, indicating an amelioration of bladder function.

Conclusion

The preliminary data described above shows that symptoms of bowel dysfunction are very individual as we observe a large variability among the population. However, satisfaction of bowel management increased while stimulation was applied so that four out of five intend to continue.

Optical Quantification of Surface Electrical Stimulation to prevent Denervation Muscle Atrophy in 15 Patients with Facial Paralysis

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Introduction

Few studies showing therapeutic potentials of electrical stimulation (ES) of the facial surface in patients with facial palsy have been published so far. Not only muscular atrophy of the facial muscles but facial disfigurement represents the main issue for patient well-being. Therefore, objective methods are required to detect ES effects on facial symmetry within patients with complete unilateral facial paralysis.

Methods

Only patients with one-sided peripheral complete facial paralysis confirmed by needle-EMG were included and underwent ES twice a day for 20 min until the event of reinnervation or for a maximum of 1 year. ES-parameters were set during the first visit and confirmed/adapted every month thereafter. At each visit, patients underwent needle-electromyography, 2D-fotographic documentation and 3D-videos. Whereas 2D-images allow Euclidean measurements of facial symmetry, 3D-images permit detection of metrical divergence within both sides of face. Using the 2D and 3D-fotographic documentation, we aim to prove that ES is able to prevent muscular atrophy in patients with facial paralysis.

Results

In total 15 patients were recruited (medium 53 years, min. 25, max. 78; 8 female, 7 male). They underwent ES for a maximum of one year without serious adverse events. All patients were able to follow the ES protocol. On a short term, we could detect positive effects of ES on the extent of asymmetry of mouth corners. Preliminary results show positive effects leading to improvement of symmetry of denervated faces.

Conclusion

A positive short-term effect of ES on facial symmetry in patients with total paralysis could be shown. The improvement of optical appearance during ES has a positive effect on patients' satisfaction and resembles a promising, easily accessible marker for facial muscles in facial paralysis patients. Improving facial symmetry by ES might also be linked to preventing facial muscle atrophy.

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Surface Electrostimulation prevents Denervated Muscle Atrophy in Facial Paralysis: Ultrasound Quantification

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Introduction

Sparse evidence of the potentialities of surface stimulation (ES) for preventing muscle atrophy in patients with acute or chronic facial palsy have been published so far. Especially studies addressing objective imaging methods for paralysis quantification are currently required. Facial muscles as principal target of ES can be directly quantified via ultrasound, a swiftly feasible imaging method. Our study represents one of the few systematic evaluations of this approach within patients with complete unilateral facial paralysis.

Methods

A well-established ultrasound protocol for the quantification of area and grey levels was used to evaluate therapeutical effects on patients with facial paralysis using ES. Only patients with complete facial paralysis confirmed by needle-electromyography were included. Individual ES parameters were set during the first visit and confirmed/adapted every month thereafter. At each visit patients additionally underwent facial needle-electromyography to rule out reinnervation as well as ultrasound imaging of 7 facial and 2 chewing muscles.

Results

In total 15 patients were recruited (medium 53 years, min. 25, max. 78; 8 female, 7 male). They underwent ES for a maximum of 1 year without serious adverse events. All patients were able to follow the ES protocol. First results in the assessment of ultrasound imaging already indicate that electrically stimulated paralytic muscles do not experience any further cross-sectional area decrease in comparison to the contralateral side. Non-stimulated muscles do not provide significant changes. Similar effects on grey levels currently remain to be assessed to draw further conclusions.

Conclusion

ES is supposed to decelerate the process of atrophy of facial muscles in patients with complete facial paralysis. Thus, the muscular cross-sectional area does not seem to aggravate during the period of electrostimulation within sonographic assessment. This demonstrates the benefit of ES regarding the facial muscle atrophy in patients with complete facial paralysis.

Evaluation of mechanic muscle reflex responses elicited by transcutaneous spinal cord stimulation

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Introduction

To ensure excitation of afferent nerve fibers during transcutaneous spinal cord stimulation (tSCS), reflex responses (RR) in peripheral leg muscles elicited by double stimuli pulses are evaluated in the corresponding surface electromyographic (sEMG) signals. Amplitudes and suppression of the RRs provide feedback on tSCS intensity and electrode position. However, using sEMG sensors involves time consuming skin preparation and electrode placing.

Methods

For increasing the usability in a clinical environment, a new evaluation approach is examined by placing accelerometers on the muscle bellies using elastic straps. The acceleration signal represents force development in the muscles through the mechanical oscillation of the muscle fibers. Therefore, the signal shows longer oscillations than the sEMG data, which causes the responses of the double stimuli to overlap. Thus, double as well as single stimulation pulses are applied to extract the acceleration responses on the first and second stimuli. EMG and acceleration of different leg muscles are recorded in two subjects to expose possible correlations in the electric and mechanic RRs.

Results

The amplitude parameters of the RRs of EMG and acceleration signals indicate good correlation. However, in some muscles the regression of the second and first stimuli differ. When a suppression of the RR occurs after the second stimuli in the sEMG signal, the acceleration signal contrarily shows an increase in amplitude. This observation might be caused by twitch summation during double pulses, leading to an increase in muscular force. The effect could potentially be eliminated with a constant factor applied to the amplitude of RRs in the acceleration signal.

