Review

Neuromuscular Stimulation as an Intervention Tool for Recovery from Upper Limb Paresis after Stroke and the Neural Basis

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Abstract: Neuromodulators at the periphery, such as neuromuscular electrical stimulation (NMES), have been developed as add-on tools to regain upper extremity (UE) paresis after stroke, but this recovery has often been limited. To overcome these limits, novel strategies to enhance neural reorganization and functional recovery are needed. This review aims to discuss possible strategies for enhancing the benefits of NMES. To date, NMES studies have involved some therapeutic concerns that have been addressed under various conditions, such as the time of post-stroke and stroke severity and/or with heterogeneous stimulation parameters, such as target muscles, doses or durations of treatment and outcome measures. We began by identifying factors sensitive to NMES benefits among heterogeneous conditions and parameters, based on the “progress rate (PR)”, defined as the gains in UE function scores per intervention duration. Our analysis disclosed that the benefits might be affected by the target muscles, stroke severity and time period after stroke. Likewise, repetitive peripheral neuromuscular magnetic stimulation (rPMS) is expected to facilitate motor recovery, as already demonstrated by a successful study. In parallel, our efforts should be devoted to further understanding the precise neural mechanism of how neuromodulators make UE function recovery occur, thereby leading to overcoming the limits. In this study, we discuss the possible neural mechanisms.

Keywords: cortical reorganization; functional near-infrared spectroscopy; upper extremity paresis; neuromuscular electrical stimulation; neuronal plasticity; neurorehabilitation; repetitive peripheral neuromuscular magnetic stimulation

1. Introduction

Stroke is a leading cause of disability, with a greater incidence in older age groups. Poststroke disabilities affect upper extremity (UE) function. More severe UE paresis in patients with stroke more profoundly impairs the performance of daily living activities. Full recovery from UE paresis for all survivors is the ultimate goal during rehabilitation intervention. Neuromodulators at the periphery, such as neuromuscular electrical stimulation (NMES), or neuromodulators over the skull, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current electrical stimulation (t-DCS), have been proven to be useful tools for treating UE paresis after a stroke [1–6]. In this review, we focus on neuromodulators at the periphery.

We begin with some therapeutic concerns regarding NMES. Specifically, NMES studies have provided heterogeneous stimulation parameters, such as target muscles, doses or durations of treatment, as well as outcome measures and/or different conditions, such as time post-stroke, and stroke severity. To the best of our knowledge, currently, there are only a few systematic reviews and meta-analyses due to the substantial heterogeneity among
the relevant studies [7–9]. A review demonstrated a statistically significant benefit from NMES applied within 2 months of onset [7]. Another review supported the supplementary use of NMES in the first 4 weeks [8]. A third review, by Howlett et al., demonstrated a major effect of NMES on upper-limb activity [9]. On the other hand, the superiority of NMES compared to standard care was still reportedly controversial [10], perhaps because of a lack of optimal treatment parameters for NMES application. To determine whether these factors may influence motor recovery, we focus on the “progress rate (PR)” as an index of gains, defined as the gains in UE function scores (Fugl–Meyer upper extremity scores) divided by treatment duration. These attempts may offer some clues regarding the optimal parameters and/or conditions for maximizing the NMES benefits for UE motor recovery after stroke, thereby, hopefully, overcoming the disability.

This is followed by a description of the expectations from and the possibility of repetitive peripheral neuromuscular magnetic stimulation (rPMS), which is probably comparable to the usefulness of NMES. As might be expected, a recent report indicated the effectiveness of rPMS in UE motor recovery in the acute phase of a stroke [11].

We end this article by discussing the possible mechanism through which neural reorganization occurs during the administration of NMES or rPMS to affected muscles. As another step toward overcoming motor disability after a stroke, our continuous efforts should be devoted to providing further understanding of the mechanism underlying NMES or rPMS benefits.

2. Materials and Methods

Search Strategy

The references used in this review were obtained in January 2021 by a search of MEDLINE, PubMed, Web of Science and Cochrane Library online databases. Articles published between inception and January 2021 were retrieved using the following search terms: FES, neuromuscular electrical stimulation (NMES), upper extremity, stroke (Figure 1).

Inclusion criteria were as follows: (1) patients > 18 years diagnosed with ischemic or hemorrhagic stroke, (2) first stroke onset and single lesion, (3) duration and dose described, (4) target muscles described, (5) available outcome measures of pre- and post-treatment, (6) transcutaneously non-invasive NMES. Exclusion criteria: (1) adolescents/children, (2) multifocal or recurrent stroke, (3) t-DCS or rTMS, (4) robotics, (5) virtual reality, (6) peripheral nerve stimulation (including invasive (implanted or percutaneous) stimulation and PNS at a level above the sensory threshold but below the motor threshold), (7) sensory stimulation (including somatosensory stimulation, priming, mobilization and tactile stimulation (MTS), proprioceptive stimulation, transcutaneous vague nerve stimulation, cervical spine afferent stimulation), (8) review or case studies. As a result, a total of 23 RCT trials was included (n = 833 participants) [12–34]. Seven RCT trials explored the effectiveness of NMES on UE function for acute patients (n = 250). Seven RCT trials dealt with subacute patients (n = 248), and nine RCT trials were for chronic patients (n = 335) (Table 1).

