Neurointerface with Oscillator Motifs for inhibitory effect over antagonist muscles for compensation of spastical syndrome

Yulia Mikhailova
B-Rain Labs LLC.

Anna Pozdeeva
B-Rain Labs LLC.

Alina Suleimanova
B-Rain Labs LLC

Alexey Leukhin
B-Rain Labs LLC

Alexander Toschev
B-Rain Labs LLC

Timur Lukmanov
Children's Republican Clinical Hospital of the Ministry of Health of the Republic of Tatarstan

Elsa Fatykhova
Children's Republican Clinical Hospital of the Ministry of Health of the Republic of Tatarstan

Evgeni Magid
Kazanskij Privolžskij Federal'nyj Universitet: Kazanskij Privolzskij federal'nyj universitet

Igor Lavrov
Mayo Clinic

Max Talanov (✉ max.talanov@gmail.com)
B-Rain Labs LLC
https://orcid.org/0000-0002-6727-0983

Research Article

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**Abstract:**
The inhibitory management effect is usually underestimated in artificial control systems, using biological analogy. According to our hypothesis, the muscle hypertonus could be effectively compensated via stimulation by bio plausible patterns. We proposed the approach for the compensatory stimulation device in development of previously presented architecture of neurointerface, where (1) neuroport is implemented as DAC and stimulator, (2) neuroterminal – as neurosimulation of a set of oscillator motifs on one-board computer. In the set of experiments with 5 volunteers we measured the efficacy of motor neuron inhibition via antagonist muscle or nerve stimulation registering muscle force with and without antagonist stimulation. For the agonist activation, we used both voluntary activity and electrical stimulation. In the case of stimulation of both agonist and antagonist muscles and nerves, we experimented with delays between muscles stimulation starts in the range 0...20 ms. We registered the subjective discomfort rate. We didn’t identify a significant difference between antagonist muscle and nerve stimulation in both voluntary and stimulation of agonist activity. We determined the most effective delay between stimulation of agonist and antagonist muscle/nerve as 10–20 ms.
Neurointerface with Oscillator Motifs for inhibitory effect over antagonist muscles for compensation of spastical syndrome

Yulia Mikhailova$^{1,2}$, Anna Pozdeeva$^{1,2}$, Alina Suleimanova$^1$, Alexey Leukhin$^{1,2}$, Alexander Toschev$^{1,2}$, Timur Lukmanov$^3$, Elsa Fatykhova$^3$, Evgeni Magid$^{2,6,7}$, Igor Lavrov$^{2,4,5}$, Max Talanov$^{1,2}$

Abstract—The inhibitory management effect is usually underestimated in artificial control systems, using biological analogy. According to our hypothesis, the muscle hypertonus could be effectively compensated via stimulation by bio plausible patterns. We proposed the approach for the compensatory stimulation device in development of previously presented architecture of neurointerface, where (1) neuroport is implemented as DAC and stimulator, (2) neuroterminal – as neurostimulation of a set of oscillator motifs on one-board computer. In the set of experiments with 5 volunteers we measured the efficacy of motor neuron inhibition via antagonist muscle or nerve stimulation registering muscle force with and without antagonist stimulation. For the agonist activation, we used both voluntary activity and electrical stimulation. In the case of stimulation of both agonist and antagonist muscles and nerves, we experimented with delays between muscles stimulation starts in the range 0...20 ms. We registered the subjective discomfort rate. We didn’t identify a significant difference between antagonist muscle and nerve stimulation in both voluntary and stimulation of agonist activity. We determined the most effective delay between stimulation of agonist and antagonist muscle/nerve as 10–20 ms.

