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研究課題名（和文）Development of a neuromodulation method for facilitation of corticospinal plasticity

研究課題名（英文）Development of a neuromodulation method for facilitation of corticospinal plasticity

研究代表者
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研究成果の概要（和文）：我々は、ヘビアン学習を用いた上肢運動回復の基礎メカニズムを解明するために、脳と機能的電気刺激（FES）を対にして活性化する方法を開発した。まず、脳を制御するFESシステムを試験し、FESが皮質脊髄の興奮性変調を迅速に誘導することを実証した。 次に、反復経頭蓋磁気刺激（rTMS）間欠シータバースト刺激（iTBS）プロトコルを用いて運動皮質（M1）を活性化する非侵襲的脳刺激とFESを比較検討した。その結果、皮質回路とFESのペア活性化が神経調節に最も効果的であることを明らかにした。また、経皮的脊髄刺激（tSCS）と呼ばれる脊髄回路を活性化する新しい技術も開発しました。

研究成果の学術的意義や社会的意義
Our research findings elucidated the underlying mechanisms implemented through paired brain and FES or tSCS. This can be used in neurorehabilitation practice to rapidly neuromodulate the central nervous system excitability, which could improve motor function after neurological injuries.

研究成果の概要（英文）：We developed a method for paired activation of the brain and functional electrical stimulation (FES) to elucidate the underlying mechanisms of upper limb motor recovery using Hebbian learning. We first tested the brain-controlled FES system and demonstrated that FES rapidly induced corticospinal excitability modulation. We then compared non-invasive brain stimulation to activate the motor cortex (M1) with FES using repetitive transcranial magnetic stimulation (rTMS) intermittent theta burst stimulation (iTBS) protocol. Our results showed that paired activation of cortical circuits and FES is most effective in neuromodulation. We also developed a novel technique to activate the spinal circuits which is called transcutaneous spinal cord stimulation (tSCS).

研究分野：neuroplasticity

キーワード：brain stimulation　neuroprosthetics　upper-limb　rehabilitation　neuroplasticity

様　式　C－１９、F－１９－１、Z－１９（共通）

１．研究開始当初の背景

Upper-limb function impairment is one of the most devastating consequences of SCI, which is accompanied by maladaptive reorganization within the central nervous system, including increased spasticity, decreased corticospinal excitability, as well as displacement of cortical representations. Functional electrical stimulation (FES) and transcutaneous spinal cord stimulation (tSCS) can be used to artificially contract muscles by applying short electric impulses on the surface of the skin over the muscle nerves. Ensuring temporal synchronization of motor tasks at the precise time when the users attempt to perform movements in important for neuromodulation and neuroplasticity. Moreover, the ability to effectively engage the spinal interneuronal networks is essential for inducing neuroplastic changes. The nervous system's ability to reorganize itself also requires precise temporal synchronization of residual voluntary commands and successful execution of the intended task FES or tSCS technologies. Such positive reinforcement, known as Hebbian learning. However, it is not clear now FES and BCI-controlled FES affect the central nervous system excitability.

２．研究の目的

The objectives of this research project were to: (1) develop neuroprosthetic technology that can activate upper-limb muscles through tSCS; and (3) test the feasibility of using brain and peripheral circuits activation neuroprosthetic to examine how paired activation contributes to central nervous system neuromodulation.

３．研究の方法

Based on these objectives, we developed a novel tSCS method for activation of dorsal root spinal circuits and demonstrated that it can be effective in recruiting upper limb motor pools. We then also developed a method for pairing cortical and spinal circuits using non-invasive brain stimulation through intermittent theta burst stimulation (iTBS) and FES and brain-computer interface (BCI) controlled upper limb FES and demonstrated their effectiveness in neuromodulation applications.

４．研究成果

Related to the specific project objectives, the following achievements were realized:

(I) "Develop a novel tSCS method" – Transcutaneous spinal cord stimulation (tSCS) is an new neuromodulation technique with significant potential for enhancing upper limb function following incomplete spinal cord injury, stroke or brain injury. Our research findings have demonstrated that cervical tSCS can effectively engage sensory pathways, leading to transsynaptic convergence on motor pools responsible for upper limb muscles (de Freitas et al. 2022 [J1]). Additionally, we have demonstrated substantial recruitment of cutaneous and proprioceptive fibers (de Freitas et al. 2022 [J2]), along with the selective activation of motor pools for proximal or distal upper limb muscles (de Freitas et al. 2021 [J10]), thereby facilitating improvements in grasping or reaching neuromotor recovery. Gaining a deeper understanding of these targeted neural activations is crucial for maximizing the potential of tSCS in promoting neuroplasticity.