Statistical analyses were performed by Kruskal–Wallis Test and Mann–Whitney U test for nonparametric data using SPSS ver. 26. Results were accepted as statistically significant at p < 0.05. Finally, the effect size (r value) of outcome measures was calculated to measure the magnitude of the treatment effect: \( r = \frac{Z}{\sqrt{N}} \), where N is the total number of samples. r values of 0.1, 0.3 and 0.5 represent small, moderate and large effect sizes, respectively.
Figure 1. Flow diagram for included studies.
Table 1. Summary of the included NMES studies.

| Author            | Year  | Design       | Numbers                  | Phase   | Time to start | Duration | Dose | Target Muscles                  | Disability Pretreatment | Outcome Measures | Progress Rate | Results                                                      |
|-------------------|-------|--------------|--------------------------|---------|---------------|----------|------|---------------------------------|------------------------|------------------|---------------|--------------------------------------------------------------|
| Francisco et al.  | 1998  | RCT          | Infarct (n = 9) NMES (n = 4) Contr. (n = 5) | acute   | NMES 17.5 day Contr. 18.2 day | length of stay: NMES 33.0 days Contr. 25.8 days | 5 times/week 30 min × 2 sessions/day | ECRL ECRB | severe: NMES 12.5 Contr.21 | FMA 12.5 vs. 21.2→37 vs. 31 | 1.039 (NMES) 0.54 (contr.) | Significant improvement in Exp Upper extremity Fugl-Meyer motor assessment (p < 0.05) |
| Chae et al.       | 1998  | RCT          | NMES (n = 14) Contr. (n = 14) | acute   | 15.7 days | Total of 15 sessions | 60 min session/day | EDC ECR | severe: NMES11.1 Contr.8.3 | FMA 11.1 vs. 8.3 (cotr.)→13.1 6.5 | 0.13 (NMES) | Significant improvement in Exp/FMA Before treatment (p = 0.05) 4 weeks (p = 0.05) (12 weeks (p = 0.06) No significant difference was found in FIM. Significant improvement in Exp Isometric strength of wrist extensors (4 weeks; p = 0.004, 32 weeks; p = 0.014 ARAT (4 weeks-Grasp/Grip; p = 0.013, 32 weeks-Grasp/Grip; p = 0.02) |
| Powell et al.     | 1999  | RCT          | Stroke (n = 60) NMES (n = 30) Contr. (n = 30) | acute   | NMES 23.9 days Contr 22.9 days | 8 weeks | 30 min × 3 sessions/day | ECRL ECRB ECU EDC | severe: NMES 6 Contr. 0 | ARAT 6 vs. 0 | 1.33 (NMES) | Significant improvement in Exp BBT (p < 0.05) Force-generation task; sustained muscular contraction (p < 0.05) Nonparametric tests of covariance (ancova) identified a significant between-group difference between the beginning and end of the treatment period. |
| Cauraugh et al.   | 2000  | RCT          | Infarct (n = 11) NMES (n = 7) Contr. (n = 4) Stroke (n = 22): 21 infarct 1 ICH-cyclic | chronic | 3.49 years | 2 weeks | 3 times/week 30 min × 2 sessions/day | EDC ECU | moderate: NMES 7 Contr.3 | BBT 7 vs. 3→15 vs. 4 | 1.33 (NMES) | Significant improvement in Exp/FMA Before treatment (p = 0.05) 4 weeks (p = 0.05) (12 weeks (p = 0.06) No significant difference was found in FIM. Significant improvement in Exp Isometric strength of wrist extensors (4 weeks; p = 0.004, 32 weeks; p = 0.014 ARAT (4 weeks-Grasp/Grip; p = 0.013, 32 weeks-Grasp/Grip; p = 0.02) |
| Mann et al.       | 2005  | RCT          | Stroke (n = 22): 21 infarct 1 ICH-cyclic | chronic | 12 months | 12 weeks | 10 to 30 min twice sessions/day | triceps brachialis ECR EDC | moderate: NMES20.0 Contr.14.3 | ARAT 20.0 14.3→34.4 24.4 | 0.17 (NMES) | The acute FES group also improved more than the control group in terms of the BI, FMA, and CMSMR (p < 0.05). The chronic group tended to score slightly higher after FES therapy as compared with baseline for most measures, but the differences were not statistically significant. |
| Thrasher et al.   | 2008  | RCT          | stroke (n = 21) subacute: NMES (n = 10) Contr. (n = 11) chronic (n = 7) | subacute chronic | subacute FES 29.8 ± 11.8 days control 28.5 ± 9.0 days chronic 2.7 ± 1.8 years | 13 weeks (acute) 16 weeks (chronic) | 5 days/week 45 min/session 45 min of NMES | not available baseline unknown | FMA 0.61 (subacute) 0.125 (chronic) | 0.513 (NMES) | After 15 training sessions, the FES group had significant improvement in FMA, FTHUE, and active range of motion of wrist extension, compared with the contr. |
| Chan et al.       | 2009  | RCT          | stroke (n = 20) NMES (n = 10) Contr. (n = 10) chronic | subacute chronic | NMES 18.1 months Contr. 12.1 months | 15 sessions in total | 10 min stretching +20 min bilateral UE training with FES or placebo ES + 60 min SC | EDS abductor pollicis longus | severe: NMES18.2 Contr.20.0 | FMA 18.2 20.0→25.9 22.1 FTHUE | 0.513 (NMES) | After 15 training sessions, the FES group had significant improvement in FMA, FTHUE, and active range of motion of wrist extension, compared with the contr. |
Table 1. Cont.