I. INTRODUCTION

There are more than 12 million suffering from spastic syndrome as the consequence of some nosological forms with disability about 12–27% [1]. The spastic syndrome affects: 20–40% of stroke survivors, 65–78% of spinal cord injury patients, and 85% of patients with multiple sclerosis. Other common causes of spastic syndrome could be brain injuries, demyelinating diseases, CNS tumors, and some inflammatory and neurodegenerative diseases impacting upper motor neurons [2], [3]. Spastic syndrome is manifested by periodic or regular involuntary hyperactivity of skeletal muscles, the cause of which is a violation of the signal from the central nervous system to the muscles. The functional rewiring of the nervous system leading to some compensation of the spastic syndrome is a widespread process from the spinal level to supraspinal structures. Clinical symptom has several phases: (1) muscle weakness formation, (2) spastic syndrome formation and (3) recovery [4]. Appearing spastic syndrome is a sequential process that goes through all the phases described above with different speeds. The muscle weakness formation phase is developed during the acute period of brain injury and is usually accompanied with deep reflexes decay, pareses development as well as muscle hypertonus formation. The muscle force is regulated by corticospinal tract decays during impairment of upper motor neurons of any etiology due to supraspinal control impairment of muscle tonus. The suprasegmental influences impairment and denervation of α-motor neurons triggers the restructuring of segmental apparatus [5]. The spastic syndrome formation phase is accompanied with reorganization of brain circuits and usually is manifested during the 1–6 weeks after CNS injury. This phase includes the development of hyperexcitability of α-motor neurons due to impairment of the afferent signal processing facilitation of Ia signaling at segmental level [6], [7], [8]. During this phase gradual increase in spastic syndrome, deep reflex and clonuses, extensor and flexor contractions and synkineses commonly happen. The further changes during the final recovery phase manifests with decrease in spastic syndrome, synergical voluntary motions, restoration of the complex movements; and restoration of normal function with voluntary locomotion [9], [10], [11]. Current understanding of the key phases represent spastic syndrome as delayed compensation to complex structural and functional reorganization of the CNS and muscles. The motoneurons of antagonist muscles are reciprocally inhibited via Ia interneurons that are activated by Ia afferent of muscle-antagonist [12], [13].

In this work we use our presented earlier approach of the neurointerface [14] to compensate for the spastic syndrome. We used the bio-plausible pattern generated with the set of with oscillator motifs (OMs) to trigger the antagonist (to spastical muscle) nerve that stimulates the inhibitory projection of agonist (spastical) muscle Ia nuclei to test the hypothesis of effective inhibition of neuronal activity thus muscle activity. We measured the agonist muscle force in both cases of the antagonist muscle and the nerve stimulation.

II. SUBJECTS AND METHODS

A. The study setup

We studied the inhibitory effect of the extensor muscle activity on the muscles: the ulnar extensor carpi (Musculus extensor carpi ulnaris) and the antagonist ulnar flexor carpi (Musculus flexor carpi ulnaris). Then, we studied the inhibition of extensor muscle with activation of the ulnar nerve, which innervates the flexor and also includes Ia afferent of
the flexor. We assume that activation of the flexor or the ulnar nerve triggered the inhibitory circuit with Ia interneuron (Fig. 1c). There are several papers dedicated to the spastic syndrome compensation due to the noninvasive electrical nerve stimulation [15], [16], [17]. More than that, attempts to compensate for spastic syndrome led to several devices developments [18], [19]. In this work we used the previously proposed approach for the neurointerface [14] using Oscillator Motifs to generate bio-plausible neural activity [20]. We used neuron circuit that consists of OMs to produce a bio-plausible pattern of neural activity. The schematic description of the study setup is presented in Fig. 1b. The hardware devices to stimulate muscle or nerve are neuroports where software that implements a spiking neural network is a neuroterminal [14]. The one-board computer generates the neuronal activity in real-time simulation. The pattern for stimulation is generated by the model of oscillator motifs (OMs). The OM, (Fig. 2a) is a basic unit of the model and produces various duration of activity [20] that depends on balance of excitatory and inhibitory weights. We used the neuronal circuit with 3 OMs (Fig. 2b) for the stimulation since previously we have indicated that the 3 OMs circuit is most comfortable for the participating volunteer [14]. This circuit was activated by stimulus with 40 Hz frequency. The generated signal was modulated with 2 kHz. A generated activity is transmitted via DAC to the stimulator that triggers
that we located in the projection of the flexor muscle at a distance of 5–8 cm from each other (Fig. 1c).