Conclusion

The results indicate that EMG and acceleration amplitudes of the RRs correlate. Therefore, replacing the tSCS evaluation with acceleration signals might be applicably if global muscle-specific factors for twitch summation suppression can be found. However, this would require further investigations with a larger group of subjects.

Hybrid FES-Exoskeleton Control for Walking Gait Correction

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Abstract

Walking gait correction is fundamental to restoring body motion function for patients. Functional Electrical Stimulation (FES) is regarded as a promising method and essential to Neurotherapy, and the exoskeleton is fast becoming a key instrument in rehabilitation. Applying FES or exoskeleton alone, however, has its inherent disadvantages. Therefore, the hybrid exoskeleton combined with FES promoted in recent years overcomes the deficiency of more degree of freedom control.

In this paper, a hybrid FES-Exoskeleton for walking gait control was first proposed and evaluated. With the Force Sensing Resistors (FSR) sensor, the exoskeleton actively assists in walking. Simultaneously, it also triggers the FES of the soleus, tibialis anterior, and gastrocnemius muscles for dorsiflexion and plantar flexion. Later, three different control strategies are employed for the pulse-width controlled FES. Eventually, an ILC with a PID controller is applied in the hybrid exoskeleton, following the best foot angle trajectory.

This study discussed the combination between FES and exoskeleton application in walking gait. The present research aimed to examine the control possibility of the hybrid exoskeleton, and the second aim of this study was to investigate different control strategies for walking gait correction. These experiments confirmed that FES can be used as rehabilitation and correction tools during walking, and PID with ILC control could better follow the ankle position.

Proof of concept for EMG-triggered multichannel electrical stimulation in moderate arm paresis in early subacute stroke patients - results from a randomized controlled trial

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Introduction

Neurorehabilitation aims to optimize task performance through the recovery of control of voluntary movements (CVM). In this proof-of-concept study, the effect of EMG-triggered multichannel functional electrical stimulation (EMG-MES) on the recovery of CVM and the ability to execute arm-hand-activities in early subacute stroke patients with moderate arm paresis was compared to that of single-channel cyclic neuromuscular electrical stimulation (cNMES).

Methods

Subacute stroke patients with moderate arm paresis (Fugl-Meyer-Assessment-Arm Section (FMA-AS) score between 19 and 47) were block-randomized and underwent three weeks of conventional neurorehabilitation therapy including task-oriented arm training and additionally received 15 sessions of either cNMES or EMG-MES. Before and after treatment, the FMA-AS, Box-and-Block Test (BBT), and Stroke-Impact-Scale (SIS) were recorded. Statistics included demographic comparison, descriptive statistics of the results, the Wilcoxon signed-rank test, and the Mann-Whitney U-test for describing group differences pre-/post-intervention.

Results

All 12 participants showed significant improvement in FMA-AS and BBT. Participants who received EMG-MES had a higher mean gain in FMA-AS than patients treated with cNMES (7.17 ± 2.2 versus 6.33 ± 4.5). Non-significant improvement was demonstrated by both groups in the SIS daily activities domain. Arm-hand use and stroke recovery was better in participants treated with EMG-MES.

Conclusion

The addition of a three-week EMG-MES treatment to conventional neurorehabilitation therapy has shown to be superior to a three-week cNMES treatment of the wrist only in this preliminary randomized clinical trial. A larger trial is recommended to confirm these preliminary findings.

Concept for an active multichannel microelectrode array embedded in a flexible multilayer foil for high-density stimulation of the retina

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Introduction

Retinitis Pigmentosa is a genetic disease damaging the photoreceptors inside the retina eventually leading to complete blindness. In past projects, restoring the loss of vision with generic retinal implants was challenging with limited success. Some of the visual prosthetics showed optimistic results, however, with limited resolution and small field of view. An active microelectrode array (MEA) with a high electrode count (>1000) embedded in a flexible foil could be a major step forward to increase the resolution of future retinal implants.

Methods

Stimulating the retina with increased spatial resolution and a decent field of view requires more than 1000 electrodes. For this purpose, an active matrix addressing could be advantageous. The active matrix realized in a crossbar array is used to control and activate the microelectrodes, individually. For this purpose, each microelectrode pixel in the array needs to have at least one selection transistor.

Results

In previous projects, we fabricated microelectrode arrays (MEAs) in a multi-layer polyimide process, where contact lines were realized by standard lithography from evaporated gold. Inter-layer connections as well as stimulation electrodes were fabricated from gold microgalvanics, while the stimulation pads were functionalized with sputtered iridium oxide (SIROF). In all the former designs, the stimulation electrodes were directly contacted to the stimulation electronics or to ASIC devices in a one-to-one fashion. As a first proof-of-concept for active addressing, an array of p-type transistors was fabricated on a silicon-on-insulator (SOI) wafer. After implantation and patterning, the polyimide multi-layer flexible foil with gold interconnects was fabricated. After back-etching of the wafer, the transistors were transferred to the flexible foil.

Conclusion

An SOI transfer process of active transistor elements to a multilayer flexible foil can be used to realize an addressable active switch matrix for large electrode counts. We will use this concept in our future generations of epiretinal implants.