| Author          | Year | Design | Numbers | Phase | Time to start | Duration | Dose               | Target Muscles               | Disability Pretreatment | Outcome Measures | Progress Rate | Results                                                                 |
|-----------------|------|--------|---------|-------|---------------|----------|--------------------|-----------------------------|-------------------------|---------------------|--------------|-------------------------------------------------------------------------|
| Hsu et al.      | 2010 | RCT    | Stroke (n = 66) Infarct (n = 33)  Low-NMES (n = 13) High-NMES (n = 8) Contr. (n = 12) ICH (n = 33) Low-NMES (n = 9) High-NMES (n = 14) Contr. (n = 10) | acute (<1mo) | NMES (23.9 days) | 4 weeks  | 5 times/week Low-NMES 30 min session/day High-NMES 60 min session/day | Spasticity / Completely Paralyzed EDC / ECR Completely Paralyzed FDC Shoulder Subluxation supraspinatus post. deltoid | severe: L-NMES 8.3 H-NMES 7.5 Conr.6.6 | FMA 6.6 (ctr.) 8.3 (L) 7.5 (H) → 14.2 28.1 25.5 (after) ARAT 0.5 0.7 0.5→3.5 8.5 (after) | 0.99 (Low NMES) 0.9 (High) 0.38 (control) | Significant improvement in Low-NMES & High-NMES at 4 weeks and 12 weeks (follow up), when compared with the Contr. No significant difference was found between the 2 Exp groups. Motor Activity Log: no significant difference was found among the 3 groups. |
| Yun et al.      | 2011 | RCT    | stroke (n = 60) Infarct 46 MT + NMES (n = 20) NMES (n = 20) MT (n = 20) | acute (<1mo) | MT + NMSE 25.6 ± 14.4 days MT 23.9 ± 10.5 days NMES 28.1 ± 12.8 days | 3 weeks  | 30 min/session 5 days/week | EDC extensor pollicis brevis severe MT + NMSE 4.3 MT 5.3 NMS 5.3 | FMA 4.3 5.3 13.5 grip power 1.2 1.3 12.2→2.8 2.4 2.5 (MT + NM) 1.09 (MT) 0.39 (NM) 0.66 | Compared with the control group, the HANDS group showed significantly greater gains in distal (wrist/hand) portion of FMA and ARAT. |
| Shindo et al.   | 2011 | RCT    | stroke (n = 20) Infarct 15 HANDS (n = 10) Contr. (n = 10) | subacute | HANDS 34.4 days Contr. 37.0 days | 3 weeks  | 8h h/day + 1 h SC 5 days/week | EDC moderate: NMES 31.3 Contr. 30.5 | FMA 11.3 30.5→43.5 36.0 ARAT 17.7 22.8→30.9 31.1 MAL (HANDS) 0.83 (control) 0.37 | | |
| Lin and Yan     | 2011 | RCT    | stroke (n = 37) Infarct 25 NMES (n = 19) Contr. (n = 18) | subacute | NMES 43.5 days Contr. 41.3 days | 3 weeks  | 5 day/w, 3 weeks PT 30 min/day OT 5 day/min 5 day/w, 3 weeks | deltoid muscle middle of the supraspinatus muscle wrist extensor severe NMES 8.4 Contr. 8.2 | FMA 8.4 8.2→15.9 12.5 | NMES 0.5 | |
| Page et al.     | 2012 | RCT    | stroke (n = 32) Infarct 60 min-NMES (n = 9) 120 min-NMES (n = 8) 30 min home ex. (n = 7) Infarct (n = 10) ICH (n = 6) active ROM cyclic NMES EMG-NMES | chronic | >6 months | 8 weeks  | 5 sessions/week | extensor digitorum extensor pollicis brevis flexor digitorum superficialis flexor pollicis longus thenar muscles moderate: 30 min-NMES 21.6 60 min-NMES 26.6 120 min-NMES 27.1 Contr. 25.6 | FMA 21.6 26.6 27.1 25.6→22.9 27.9 31.3 26.9 ARAT AMAT BBT 7.5 6.9 7.9→1.6 4.8 12.5 7.7 (30 NM) 0.03 (60 NM) 0.03 (120 NM) 0.105 (home) 0.03 | 120 min a day of RTP augmented by ESN use elicits the largest and most consistent UE motor changes in moderately impaired stroke subjects. |
| Hara et al.     | 2013 | CT     | ICH (n = 6) active ROM cyclic NMES EMG-NMES | chronic | Contr. (22.9 days) | 5 months | 1–2 times/week 40 min session/day | FDC EDC moderate:24 grip power 6.3→18.4 | FMA 24→44 grip 6.3→18.4 | 0.5–1 | Significant improvement in EMG-FES, when compared with voluntary muscle contraction (VOL) and simple electrical muscle stimulation (ES) |
Table 1. Cont.