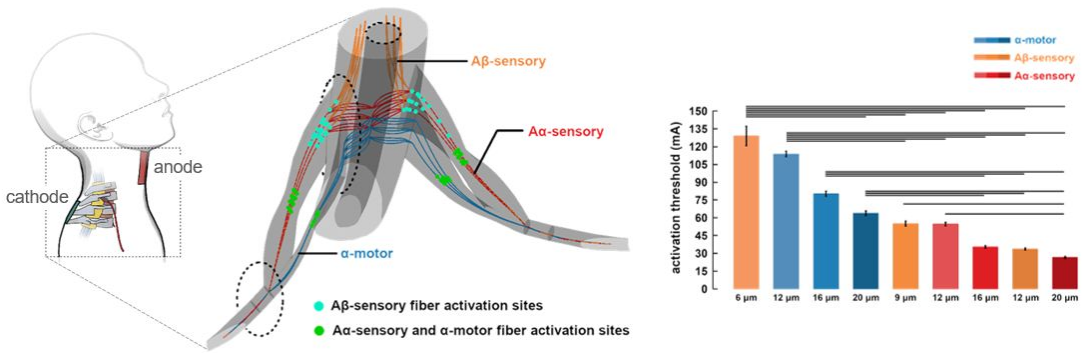

Figure 1: tSCS method for activation of the dorsal root sensory fibers through electrical stimulation applied at the cervical spinal cord [J1 and J2].

(II) "Neuromodulation using paired cortical and peripheral circuits" – We implemented and tested a BCI-controlled FES system to prove the underlying mechanisms of associative stimulation for recovery of upper-limb function. Notably, using the BCI-controlled FES system, we first demonstrated that it could elicit rapid corticospinal excitability modulation of the stimulated muscles, while random delivery of FES alone was not effective (see Suzuki et al. 2022 [J5]). For a summary,

also see Figure 2. We also compared an intervention using primary motor cortex (M1) BCI to control FES to non-motor area BCI-controlled intervention. Our results demonstrated that M1-based BCI-controlled FES intervention was superior to elicit corticospinal modulation (see Yamanouchi et al. unpublished), likely by focusing motor cortical activations. Therefore, we developed a BCI-controlled FES system and demonstrated that using this system can result in presynaptic cortical facilitation followed by postsynaptic FES sensorimotor activation to elicit rapid corticospinal facilitation through Hebbian learning. These findings are consistent with our results indicating that cortical facilitation before FES is necessary to elicit neural plasticity (see Cao et al. 2022 [J3]) which are shown in Figure 3. Finally, we proved that paired activation through iTBS and FES could be most effective means for neuromodulation (see Cao et al. 2022 [J3] as shown in Fig 3 right side). A book chapter a textbook titled Neurorehabilitation Technology edited by Dr. Volker Dietz (see Popovic, Masani and Milosevic, 2022 [B1]) and a review article (see Milosevic et al. 2020 [J14]) are published to summarize these proposed neuromodulation mechanisms in neurorehabilitation applications.

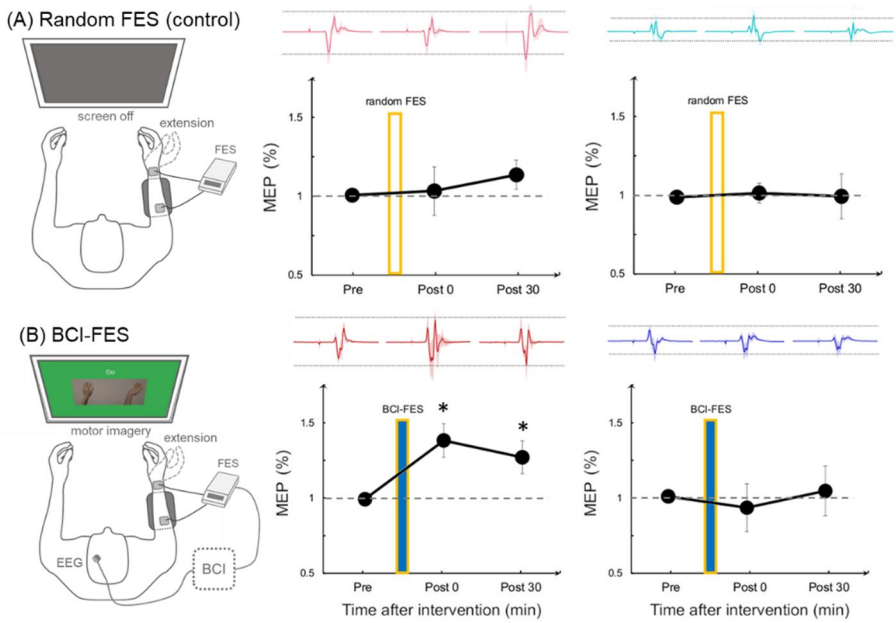

Figure 2: BCI-FES system intervention resulting in rapid corticospinal facilitation. See [J5].