The effect of neuromuscular electrical stimulation on skin temperature in individuals with spinal cord injury: A prospective non-controlled intervention study

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Introduction

The research on the effect of neuromuscular electrical stimulation (NMES) protocol on skin temperature (Tsk) in individuals with spinal cord injury (SCI) is a prospective non-controlled intervention study.

Methods

47 individuals with SCI were recruited from the outpatient clinic. NMES was applied to the tibialis anterior (TA) muscles. Four assessments were performed: baseline, shortly after the end of NMES session (t0), 10 min after the end of NMES (t10) and 20 min after the end of NMES (t20). The intensity used was 1.5 mA RMS (root mean square) depending on the individuals. The variables were Tsk at forehead, dermatome C2 and L5 bilaterally. The measurement device was a non-contact infrared thermometer.

Results

Results of this study demonstrated that after NMES the stimulated dermatome (L5), showed an increase in local Tsk. In addition, the t20 shows that the Tsk did not drop to the baseline, being still significant in the analyzed group.

Conclusion

The implications for rehabilitation practice and the positive effects of NMES are fundamental to improvement of the blood microcirculation and local metabolism.

A feasibility study on the clinical use of neuromuscular electrical stimulation towards neurogenic bladder in spinal cord injured individuals

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Abstract

This research assesses the effect of tibial nerve electrical stimulation on urinary incontinence in individuals with spinal cord injury (SCI) being a prospective non-controlled intervention study. 8 individuals with SCI were recruited from the outpatient clinic. This study demonstrates results of NMES (neuromuscular electrical stimulation) applied to the tibial nerves for 12 weeks. Results:Two questionnaires were applied (Neurogenic Bladder Symptom Score-NBSS and Qualiveen-SF) and presented a tendency to improve symptoms and quality of life, however, without statistical significance. With the urodynamic data: maximum cystometric capacity increased with a mean of 285.6 ml pre, to 314.8 ml post NMES (P-Value: 0.554); compliance increased from 26.38ml/cmH2O pre NMES to 29.88ml/cmH2O post NMES (P-Value: 0.461); detrusor hyperactivity in the filling phase occurred in all patients in the pre NMES assessment; the maximum amplitude of the detrusor pressure in mean detrusor overactivity after NMES increased from 62.0 to 66.6 cmH2 (P-Value: 0.674); urinary leakage pressure during detrusor overactivity pre NMES were mean of 54.0 and 53.2 after (P-Value:1). Conclusion: The implications for rehabilitation practice and the positive effects of NMES are fundamental to improving the quality of life and reducing urinary incontinence on these individuals.

Exploring methods for targeted activation of the sympathetic nervous system without exercise

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Introduction

When using functional electrical stimulation (FES) for cycling in individuals with spinal cord injury (SCI) during FES-cycling, a rapid onset of muscular fatigue can be observed. Among other reasons, missing neural feedback from the lower extremities might be responsible for a reduced sympathetic response during stimulation. Therefore, this project explores different methods to activate the sympathetic nervous system to increase the heart rate to allow better blood circulation and oxygenation in the working muscles.

Methods

Six techniques were selected to be tested on 10 healthy participants in the context of pilot measurements. Those were the cold pressor test with both hands, a virtual reality rollercoaster ride, the hot water immersion test with two hands, the Wim Hof breathing method, the Valsalva manoeuvre and the ingestion of Capsaicin through Prik Jinda chilli peppers.

Results

The results showed a significant increase in average as well as peak heart rate during all methods performed. From baselines of around 68 bpm, the strongest increases in both parameters were found for the Valsalva manoeuvre (to 118$\pm$SD bpm peak, 91 bpm average), the Wim Hof breathing method (to 112$\pm$SD bpm peak, 86$\pm$SD bpm average) and Capsaicin ingestion (to 103$\pm$SD bpm peak, 80$\pm$SD bpm average).

Conclusion

The methods as they were performed in this project, are not all directly applicable to FES-Cycling but rather serve as exploration how efficiently which stimuli can increase the heart rate. In future research, adaptation or combination of techniques might help to increase performance during FES-Cycling.

Clinical outcomes of neuromuscular electrical stimulation applied to different neurologic levels of spinal cord injuries a pilot study

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Introduction

Electrical stimulation is a tool that has been used in various ways in the rehabilitation of spinal cord injuries. Surface electromyography is an effective method for assessing the many conditions in which the patient is. Objective of the study is to evaluate the benefits through neuromuscular electrostimulation in patients with spinal cord injury and possible neuroplasticity gain observed in electromyography.

Methods

This is a pilot study on the evolution of clinical cases of different neurological levels of spinal cord injury.

Results

It was observed that the spinal cord injured patients analyzed in this preliminary study showed possible gain in neuroplasticity.

Effect of FES controlled cycling training on cardiovascular and pulmonary systems in a spinal cord injured patient

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Introduction

The results of two spiroergometric measurements are presented that were taken from a spinal cord injured patient who participated in FES cycling training sessions for 11 months.

Methods

The two measurements were taken 4 and 11 months after starting the training program. We investigated the respiratory exchange ratio (RER) and ventilation (VE/VO2, VE'/VCO2) ratios and the cycling cadence in the two investigated training sessions.