| Author          | Year | Design          | Numbers          | Phase            | Time to start | Duration | Dose            | Target Muscles | Disability Pretreatment | Outcome Measures          | Progress Rate | Results                                                                                     |
|-----------------|------|-----------------|------------------|------------------|---------------|----------|-----------------|----------------|-------------------------|--------------------------|---------------|--------------------------------------------------------------------------------------------|
| Boyaci et al.   | 2013 | RCT             | EMG NMES (n = 11) | Cyclic            | 3 weeks       | 5 time/week | Wrist and Fingers extensor | moderate:active | N29.27 passive           | 34.80 contr.              | (A-NM) 0.53 | No significant difference was found in FMA-UE and MAL-AOU                               |
|                 |      |                 | Placebo Contr. (n = 10) | Passive-NMES (33.7 weeks) Contr. (22.1 weeks) |               |          |                 |                |                         |                           |               |                                                                             |
|                 |      |                 |                  | Active-NMES (38.1 weeks) |               |          |                 |                |                         |                           |               |                                                                             |
|                 |      |                 |                  |                              |               |          |                 |                |                         |                           |               |                                                                             |
| Kim et al.      | 2015 | RCT             | stroke (n = 20)   | chronic           | 4 weeks       | 5 sessions/week | EDC | moderate 48.6   |                           |                           | 49.7−54.6 50.5 | No significant difference among 3 conditions was found in FMA-UE and AMAT          |
|                 |      |                 | NMES (n = 10)    |                  |               |          |                 |                |                         |                           |               |                                                                             |
|                 |      |                 | Contr. (n = 10)  |                  |               |          |                 |                |                         |                           |               |                                                                             |
| McCabe et al.   | 2015 | RCT             | stroke (n = 35)  | chronic           | over 1 years  | 60 sessions | EDC | moderate 48.6   |                           |                           | 49.7−54.6 50.5 | No significant difference among 3 conditions was found in FMA-UE and AMAT          |
|                 |      |                 | robotics + ML (n = 12) |                  |               |          |                 |                |                         |                           |               |                                                                             |
|                 |      |                 | NMES+ML (n = 12) |                  |               |          |                 |                |                         |                           |               |                                                                             |
| Amasyali et al. | 2016 | RCT             | Infarct (n = 24)| subacute         | 3 weeks       | 5 time/week | Wrist and Fingers extensor | moderate:        | Mirror 36.5 Nemesis 41.0 | 19.5 ARAT 0.62  | mirror 0.80   | Increments in the FMA and BBT scores for the Exp group were significantly higher than the control group. |
|                 |      |                 | MT (n = 9)       |                  |               |          |                 |                |                         |                           |               |                                                                             |