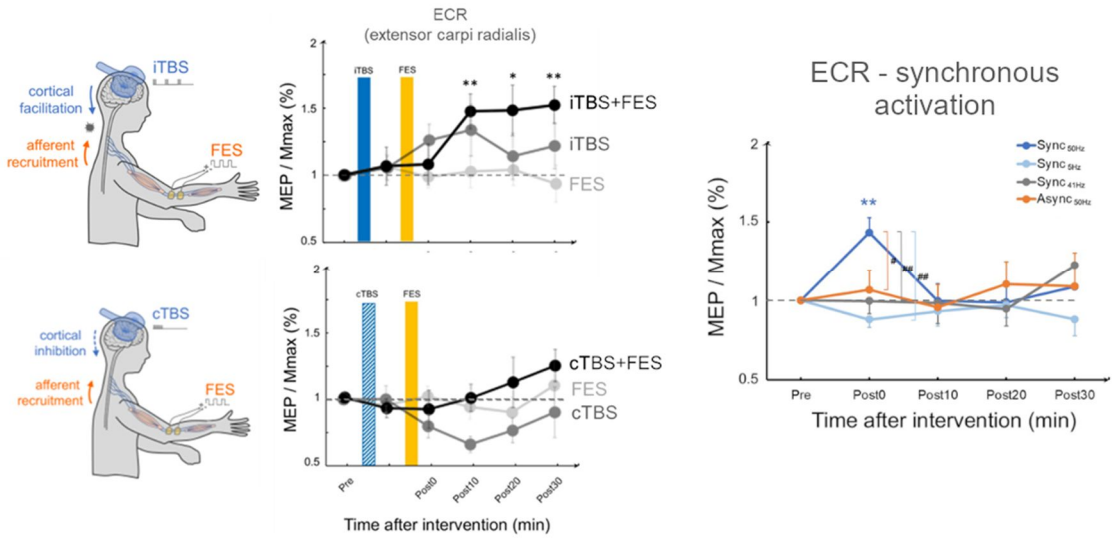

Figure 3: Cortical faciliatory priming (iTBS) followed by FES system intervention resulting in rapid corticospinal facilitation (TOP). Cortical inhibitory priming (cTBS) followed by FES system intervention resulting in rapid corticospinal facilitation (TOP). See [J3].

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[A7] **M. Milosevic**, "Neurophysiological Mechanisms of Cortical Priming and Brain-Controlled Functional Electrical Stimulation in Rehabilitation," Presented at the Mini Symposium of the 10th International IEEE EMBS Conference on Neural (oral presentation), Virtual, May 4-6, 2021.

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５．主な発表論文等

〔雑誌論文〕　計18件（うち査読付論文　17件／うち国際共著　17件／うちオープンアクセス　9件）

１．著者名 de Freitas Roberto M、Capogrosso Marco、Nomura Taishin、Milosevic Matija	４．巻 In press
２．論文標題 Preferential activation of proprioceptive and cutaneous sensory fibers compared to motor fibers during cervical transcutaneous spinal cord stimulation: A computational study	５．発行年 2022年
３．雑誌名 Journal of Neural Engineering	６．最初と最後の頁 ～
掲載論文のDOI（デジタルオブジェクト識別子） なし	査読の有無 有
オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 Cao Na、Sasaki Atsushi、Yuasa Akiko、Popovic Milos R.、Milosevic Matija、Nakazawa Kimitaka	４．巻 In press
２．論文標題 Short-term facilitation effects elicited by cortical priming through theta burst stimulation and functional electrical stimulation of upper-limb muscles	５．発行年 2022年
３．雑誌名 Experimental Brain Research	６．最初と最後の頁 ～
掲載論文のDOI（デジタルオブジェクト識別子） 10.1007/s00221-022-06353-3	査読の有無 有
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１．著者名 Kato Tatsuya、Kaneko Naotsugu、Sasaki Atsushi、Endo Nozomi、Yuasa Akiko、Milosevic Matija、Watanabe Katsumi、Nakazawa Kimitaka	４．巻 55
２．論文標題 Corticospinal excitability and somatosensory information processing of the lower limb muscle during upper limb voluntary or electrically induced muscle contractions	５．発行年 2022年
３．雑誌名 European Journal of Neuroscience	６．最初と最後の頁 1810～1824
掲載論文のDOI（デジタルオブジェクト識別子） 10.1111/ejn.15643	査読の有無 有
オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