Results

In the first assessment, the RER was below 1, which is the anaerobic training limit. Seven months later, in the second assessment, the RER value exceeded the anaerobic limit a few times and remained above it at the end of the session. The VE /VO2 and VE/VCO2 curves did not intersect during the first assessment. In the second one, the VE/VO2 and VE/VCO2 curves intersected several times and the oxygen quotient curve exceeded the carbon dioxide quotient curve. The patient achieved a low but similar cycling speed during the two assessments.

Conclusion

Through the activation of paralyzed muscles with FES cycling we are able to train the paraplegic patient in aerobic and anaerobic training zones. This is shown by the value of RER, which reached the anaerobic training limit during the second assessment and remained in the anaerobic range for longer time.

Evaluation of closed-loop vagus nerve stimulation for heart rate control in a Langendorff-perfused isolated rabbit heart with intact cardiac-vagal innervation

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Introduction

Closed-loop vagus nerve stimulation (VNS) is a potential non-pharmacological treatment for persistent tachycardia. This study aimed to develop a control strategy (CS) that allows lowering the heart rate (HR) to the desired level based on a previously developed numerical model and an ex-vivo experimental setup.

Methods

A proportional-integral controller was implemented that modulates the current amplitude of the biphasic stimulation signal between 0 and 6 mA. The CS performance was quantified by the rise time (Tr), percentage overshoot (%OS), and controller stability as the mean squared error (MSE) between the desired- and the instantaneous HR for a step response reducing the HR by 20 bpm from baseline. Optimal controller gains were identified from simulations of a virtual study population consisting of 50 virtual individuals. The CS was evaluated in one Langedorff-perfused rabbit heart with intact cardiac-vagal innervation. The experiment was approved by the local ethics committee (BMBWF 2020-0.016.858 - GZ 2020-0.016.858).

Results

Optimal controller gains identified from the simulations were 0.008 and 0.01 for the proportional- and integral gains, respectively. In the virtual population these gains resulted in Tr = 4.4 $\pm$ 5.3 s, %OS = 3.4 $\pm$ 2.6 %, and MSE = 3 $\pm$ 2.9 bpm. Likewise, these gains led to excellent controller performance in the isolated heart experiment reducing the baseline HR from 169 bpm to 149.5 bpm with Tr = 7.7 s, %OS = 0 %, and MSE = 3 bpm.

Conclusion

The first experimental outcomes were very encouraging, and further experiments are ongoing for a more thorough evaluation and possible optimization of the CS. The results from the ex-vivo setup form an important step towards closed-loop VNS for in-vivo HR control.

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A novel model of an ex-vivo innervated isolated rabbit heart for selective cardiac vagus nerve stimulation

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Introduction

Neuromodulation of the cardiac autonomic nervous system is evolving as a novel approach in the treatment of pathological cardiac conditions. The purpose of this study was to develop a novel isolated Langendorff-perfused rabbit heart preparation with intact vagal cardiac innervation.

Methods

New Zealand White (n=6, 2.8-3.3 kg, age of 3-4 months) rabbits were used. The right vagus nerve was dissected from the nodose ganglion down to the heart including cardiac branches. The innervated-heart preparation was then connected to an erythrocyte-perfused working heart system. For nerve stimulation, a bipolar set of needle electrodes was used.

Results

During the experiment, the nerve was immersed in isotonic sodium chloride in order to maintain the excitability of the nerve to the electrical stimulation. The baseline heart rate was about 170-180 beats min-1, which could be decreased by 10-15% after stimulation of the right vagus nerve. In total, the vagus nerve was stimulable for up to four hours ex-vivo.

Conclusion

Taken together, this setup enables to measure the direct effects of cardiac VNS on changes in heart rate and the consequence of VNS on left ventricular hemodynamic function. In addition, this model provides a well controllable experimental environment that allows to study electrical neuromodulation of the cardiac autonomic nervous system.

Acknowledgements

This work was funded by the European Project “NeuHeart” (Grant agreement ID: 824071).

Assessing Novel Functional Electrical Stimulation (FES) Activation Patterns with Cycling Ergometer

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Introduction

By evoking contractions in paralyzed muscles, functional electrical stimulation (FES) cycling provides health benefits of exercise to persons with spinal cord injury (SCI). However, two of the main reasons why FES cycling has not gained widespread application are rapid muscle fatigue and low output power. The aim of this work is to develop a platform and design the experimental protocol for assessing muscle fatigue and power output produced while cycling by stimulating paralyzed muscles with novel stimulation patterns in participants with SCI.

Methods

A wall-mounted ergometer equipped with force measuring pedals, encoder and stimulator was developed. DC motor drive system, designed to assist participants while maintaining constant cadence, was adapted to the system. One adult with a motor-complete SCI (ASIA B at the neurological levels C6-C7), experienced with FES cycling, participated in the experiment. Each of the two multiday sessions began with a warm-up phase followed by two 5-minute trials separated by a rest period. The trials consisted of conventional (singlets, fixed frequency) or novel stimulation patterns (doublets, stochastic randomization, interferential stimulation).