| Kwakkel et al.  | 2016 | RCT             | Infarct (n = 101)| acute            | 3 weeks       | 7 times/week | 60 sessions | ECR EDC | moderate:               |                           |                           | 0.58             | No significant difference was found in FMA-UE, ARAT and MAL-AOU                     |
|                 |      |                 | NMES (n = 50)   |                  |               |          |                 |                |                         |                           |               |                                                                             |
|                 |      |                 | Contr. (n = 51)  |                  |               |          |                 |                |                         |                           |               |                                                                             |
| Wilson et al.   | 2016 | RCT             | Cyclic NMES (n = 39) | subacute        | 8 weeks       | 7 times/week | 60 min × 2 sessions/day | moderate: active | 26.8 (S) 29.8 (EMG) | 27.5 (Cyc) 29.8 (EMG) | 27.5 (Cyc) | There was no significant difference in the improvement among groups in the FMA, FMA Wrist and Hand or the mAMAT |
|                 |      |                 | Sensory stim. (n = 41) |                  |               |          |                 |                |                         |                           |               |                                                                             |
|                 |      |                 |                  | Sensory triggered (2.9 months) |               |          |                 |                |                         |                           |               |                                                                             |
|                 |      |                 |                  | Sensory (3.2 months) |               |          |                 |                |                         |                           |               |                                                                             |
| Author            | Year | Design | Numbers | Phase       | Time to start | Duration                | Target Muscles | Disability Pretreatment | Outcome Measures | Progress Rate | Results                                                                 |
|-------------------|------|--------|---------|-------------|---------------|------------------------|----------------|------------------------|-------------------|---------------|--------------------------------------------------------------------------|
| Carda et al.      | 2017 | RCT    | Infarct (n = 11) | NMES (n = 5) | Contr. (n = 6) | 2 weeks: 10 sessions in total | NMES (52 months) | Contr. (41.5 months) | Not noted | severe: 11 (NS) 13.2 (SN) | FMA 11 (NS) 13.2 (SN)→23.2 17.5→27.4 20.4 WMFT MAL | N-S 1.22 | Significant improvement in Exp Fugl-Meyer Motor Assessment (p < 0.05) No significant difference was found in Wolf Motor Function Test and Motor Activity Log |
| Jonsdottir et al. | 2017 | RCT    | Infarct (n = 56) | Hemorrhage (n = 12) | NMES (n = 32) | Contr. (n = 36) | 5–6 weeks: 25 sessions in total | wrist extensor ant. deltoid | moderate: NMES 28.0 Contr. 32.0 | FMA NMES 28.0 Contr. 32.0→39.0 36.0 ARAT 6.0 6.5→21.0 12.5 | NMS 0.44 contr. 0.16 | Significant improvement in both groups FMA Upper extremity, ARAT No significant difference in Exp, when compared with the Con |
| Qian et al.       | 2017 | RCT    | Infarct (n = 9) | ICH (n = 15) | NMES (n = 14) | Contr. (n = 10) | 4 weeks: 20 sessions in total | biceps brachii triceps brachii FCR ECU EDC | severe: NMES 22.3 Contr. 20.3 | FMA NMES 22.3 Contr. 20.3→43.8 30.1 ARAT 15.7 12.0→29.2 24.2 | NMS 1.06 contr. 0.49 | Significant improvement in both groups FMA, ARAT and FIM (p < 0.001, effect sizes > 0.279) |
| Obayashi et al.   | 2020 | RCT    | Infarct (n = 15) | ICH (n = 2) | NMES (n = 8) | Contr. (n = 9) | acute (10 days) | coupledNMES (7 days) | CoupledNMES (10.87 sessions) | severe: coupledNMES 20.2 Contr. 19.0 | FMA coupledNMES 19.0→42.0 36.5 WMFT 22.3 18.2→38.1 30.4 BBT 5.6 3.4→11.1 6.0 | NMS 2.54 contr. 1.10 | Significantly different in Exp Progress rate; FMA upper extremity (p = 0.036, r = 0.50) No significant difference was found in WMFT and BBT. |