We have used four protocols of the study (Fig. 1d): (1) the voluntary extension with the ulnar flexor muscle stimulation, (2) the voluntary extension with the ulnar nerve stimulation because this nerve includes afferents and efferents of the antagonist muscle (flexor), (3) the stimulation of the extensor and flexor muscles with delays, (4) the stimulation of the extensor muscle and the ulnar nerve with delays. During the first phase of the study we had recorded the muscle force (Fig. 1a,d) of the participant’s voluntary activity when the volunteer unbended the palm at a comfortable level of muscle tension and maintained throughout the entire study protocol. During the second phase, we turned on the flexor muscle stimulation adjusting the stimulation current according to a volunteer’s comfort level and subjective assessment of the muscle extension decrease. We recorded the muscle force of the extensor with flexor stimulation.

For the second protocol we stimulated ulnar nerve that includes Ia afferents of antagonist instead of flexor muscle in particular: stimulation electrodes were placed on the ulnar nerve: the cathode is at the cubital canal and the anode at the projection of the ulnar flexor muscle.

We used the third protocol (Fig. 1d) to identify and measure most effective delays between stimulation of flexor and extensor muscles (0, 5, 10, 15, 20 ms). We assume that if the flexor (agonist) is stimulated earlier than the extensor (agonist) the activity of the agonist is reduced through the inhibitory interneuronal pool in the spinal cord. We located the electrodes for transcutaneous stimulation of the flexor and extensor in the projection of the muscles at a distance of 5–8 cm between cathode and anode. We stimulated the agonist muscle increasing the current to a comfortable level for the volunteer and recorded the muscle force. Later we stimulated the antagonist muscle with an earlier signal relative to the agonist with preset delay and recorded the muscle force.

In the case of the fourth protocol we run the stimulation similarly with the third protocol except for the antagonist ulnar nerve instead of the flexor muscle.

III. Results

Firstly, we studied the inhibitory effect produced by the antagonist muscle (flexor) or the ulnar nerve stimulation during the voluntary extension. We recorded the extensor muscle force during voluntary activity. The average muscle force was 2.5 ± 1.1 kgf (Fig. 3a). Then, we stimulated the antagonist muscle and the extensor muscle force decreased significantly to 0.48 ± 0.33 kgf (p < 0.05) (Fig. 3a). The registered subjective discomfort rate was 2.3 ± 1.1 out of 10 where 10 is the most discomfort. Further, we conducted studies with the ulnar nerve stimulation during voluntary extension. The average muscle force during voluntary activity was 2.85 ± 0.13 (Fig. 3b). Then, we stimulated the ulnar nerve that includes afferents and efferents fibers of the flexor muscle and the extensor muscle force decreased considerably to 1.1 ± 0.8 kgf (p < 0.05) (Fig. 3b). The discomfort rate was 2.9 ± 1.6 out of 10. The antagonist muscle or nerve (Fig. 1b). To assess the effect of inhibition, we recorded the muscle force during voluntary activity and stimulation as well as during the inhibitory effect produced by the antagonist’s muscle or nerve activation (Fig. 1a).

The study setup for recording muscle force included: the lower plate, the upper plate, fasteners, the clamp, and the dynamometer (Fig. 1a). The volunteer’s hand, palm down, was placed on the lower plate (15 x 30 cm) with the hole in the left side. The top plate (4 x 14 cm) with the hole in the left side was placed above the palm. Two plates were connected with the fastener that was located between the middle and ring fingers of a volunteer. The clamp of the fastener located on the upper plate was used to change the distance between the plates to securely fix a volunteer’s hand. Thus, during the muscle force increase, the immobilized palm pressed on the top plate that pulled the dynamometer lever indicating the change of force.

B. Research involving humans and animals statement

Five healthy volunteers participated (3 male, 2 female, age: 23 ± 2) in the current study.

C. Informed consent

All participants gave an informed written consent to participate in the study, in accordance with the Declaration of Helsinki, and were introduced to the study protocol.

D. The stimulation protocols

For the non-invasive stimulation, we used two hypoallergenic reusable gel electrodes VUPIESSE 32 mm x 32 mm
Fig. 3. (a) The extensor muscle force with voluntary activity and during antagonist muscle stimulation (inhibitory effect). (b) The extensor muscle force with voluntary activity and during the ulnar nerve stimulation. (c) The extensor muscle force before antagonist muscle stimulation and during the ulnar nerve stimulation, that innervates the flexor and includes Ia afferent of the flexor, stimulation with the range of delays. (d) The extensor muscle force before antagonist muscle stimulation and during the ulnar nerve, that innervates the flexor and includes Ia afferent of the flexor, stimulation with the range of delays.