Results

The ergometer produces cycling movement at a cadence of up to 100RPM while the encoder provides the position of the crank with a precision of 6000 pulses per revolution. Each pedal, equipped with a six-component force-torque sensor, measures the applied mechanical torque values up to 90Nm. Force-angle curves were successfully recorded during both sessions consisting of trails with constant-frequency trains and variable-frequency trains. Mean power, peak power and fatigue index were calculated and compared.

Conclusion

We have developed a FES cycling ergometer and designed an experimental protocol for assessing fatigue and output power. The ergometer has proven to be important for further research of novel stimulation patterns which will lead to the increase of the efficiency of FES and consequently, its application reach.

Unilateral electrostimulation of the internal branch of the Superior Laryngeal Nerve for the treatment of spasmodic dysphonia and voice tremor

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Introduction

Spasmodic dysphonia (SD) is a chronic (long-term) voice disorder, characterized by involuntary movements of one or more muscles of the larynx. With spasmodic dysphonia, movement of the vocal cords is forced and strained resulting in a jerky, quivery, hoarse, tight, or groaning voice. Voice tremor (VT) describes a periodic fluctuation in loudness and pitch and a resulting decrease in overall voice quality. Presently the standard treatment is based on the off-label administration of Botulinum toxin. The aim of our study is to determine whether unilateral electrostimulation of the internal branch of the superior laryngeal nerve (iSLN) is effective for the treatment of SD and/or VT

Methods

So far, 13 patients completed the study, 8 suffering from SD only and 5 from both SD and VT. Stimulation was delivered by means of hooked-wire electrodes very close to the iSLN with an amplitude $\leq$3mA, a frequency of 60-80 Hz, and a pulse width of 0.2ms. Stimulation was conducted for 30 min every morning for 5 consecutive days. Voice strain, spasm number, voice tremor, voice range profile, and quality of life questionnaire were used to assess the effects of the stimulation

Results

Voice strain and Dysphonia Severity Index (p=0.011), and phonation effort (p=0.002) significantly decreased after 5-day stimulation (p=0.011). The fundamental frequency (p=0.002), the sound pressure level ranges (p=0.025), the maximal phonation time (p=0.029) significantly improved. The communicative participation item bank showed a significant subjective improvement (p=0.002)

Conclusion

The interim analysis of our study showed that the unilateral electrostimulation of the iSLN is promising as alternative to the off-label use of the Botulin toxin. Metanalysis should be considered to systematically compare the effects of the 2 treatments

Electrostimulation of intrinsic laryngeal muscles for the treatment of unilateral vocal fold paresis

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Introduction

Unilateral vocal fold paralysis (UVFP) is a rare disease causing clinically relevant voice impairment. The golden standard treatment is voice therapy, even though selective surface electrostimulation (sSES) could be an effective treatment. The lack of systematic trials on sSES to treat UVFP symptoms has prevented so far its implementation in the clinical routine.

Methods

we recruited 54 patients - 26 (51%) males, 25 (49%) females - with an average age of 53 $\pm$ 15 years. 3/54 (5.6%) were withdrawn after failing selection criteria. Stimulation was delivered bilaterally with an external stimulator by placing surface electrodes (40x28mm) in correspondence of the thyroarytenoid muscle (TA); in triangular waveform, at 1 Hz, with an amplitude $\leq$20mA. Pulse widths (PWs) of 1, 10, 25, 50, 100, 250, and 500 ms were tested. Selective stimulation was deemed successful if both VFs reached a median position at rest and/or during phonation. Unspecific responses comprised swallow/coughing reflex, and/or strap/platysma muscles twitches.

Results

Bilateral VF adduction was observed in 90.2% at rest and about 80% of the cases during phonation while applying a 100 ms PW. PWs of 50 or 250 ms with a slightly lower frequency achieved the same results. The average amplitude ranged between 6.5 and 8.5 mA. Application of a 500 ms PW increased the risks of triggering a swallow reflex before a selective VF adduction could be observed, while the use of PWs < 50ms tended to trigger an immediate unspecific response of the strap/platysma muscles.

Conclusion

Our results show that sSES can elicit the selective and simultaneous VF adduction both at rest and during phonation without unspecific response as long as both the PW and amplitude are correctly selected. PWs between 50 and 250 ms correlate with the most specific results. Electrode placement is essential to elicit a specific target muscle response.

Is needle electrostimulation a useful screening tool for a laryngeal and facial pacemaker?

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Introduction

Electrostimulation implants could provide targeted and rapid help in unilateral vocal fold palsy (UVFP) and facial palsy (FP). In contrast to surgical solutions, they could provide functional and dynamic solutions with lower surgical risk and faster recovery times. We compare the stimulation parameters collected in facial and laryngeal direct muscle stimulation to show the potential of pacemakers, but also to evaluate the required stimulation parameters.

Methods

8 patients with UVFP (duration: 4-22 years) and 11 patients with FP (duration: 0.1-16 years) were included in two prospective studies. During routine laryngeal surgeries, the thyroarytenoid and lateral cricoarytenoid muscles were directly electrostimulated. In the face, needle stimulation was not only possible during open surgery but also in awake patients inserting needle electrodes under sonographical control into the zygomaticus muscle (ZYG). The paretic muscles were stimulated with the following parameters: Amplitude 0.1-10 mA, phase duration 0.1-5 ms, frequency 1-40 Hz. Adductor movements of the stimulated paretic vocal fold or movements of the corner of the mouth in response to stimulation were recorded.