AMAT: arm motor ability test; ARAT: action research arm test; Contr.: control; ECRL: extensor carpi radialis longus; ECRB: ECR brevis; EDC: extensor digitorum communis; ECU: extensor carpi ulnaris; FDC: flexor digitorum communis; FDS: flexor digitorum superficialis; EIP: extensor indicis proprius; ICH: intracerebral hemorrhage; mCIMT: modified constraint-induced movement therapy; ML: motor learning; NMES: neuromuscular electrical stimulation; TOT: task-oriented training; MT: mirror therapy; SC: standard care; w: week.
3. Results

3.1. Heterogeneous NMES Conditions

The NMES conditions among the included studies were generally heterogeneous, such as treatment intensity, dose of intervention (30 min to 9 h per day), duration of intervention (10 days to 5 months), time since stroke (7 days to 3.49 years from onset), severity of paresis and stimulated target muscles.

3.2. Effects of Time Post-Stroke on NMES Benefits

The participants received NMES at different times following stroke, categorized by three phases of stroke: acute (<1 month from onset), subacute (>1 month – <6 months) and chronic (>6 months). The average PR was 0.951 ± 0.293 (mean ± SE) for acute patients (n = 7 studies), 0.547 ± 0.142 for subacute patients (n = 7) and 0.382 ± 0.113 for chronic patients (n = 11) (Figure 2). There was only a trend toward the usefulness of early intervention. Statistically, however, there was no significant difference among the three phases (p = 0.16 by Kruskal–Wallis Test). Furthermore, we found no correlation between time since stroke (within 1 month: 5 trials) and PR.

![Progress rate of patients at acute, subacute and chronic phases. Error bars indicate standard errors. There were no significant differences, only a trend, among the three phases. FMA: Fugl-Meyer motor assessment scale for upper extremity; mo: month.](image)

Figure 2. Progress rate (FMA) of patients at acute, subacute and chronic phases. Error bars indicate standard errors. There were no significant differences, only a trend, among the three phases. FMA: Fugl-Meyer motor assessment scale for upper extremity; mo: month.

3.3. Influence of Stroke Severity

The prognosis of motor recovery may depend on the post-stroke severity of UE paresis. Likewise, the severity of UE paresis may influence the efficacy of NMES in UE function. We investigated whether patients with relatively severe paresis would experience greater motor recovery through the application of NMES. The mean FMA pre-treatment score was 21.06. When two groups were classified based on the mean, the PR of the under-mean group (mean FMA score: 11.3 ± 1.98) was 0.94 ± 0.20 and that of the over-mean group (29.93 ± 2.39) was 0.334 ± 0.08 (Figure 3). The PR differed significantly between the groups (z = 2.614, p = 0.009). The under-mean group demonstrated a large effect size (r = 0.60) on FMA-UE, suggesting the high clinical significance of FMA-UE. This suggests that NMES might be more effective for patients with severe UE paresis than for those with moderate paresis. However, we could not find a significant correlation between FMA-UE scores at pre-treatment and PR.
3.4. Target Muscles: Whole UE Versus Wrist/Finger Extensors

Most of the included studies preferred to only apply NMES to the wrist and finger extensors as the target muscles. When the preferred target muscles were the wrist and finger extensors/flexors, the PR was 0.398 ± 0.08 (mean ± SE), whereas in the case of the whole UE, including the shoulder flexors, elbow extensors/flexors, wrist extensors/flexors and finger extensors, the PR was 1.01 ± 0.27 (Figure 4). The PR of the FMA-UE scores differed significantly between the finger/wrist group and the whole-UE group (z = 2.393, p = 0.017). The whole-UE group demonstrated a large effect size (r = 0.54) on FMA-UE, suggesting the high clinical significance in FMA-UE. This finding suggests that the application of NMES to the whole UE might be advantageous compared to its application to the wrist/fingers to regain post-stroke UE function.

3.5. Influence of Dose and Duration on NMES Benefit

The length of the dose (20 min to 9 h per day) and duration (10 days to 5 months) of NMES treatment varied widely among the included studies. The mean dose was 80.68 ± 22.73 min (SE) and the mean duration was 29.15 ± 4.23 days. Unexpectedly,
neither the correlation between treatment dose and PR nor between duration and PR was significant.

3.5. Influence of Dose and Duration on NMES Benefit

The length of the dose (20 min to 9 h per day) and duration (10 days to 5 months) of NMES treatment varied widely among the included studies. The mean dose was 80.68 ± 22.11 minutes per day and the mean duration was 25 ± 20.13 days. No significant correlation was found between treatment dose and PR, nor between duration and PR.

3.6. Sensitivity of Measure Outcomes to Motor Function

The most frequently used measure was FMA (20/23 trials) among the included studies. The Action Research Arm Test (ARAT) followed (seven trials) (Figure 5). Four studies used the box and block test (BBT) and two studies selected the Wolf motor function test (WMFT). According to data from Obayashi et al. [11,32], the FMA scores were closely associated with those of WMFT (R² = 0.723) (Figure 6a). By contrast, both the FMA and WMFT scores showed no association with the BBT scores (Figure 6b,c).

![Preference of outcome measures](image)

Figure 5. The preference of outcome measures used is shown. FMA: Fugl-Meyer motor assessment scale for upper extremity; ARAT: action research arm test; BBT: box and block test; AMAT: arm motor ability test; WMFT: Wolf motor function test; FTHUE: functional test for hemiparetic upper extremity.

![Figure 6](image)

Figure 6. The sensitivity of outcome measures to UE motor function. Comparisons of sensitivity were made among FMA, WMFT and BBT as (a) WMFT vs. FMA, (b) FAM vs. BBT, (c) WMFT vs. BBT. Note that FMA has almost the same sensitivity to severe UE motor function as WMFT, and that of FMA has a close association with WMFT, while BBT is less sensitive than FMA and WMFT.