### TABLE I

<table>
<thead>
<tr>
<th>Time (ms)</th>
<th>Flexor Voltage (V)</th>
<th>Extensor Voltage (V)</th>
<th>Extensor Force (kgf, mean ± std)</th>
<th>Extensor Force with Inhibition (kgf, mean ± std)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ms</td>
<td>13.2 ± 4</td>
<td>25.4 ± 4.6</td>
<td>1.09 ± 0.93</td>
<td>0.27 ± 0.17</td>
</tr>
<tr>
<td>5 ms</td>
<td>12 ± 3</td>
<td>26.4 ± 3.5</td>
<td>1.17 ± 0.55</td>
<td>0.28 ± 0.14</td>
</tr>
<tr>
<td>10 ms</td>
<td>11 ± 2.6</td>
<td>25.4 ± 4.6</td>
<td>0.88 ± 0.5</td>
<td>0.27 ± 0.20</td>
</tr>
<tr>
<td>15 ms</td>
<td>11.4 ± 2.6</td>
<td>25 ± 4.1</td>
<td>1.17 ± 1</td>
<td>0.28 ± 0.24</td>
</tr>
<tr>
<td>20 ms</td>
<td>11.6 ± 3.2</td>
<td>25.8 ± 5.1</td>
<td>0.94 ± 0.59</td>
<td>0.18 ± 0.09</td>
</tr>
</tbody>
</table>

### TABLE II

<table>
<thead>
<tr>
<th>Time (ms)</th>
<th>Flexor Voltage (V)</th>
<th>Extensor Voltage (V)</th>
<th>Extensor Force (kgf, mean ± std)</th>
<th>Extensor Force with Inhibition (kgf, mean ± std)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 ms</td>
<td>10 ± 3.5</td>
<td>25.4 ± 4.6</td>
<td>1.60 ± 0.84</td>
<td>0.44 ± 0.34</td>
</tr>
<tr>
<td>5 ms</td>
<td>9.2 ± 3.7</td>
<td>25.4 ± 4.6</td>
<td>1.30 ± 0.38</td>
<td>0.37 ± 0.30</td>
</tr>
<tr>
<td>10 ms</td>
<td>9.2 ± 3.7</td>
<td>25.4 ± 4.6</td>
<td>1.19 ± 0.23</td>
<td>0.31 ± 0.17</td>
</tr>
<tr>
<td>15 ms</td>
<td>9.4 ± 4.4</td>
<td>25.4 ± 4.6</td>
<td>0.93 ± 0.31</td>
<td>0.16 ± 0.06</td>
</tr>
<tr>
<td>20 ms</td>
<td>9.4 ± 4.8</td>
<td>25.4 ± 4.6</td>
<td>1.00 ± 0.40</td>
<td>0.18 ± 0.07</td>
</tr>
</tbody>
</table>