Results

Motor response could be evoked in 6/8 patients in the larynx and 11/11 in the face. There were no adverse events or painful sensations. Nonspecific activations of other muscles could be avoided by selecting the right parameters. Disease duration had no effect on muscle response. With FP, mouth angle elevation was inducible with a phase duration of 0.5-5 ms and amplitudes of 1.5-2.5 mA. In UVFP cases, stimulation with 2.5-3 mA, 1ms phase duration at a frequency of 30 Hz caused partial medialization movements of the paretic vocal fold in 4/6 patients.

Conclusion

Electrostimulation in UVFP and FP seem to have similar stimulation parameters. By direct needle stimulation, we are now able to predict the required stimulation parameters for a laryngeal and a facial pacemaker.

Is surface electrostimulation a useful screening tool for a facial pacemaker?

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Introduction

An electrostimulation implant ("facial pacemaker") could be an alternative to surgeries and provide targeted and instant help in facial paralysis. This study aimed to show whether surface electrostimulation may be useful as a screening tool for patients where a facial pacemaker may be indicated and to predict the required stimulation parameters.

Methods

7 patients with facial paralysis (duration FP: 0.1-16 years) were included in this prospective study. Surface electrodes attached on the skin above the zygomaticus muscle and needle electrodes placed under sono-control into the muscle were used to stimulate with the following parameters: amplitude 0.1-10mA, phase duration 1-1000ms for surface electrodes and 0.1-5ms for needle electrodes. Movements of the corner of the mouth in response to stimulation was recorded.

Results

A muscle contraction was elicitable in 7/7 patients with both types of electrodes. There were no adverse events. Disease duration had no effect on muscle response. With facial paralysis, mouth angle elevation was elicitable with pulse widths (PWs) of 15-1000ms and amplitudes of 1.0-10mA for surface electrodes, and 0.5-5ms PWs and amplitudes of 1.0-3.5mA for needle electrodes. A good motor response by surface stimulation with 50-250ms PWs allowed to predict a good response with needle stimulation of 1-2ms in 7/7 patients. The amplitude for good motor response by surface stimulation allowed to predict the amplitude needed with needle stimulation in 5/7 FP patients.

Conclusion

Preliminary results show that electrical stimulation of the zygomaticus muscle via surface electrodes may be useful as a screening tool for a facial pacemaker, but also for classic nerve reinnervation surgeries. By simulating the stimulation conditions with the needle stimulation, we are able to predict the required stimulation parameters but also the good tolerance for a facial pacemaker in patients with only a motor deficit and intact sensibility of the face.

Electrical imaging of axonal stimulation in the retina

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Introduction

Stimulation of axons or its avoidance plays a central role for neuroprosthetics and neural-interfaces research. One peculiar example constitutes retinal implants. Retinal implants aim to artificially activate retinal ganglion cells (RGCs) via electrical stimulation. Such stimulation, however, often generates undesired stimulation of RGC axon bundles, which leads to distorted visual percepts. In order to establish stimulation strategies avoiding axonal stimulation it is necessary to image the evoked activity in single axons.

Methods

Using a high-density CMOS-based microelectrode array comprising 4225 electrode and 1024 stimulation electrode we electrically imaged axonal stimulation in ex vivo mouse retina. After precisely localizing the sample on the sensor array, we used a subset of the stimulation electrodes to deliver a localized stimulation to the retina. Then, we analyzed the response via stimulus triggered averages.

Results

We demonstrate signal propagation tracking via stimulus triggered average during high frequency (100 Hz) sinusoidal electrical stimulation. We applied the technique to investigate the characteristic, antidromic or orthodromic, of the elicited axonal signal.

Conclusion

Stimulus triggered average is an effective technique to study axonal action potential propagation in the retina. The technique can be applied to investigate axonal stimulation in the retina to develop optimal stimulation strategies for retinal implants.

Semi-Automatic Detection and Analysis of Rhythmic Electromyographic Activity evoked by Epidural Electrical Stimulation in Spinal Cord Injury

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Introduction

Rhythmic movement patterns in the lower limbs can be elicited by epidural electrical stimulation (EES) in individuals paralysed by spinal cord injury. Analysing the associated electromyographic (EMG) activities allows for insights on how human spinal rhythm and pattern generating circuits operate. In order to avoid potential selection bias, we developed an algorithm to semi-automatically detect and extract parameters of rhythmic EMG activity from a large dataset.

Methods

EES was applied to the lumbar spinal cord of seven individuals with chronic motor-complete spinal cord injury at levels ranging from low cervical to mid-thoracic. Stimulation frequencies from 2 to 120 Hz, and amplitudes up to 10.5 V were applied. EMG responses were acquired from quadriceps, hamstrings, adductors, tibialis anterior, and triceps surae bilaterally in the supine position. A total of 75 hours of EMG recordings containing various non-modulated and modulated responses was available for this retrospective study. Envelopes were created for each EMG channel by using the Teagan-Kaiser energy operator (TKEO) and subsequent second-degree Savitzky-Golay smoothing. 20-seconds-wide moving windows running along the envelope signals rendered autocorrelograms, which were each analysed for peaks corresponding to periodicities ranging from 0.1 to 2 Hz, i.e., frequencies matching slow to fast walking gait. Close or overlapping windows tagged as rhythmic were stitched together into a sequence of ongoing rhythmic activity. Each sequence was visually confirmed using a custom GUI.