4. Discussion

In this review, we confirmed that NMES was effective for the functional recovery of UE paresis in all phases of stroke. We identified crucial factors that influence NMES benefits, such as target muscles, severity and outcome measures. However, these factors are only the tip of the iceberg, and their identification is followed by descriptions of possible considerations likely to contribute to maximizing the effectiveness of neuromodulators in motor recovery or minimizing recovery limits.

4.1. Time to NMES following Stroke: Is Earlier Intervention More Effective?

In general, the greatest gain in recovery tends to occur immediately after stroke, with slower gains over time [35]. A previous study suggested that critical time windows exist during which the brain is more responsive to training-dependent plasticity [36]. In particular, the first month after stroke onset offers the highest rate of recovery. Another study suggested that intervention training in the early phase of stroke can promote motor
improvement rapidly, with a delayed enlargement of the motor map relative to behavioral changes [37]. With regard to the effectiveness of rTMS, there may be optimal time windows for motor recovery as well. A recent study suggested the timing-dependent effectiveness of rTMS applied pos-stroke in the following descending order: acute phase > subacute phase and >chronic phase [38]. The same may be true for other neuromodulators. Therefore, we anticipated the superiority of earlier intervention with NMES over later intervention in terms of functional recovery. However, there was only a trend toward the usefulness of early intervention of NMES, but no significance (Figure 2). Furthermore, there was no correlation between the time since stroke and PR. These results may, however, be mainly due to a lack of statistical power because of the small sample size.

Interestingly, a recent report discovered the surprising role of reactive astrocytes as phagocytes in the clearance or synaptic remodeling of the penumbra area in the acute phase (from 7 days of onset) of cerebral infarct [39]. This supports the concept that early intervention may provide the advantage of motor recovery after a stroke. Accordingly, it is plausible that NMES is most effective when it is applied during the optimum therapeutic window.

4.2. Stroke Severity

Although neural reorganization occurs soon after stroke, functional recovery by conventional intervention has often been limited. The probability of motor recovery after a stroke depends on its severity, and a prognosis of functional recovery may be formed within 12 weeks of stroke onset [40]. Neurological impairments recover most dramatically within 30 days of stroke onset, but patients with moderate and severe disability recover within up to 3 and 6 months, respectively [41]. So far, the relationship between NMES benefits and severity has remained unclear. The present findings suggest that survivors of severe stroke may be more sensitive to NMES than survivors of moderate stroke, regardless of the length of time since stroke (Figure 3). On the other hand, our results suggest that there is no correlation between severity and PR; this implies the existence of a therapeutic window for NMES in terms of severity. Further study is required.

4.3. Target Muscles

Our results suggest that the application of NMES to the whole UE was more effective for the UE function of stroke survivors than its application to the wrist and finger extensors (Figure 4). These findings indicate that NMES benefits may depend upon the muscles targeted by NMES. In the included studies, the majority of NMES studies applied NMES to the wrist/ finger extensors. Some authors claimed that NMES was applied to the wrist/finger extensors because of the time required to apply the multiple electrodes to cover the whole UE. Nevertheless, our present analysis suggests that the application to the whole UE is strategically advantageous in the enlargement of ADL as well as motor recovery compared to the wrist/fingers. A recent report also supports this view [32].

4.4. Is a Higher Dose of NMES More Beneficial?

In general, higher doses and longer duration of standard care intervention may produce better functional outcomes. Typically, the efficacy of constrained-induced (CI) therapy may support this view. In fact, few studies seem to have paid attention to this consideration. Intuitively, it was expected that a higher dose of NMES is more effective for motor recovery. However, the present findings suggest that higher dose and/or longer duration may not always produce better outcomes. The dose–response relationship between NMES and UE function for stroke patients remains uncertain [19,22]. A trial by Hsu et al. compared the NMES benefits between low doses (30 min/session) and high doses (60 min/session) of NMES and reported no significant difference [19]. In a study by Page et al., three different doses (30 min, 60 min, 120 min) of NMES were applied for the chronic phase; the authors suggested that a dose of 120 min is most effective for UE function [22]. They also suggested that future studies should investigate various combinations of treatment dose administration for designing intervention programs suitable for clinical practice. In addition, a recent
study demonstrated that 20 min of NMES could facilitate UE motor recovery in the acute phase of stroke [32]. It implied that, by comparison, lower doses and shorter durations of intervention ameliorate UE disability during the early acute phase of stroke. In support of this, the effective threshold of minimal dose and duration needs to be identified.

4.5. Which of the NMES Modes Is More Effective?

NMES features two modes, the EMG-triggered mode and the cyclic mode. As well as EMG-triggered NMES, the post-stroke application of cyclic NMES to UE paresis after stroke was considered effective for UE improvement [16]. Most of the included studies (21/23 trials), however, used EMG-triggered NMES; therefore, we could not compare the NMES benefits between the two modes, leaving us unable to address the issue of whether cyclic or EMG-triggered NMES is more effective.