The extensor muscle stimulation had a stronger inhibitory effect on the extensor muscle force decrease than the ulnar nerve stimulation (0.48 ± 0.33 kgf vs. 1.1 ± 0.8 kgf, *p < 0.05*). The voltage of the flexor muscle stimulation was higher than the ulnar nerve voltage stimulation (15.2 ± 4.8 V vs. 11.2 ± 2.9 V, *p < 0.1*) because the nerve stimulation influenced muscle
The discomfort rate with the extensor and flexor muscle stimulation was (4.2 ± 2.2) in the mode without inhibition with flexor muscle stimulation are presented in Table I. The extensor muscle force decreased significantly with flexor muscle stimulation (p < 0.05). The strongest drop in the extensor muscle force to 0.19 ± 0.09 kgf was in the study with a 20 ms delay (Fig. 3c). The discomfort rate in this experiment was 2.4 ± 1.1 out of 10 (Fig. 4a). The most comfortable mode (1.8 ± 1.3) for the antagonist’s muscle stimulation was with a 10 ms delay. This mode also demonstrated a significant decrease in the extensor muscle force from 0.89 ± 0.5 to 0.27 ± 0.2 (Fig. 3c). The extensor muscle force declined in the mode with stimulation of the antagonists’ muscles without delay from 1.09 ± 0.93 kgf to 0.28 ± 0.17 kgf (Fig. 3c). Then, we researched the inhibitory effect produced by the ulnar nerve stimulation. The ulnar nerve innervates the antagonist muscle (flexor) and Ia afferents of the antagonist inhibiting the motor neuron of agonist muscle (extensor). Similar to the previous study with the antagonists’ muscle activation, we stimulated the extensor muscle and the ulnar nerve with different delays (0–20 ms). The results (Table II) demonstrated significant decrease in the extensor muscle force with the ulnar nerve stimulation (p < 0.05) regardless of delays. The most significant difference (p < 0.01) was observed with 10 ms delay between the ulnar nerve stimulation and the extensor muscle stimulation. In this mode, the extensor muscle force decreased from 1.19 ± 0.23 kgf to 0.31 ± 0.17 kgf (Fig. 3d). The discomfort rate was 3.4 ± 2.9 out of 10 (Fig. 4b). The most comfortable mode (2.4 ± 1.5) with the ulnar nerve stimulation was with a 20 ms delay. In this mode, the extensor muscle force also decreased considerably from 1.0 ± 0.4 to 0.18 ± 0.07 (Fig. 3d). The highest discomfort rate was (4.2 ± 2.2) in the mode without delay between the ulnar nerve stimulation and the extensor muscle stimulation. The extensor muscle force decreased in the mode without delay from 1.6 ± 0.84 kgf to 0.44 ± 0.34 kgf (Fig. 3d). The voltage for the extensor activation was consistent across all studies at 25 ± 4 V (Table I,II) whereas for the flexor muscle stimulation voltage was slightly higher (11.8 ± 3 V) than for the ulnar nerve (9.4 ± 3.5 V; p < 0.1). The average discomfort rate was insignificantly lower with the flexor muscle stimulation (2.2 ± 1.6) than with the ulnar nerve stimulation (3.3 ± 2.0). There was no significant difference (p > 0.1) in the extensor muscle force with the flexor muscle stimulation or the ulnar nerve stimulation.

IV. Conclusion

The both antagonist muscle and nerve stimulation had a reduction effect and significantly decreased the extensor muscle force. The subjective perception of volunteers was different for the antagonist muscle and the ulnar nerve stimulation. If the both muscles stimulation produced the counterforce effect the stimulation of the ulnar nerve produced the inhibitory effect decreasing the force in the agonist muscle while keeping the subjective activation from the brain. The discomfort rate was slightly higher with the nerve stimulation but insignificant. The subjective perception of volunteers that the nerve stimulation is more focused than the muscle stimulation thus discomfort rate is higher. The voltage for the flexor muscle stimulation was slightly higher than for the ulnar nerve because the nerve stimulation more directly triggered muscle. Interestingly the antagonist muscle stimulation had a stronger muscle force reduction effect than the ulnar nerve stimulation during voluntary extension. That might be connected to all factors such as higher voltage, lower discomfort rate, and effect on muscle. However, in control when extensor (agonist) muscle was activated with the same value during the study we didn’t observe a significant difference in the reduction effect on the extensor muscle force with the flexor muscle stimulation or the ulnar nerve stimulation. We also noticed that with a delay between the flexor muscle/ulnar nerve and the extensor muscle stimulation the muscle force decreased to lower values (Table I, II). We assume that during the late stimulation of the extensor (10–20 ms), its motoneurons were already partially inhibited by the antagonist Ia afferents influence. Interestingly we have to admit that, the simultaneous stimulation of agonist and antagonist muscles or nerves decreased the extensor (agonist) muscle force significantly (1.09 ± 0.93 kgf to 0.28 ± 0.17 kgf and 1.6 ± 0.84 kgf to 0.44 ± 0.34 kgf). In future we plan to extend the research with more participants, compared with traditional in neurorehabilitation domain monophasic and biphasic square pulses stimulation for both agonist and antagonist muscles.

V. Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
ACKNOWLEDGMENT

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