Results

The algorithm successfully detected different patterns of rhythmic unilateral co-contractions and locomotor-like EMG activities, some unaccounted for in previous studies. Burst onset and offset points could be acquired robustly, allowing for time-normalized phase relations between burst patterns of both unilateral muscles, and bilateral, homologous muscle pairs. Furthermore, the nature of EES-evoked EMG bursts - being composed of entrained and stimulus-triggered responses - provided for successful stimulus-based and response-based causal analysis of latencies and amplitudes at a high level of temporal resolution.

Conclusion

The portrayed algorithm is capable of providing new and extended information out of an existing dataset, which is necessary to gain further insight into the ingenuities of human motor control. For instance, rhythmic activities with constant frequency but varying interlimb phase relations were found, which point out commissural communication and continuous bilateral coupling, a characteristic not yet described in previous studies. Likewise, increased latencies of stimulation-triggered responses reveal additional central synaptic delays, and hence indicate relay through more complex circuitries when rhythmic activities are present. These insights will help further comprehend the spinal motor control circuitry after paralyzing SCI, allow comparisons to animal models of central pattern generators, and form the relevant basis for computational modelling.

Selective surface electrostimulation of synkinetic zygomatic muscle with ball electrodes

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Introduction

In the present study, we assessed the possibility to selectively stimulate a synkinetically reinnervated M. zygomaticus (ZYG) without eliciting aspecific contractions of other facial muscles. Such idea could support the development of implants for patients suffering from unilateral facial paresis (UFP).

Methods

10 patients were recruited, suffering from UFP with varying degrees of ZYG synkinesis. Onset period differed from patient to patient. 1 Hz stimulation was performed a single time per patient with STMIsola (BIOPAC Systems, Inc. Germany). 2 ball electrodes were placed on the most proximal portion of the ZYG to the mouth corner and slowly moved more distal to it on the ZYG path until no selective ZYG response could be seen. The most distal selective response parameters were analyzed, delivered as triangular and rectangular pulses.

Results

Selective ZYG stimulation was achieved over a 4.5x3cm area close to the mouth corner. The most effective pulse width (PW) was 100 or 250ms with triangular and 1s with rectangular pulses. Amplitudes in the range of 3-6MA delivered best results with all the assessed PWs besides 1ms, for which a range between 7 and 10mA was needed. Few patients reached the discomfort threshold or showed aspecific facial muscle response (e.g., masseter) before a selective ZYG stimulation could be achieved.

Conclusion

Selective stimulation of synkinetically reinnervated ZYG is achievable as long as the parameters are accurately assessed, and the stimulation is delivered on the target. Although encouraging, these preliminary results should be further confirmed for the development of implants to restore facial symmetry.

The evoked compound nerve action potential is shaped by the electrical pulse-width

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Introduction

Despite its central role in medicine electrical stimulation (ES) is still limited by its selectivity. Different reports did assess effects of different waveforms, intensities, and frequency on the activation threshold of nerve fibres with different diameters. We aimed to extend this knowledge by investigating the effect of short monophasic rectangular pulses (1, 2, 5, 10, 50, 100 and 200 µs) on the recruitment order.

Methods

The sciatic nerve of rats was stimulated, and the evoked compound nerve action potential (CNAP) measured at two sites on the tibialis nerve, using epineural electrodes. Changes in delay, amplitude, and the shape of the CNAP were analyzed.

Results

The amplitude and delay of the CNAP were significantly affected by the pulse-width (PW). The delay and duration of the compound nerve action potential increased with longer PW, while the amplitude decreased.

Conclusion

Found changes are likely caused by changes in the time point of excitation of individual neuron fibres, depending on electrical field strength and exposure time. This might be of particular interest when selecting PWs for design and validation of stimulation patterns and analysis of experimental and clinical observations.

SmartStim: A Recurrent Neural Network Assisted Adaptive Functional Electrical Stimulation for Walking

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Introduction

According to the Neuro Patience report of the Neurological Alliance, 1 in 6 people in the UK have a neurological condition. Functional Electrical Stimulation is a neuro-rehabilitation method that uses electrical nerve stimulation to restore functional muscle movements that are lost due to neurological problems such as stroke and multiple sclerosis. This neuroprosthetic device is frequently used to assist walking by treating a condition called Drop Foot, a result of paralysis of the pretibial muscles. This study proposes a two channel terrain-adaptive FES device called the SmartStim which has the ability to modulate its stimulation levels according to various obstacles such as stairs and ramps.

SmartStim Model

This system employs a sensor-based module with a Recurrent Neural Network to classify these different walking scenarios. The module is built with Inertial Measurement sensors embedded in a pair of shoes, and the RNN uses data from these sensors to predict various obstacles as the user is walking. These predictions are then used by a Fuzzy Logic Controller to control and regulate the stimulation current in two channels of the SmartStim system. In the two channels of the system one channel will help treat drop foot and the other will be used to stimulate another muscle group to help access stairs and ramps by the user.