１．著者名 Suzuki Yoshiyuki、Jovanovic Lazar I.、Fadli Rizaldi A.、Yamanouchi Yuki、Marquez-Chin Cesar、Popovic Milos R.、Nomura Taishin、Milosevic Matija	４．巻 In press
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３．雑誌名 Neuromodulation: Technology at the Neural Interface	６．最初と最後の頁 ～
掲載論文のDOI（デジタルオブジェクト識別子） 10.1016/j.neurom.2021.12.007	査読の有無 有
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1．著者名 Sasaki Atsushi、Kaneko Naotsugu、Masugi Yohei、Kato Tatsuya、Milosevic Matija、Nakazawa Kimitaka	4．巻 8
2．論文標題 Task- and Intensity-Dependent Modulation of Arm-Trunk Neural Interactions in the Corticospinal Pathway in Humans	5．発行年 2021年
3．雑誌名 eneuro	6．最初と最後の頁 ～
掲載論文のDOI（デジタルオブジェクト識別子） 10.1523/ENEURO.0111-21.2021	査読の有無 有
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1．著者名 Milosevic Matija、Nomura Taishin、Nakazawa Kimitaka	4．巻 32(3)
2．論文標題 Neurophysiological mechanisms of motor rehabilitation using functional electrical stimulation and brain-computer interface technologies	5．発行年 2021年
3．雑誌名 Japanese Journal of Musculoskeletal Medicine	6．最初と最後の頁 ～
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1．著者名 Sasaki Atsushi、de Freitas Roberto M.、Sayenko Dimitry G.、Masugi Yohei、Nomura Taishin、Nakazawa Kimitaka、Milosevic Matija	4．巻 10
2．論文標題 Low-Intensity and Short-Duration Continuous Cervical Transcutaneous Spinal Cord Stimulation Intervention Does Not Prime the Corticospinal and Spinal Reflex Pathways in Able-Bodied Subjects	5．発行年 2021年
3．雑誌名 Journal of Clinical Medicine	6．最初と最後の頁 3633～3633
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1．著者名 Milosevic Matija、Nakanishi Tomoya、Sasaki Atsushi、Yamaguchi Akiko、Nomura Taishin、Popovic Milos R.、Nakazawa Kimitaka	4．巻 15
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3．雑誌名 Frontiers in Neuroscience	6．最初と最後の頁 ～
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1．著者名 de Freitas Roberto M.、Sasaki Atsushi、Sayenko Dimitry G.、Masugi Yohei、Nomura Taishin、Nakazawa Kimitaka、Milosevic Matija	4．巻 131
2．論文標題 Selectivity and excitability of upper-limb muscle activation during cervical transcutaneous spinal cord stimulation in humans	5．発行年 2021年
3．雑誌名 Journal of Applied Physiology	6．最初と最後の頁 746～759
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2．論文標題 Muscle-specific movement-phase-dependent modulation of corticospinal excitability during upper-limb motor execution and motor imagery combined with virtual action observation	5．発行年 2021年
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1．著者名 Akihiro Nakamura, Yasuyuki Suzuki, Matija Milosevic and Taishin Nomura	4．巻 -
2．論文標題 Long-lasting event-related beta synchronizations of electroencephalographic activity in response to support-surface perturbations during upright stance: A pilot study associating beta rebound and active monitoring in the intermittent postural control	5．発行年 2021年
3．雑誌名 Frontiers in Systems Neuroscience	6．最初と最後の頁 -
掲載論文のDOI（デジタルオブジェクト識別子） 10.3389/fnsys.2021.660434	査読の有無 有
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1．著者名 Derrick Lim, Mikael Del Castillo, Austin J Bergquist, Matija Milosevic and Kei Masani	4．巻 29
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オープンアクセス オープンアクセスではない、又はオープンアクセスが困難	国際共著 該当する

1．著者名 Matija Milosevic, Cesar Marquez-Chin, Kei Masani, Masayuki Hirata, Taishin Nomura, Milos R. Popovic and Kimitaka Nakazawa	4．巻 19 (81)
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〔産業財産権〕

〔その他〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関