Results and Conclusion

The RNN module in this system has been trained and tested using the k-fold cross validation. The evaluation of this trained model shows that it can predict obstacles from the sensor data at 97% accuracy. Currently further testing is being performed to assess the working of the fuzzy logic controller in combination with the RNN in healthy individuals. It is expected that SmartStim system may aid the users to access various walking scenarios more efficiently.

How to train muscle for FES

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Introduction

Artificial activation of muscles has been used for several decades. Muscle is a plastic tissue that responds to the disuse caused by neural injury or pathology by large changes in mass and character including the properties that determine endurance.
There has been a recent dramatic improvement in the ability to follow changes in muscle cells in terms of the gene expression of their constituent fibres. These new techniques promise a new understanding of the precise relationship between activation and cellular response including growth and improvement in fatigue-resistance. This paper will present a review of the evidence linking patterns of activation to progressive changes in muscle, including disused and denervated or partially denervated muscle.

Results

New evidence from our laboratory shows that rather little daily stimulation is necessary to cause substantial changes in muscle character, and in terms of muscle growth, that daily exercise may be counter-productive. The traditional recommendation of exercise for one muscle group once every three days may have a sound cell biological basis in terms of the timecourse of the response to acute resistance exercise. Furthermore, experiments in rats appear to show a similar time course of response in that exercise every three days produces more muscle growth than exercise every day. As well as the timing of exercise, we will also consider the effect of loading or ‘intensity’ in terms of the signal for growth.

Conclusion

These new cell biological findings should influence our prescription for FES in rehabilitation, and may give opportunity to follow in very tiny biological samples the progress of training in individual participants.

Evaluation of control modalities and functional impact of a self-piloted grasp neuroprosthesis in stroke patients: preliminary results from a multi-crossover N-of-1 randomized controlled study

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Introduction

Stroke is the leading cause of acquired motor deficiencies in adults. Improving prehension abilities is challenging for individuals who have not recovered active hand opening capacities post-stroke. Functional electrical stimulation (FES) applied to finger extensor muscles to restore grasping abilities in daily life, called grasp neuroprosthesis (GNP), remains confidential in post-stroke population. Thus, we developed a GNP and control modalities adapted to the characteristics of this population and assessed its impact on functional restoration of grasping abilities.

Methods

A GNP prototype was designed with specific control modalities (voice control, foot and head movements). A software allowing configuration and monitoring, interprets user commands through input signals from sensors (IMUs and microphone) and triggers a pre-programmed external electrical stimulator. Over 5 days, the users tested and selected a preferred control modality before training with the GNP to perform unimanual and bimanual tasks in a seating position. Its functional impact was assessed in a blinded evaluation multi-crossover N-of-1 randomized controlled trial (clinicaltrials.gov: NCT04804384), followed with a QUEST questionnaire.

Results

Preliminary results from eight subjects (1 to 17 years post-stroke; Fugl-Meyer motor upper-extremity score 21 to 48/66) showed a preference for non-paretic foot triggering (7/8). All subjects selected the key-pinch task as the primary outcome and the palmar grasp task as secondary outcome. All subjects successfully completed from 83% to 100% of the tasks using the GNP (100% for 5 subjects; khi2: $p<0.001$), while none of them could complete the task without GNP activation. QUEST ranged from 29 to 35 (median of 33/40).

Conclusion

These preliminary results attest that the GNP prototype and its control modalities are well suited to the post-stroke subjects in terms of self-triggering, while allowing to restore grasping capabilities. A wearable version of this device is being developed to improve prehension at home in daily life.

Short-term effects of selective transcutaneous auricular-nerve stimulation

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Introduction

The study reported here seeks to assess a short-term effect of selective transcutaneous stimulation of auricular branch fibres of the vagus nerve (tANS) on the respiratory function of healthy female volunteers, assuming that it could be altered with the tANS.

Methods

The trials were carried out with a group of healthy female volunteers, age 22 to 25.
The devices for the tANS were custom-crafted plugs that contain four platinum stimulating cathodes (geometric surface approximately 14.58 mm^2), a hydrogel common anode (geometric surface about 400 mm^2) and a microprocessor-controlled stimulator.
The stimulating sites were indicated as left (L) and right (R) plus colour code: pole position, red (R); below pole position, yellow (Y); above bottom position, black (B); and bottom position, white (W).
The parameters of the stimuli were the following: Frequency 45.5 Hz, pulse width 200 μs, interphase delay 180 μs, pulse train duration 2.0 s and time gap between successive pulse trains 1.0 s. The intensity ic however, was pre-set until the minimum discomfort was detected.
Each 20-minute trial started with the 5-minute sham, proceeded with the 10-minute tANS and ended with the 5-minute sham.
The air-flow measuring system was developed to assess the variations in the bi-directional nasal air-flow, the changes in the rhythm and the character of the respiration. Breath length, peak-to-peak air-flow and maximum slope of air-flow were analysed within the time period of ten breaths at each of three aforementioned segments.

Results

The results show that the selective tANS had an effect on the respiratory function in all trials. The respiration became shorter, more heavy/shallow, more jerky and more frequent along with the steeper inspiration and lower peak-to-peak air flow.

Conclusion

The hypothesis that the selective tANS has a measurable effect on the respiratory function was confirmed.