EMG-triggered NMES can provide weaker contraction of target muscles in severe stroke patients than cyclic NMES, whereas survivors with moderate or mild paresis experience stronger contractions with EMG-triggered NMES than with cyclic NMES. Actually, EMG-triggered NMES for severe paretic patients cannot enhance the fully volitional contraction of target muscles. It is possible that insufficient muscle contraction by electrical stimulation may be nonproductive, resulting in unsatisfactory benefits from NMES. NMES might be more effective for motor recovery when it is appropriately decided which mode of NMES is applied to each of the paretic muscles, including the shoulder, elbow, wrist and fingers during the early acute phase of stroke. The selection of mode may depend upon the volitional contraction of each of the paretic muscles. Accordingly, a recent study examined the effect of coupled cyclic and EMG-triggered NMES with whole UE on motor function [32]. In other words, EMG-triggered NMES was applied to each of the relatively moderate paretic muscles (stroke impairment assessment set (SIAS) level 3), while cyclic NMES was applied to severe paretic muscles (SIAS 1–2). The results suggested that the PR of the FMA-UE scores differed significantly between the coupled NMES group and the standard care group (2.54 for the coupled NMES group and 1.10 for the standard care group) ($p = 0.036$). The NMES group demonstrated a large effect size ($r = 0.50$) on FMA-UE, suggesting the high clinical significance of FMA-UE. These findings suggest that a new strategy of coupled NMES, depending on the severity of targeted paretic muscles, might be more effective than the application of the alternative mode.

4.6. Sensitivity of Measure Outcomes to Motor Function

The sensitivity of outcome measures for motor function is a seemingly important factor in determining whether NMES is effective for UE function. Which of the outcome measures are the most sensitive to changes in UE function? It is likely that FMA-UE features almost the same sensitivity to severe UE paresis as WMFT-FAS (Figure 6a). BBT seemed less sensitive to UE function than FMA and WMFT (Figure 6b,c). More specifically, BBT marked zero even when the FMA scores and WMFT were estimated as 40 and 35, respectively. Accordingly, it is plausible that the included studies used FMA most frequently as outcome measures for motor recovery when applying NMES. It is notable, however, that full FMA-UE scores do not mean full recovery from paresis. For patients with mild paresis, FMA is saturated. Instead, BBT is available. This means that the sensitivity and suitability of outcome measures may depend on stroke severity. In the near future, a new universal outcome measure, independent of the severity of UE paresis, is expected to be established.

4.7. Possibility of rPMS for Recovery from UE Paresis

The use of rPMS can be characterized by penetration into deeper regions of muscles without pain. Given that peripheral stimulation for affected muscles, such as NMES, can enhance motor recovery, rPMS could improve the motor function of UE paresis. So far, however, there have been no studies to support the effectiveness of rPMS on upper extremity paresis despite some efforts using various parameters [42–47]. Recently, a study reported the effectiveness of rPMS in UE motor function recovery when applied to affected
UE muscles (shoulder, elbow, wrist, fingers) in the early acute phase of stroke (mean stroke duration of 9.2 days) [11]. The PR of the FMA-UE scores after 7.8 session-rPMS treatment (n = 10; mean scores 14.6/66 before intervention) significantly differed from the standard care (SC) group (n = 9; mean scores 19.0/66 before treatment), i.e., 2.65 for the rPMS group and 1.10 for the SC group, respectively (p = 0.003). The rPMS group demonstrated a large effect size (r = 0.68) on FMA-UE, suggesting high clinical significance in FMA-UE.

The advantages and disadvantages of rPMS have been summarized [48]. The authors of this summary pointed out that the advantages of rPMS over NMES were the absence of pain, deeper penetration, the generation of higher muscle torque and its applicability to children, while the disadvantages were the overheating of the coil and the exposure of a larger area stimulated with increased intensity. So far, however, no recommendations have been provided regarding the parameters of rPMS application, such as coil design, duty cycle, duration, frequency and intensity.

4.8. Effects of Neuromodulators: Long-Term and Long-Lasting?

When applied over motor cortical areas to treat UE paresis, rTMS and t-DCS are both expected to be potential tools for improving motor function after stroke by modulating cortical excitability [1–4]. Both modulators not only feature similar concerns as NMES, but also create two other issues that must be raised. One is that rTMS and/or t-DCS have been proven to produce a short-term effect on UE function after stroke in the acute, subacute or chronic phases, but it still remains unknown whether the beneficial effect would be long-lasting. The other is that it is unclear whether rTMS and/or t-DCS would lead to greater motor recovery following more treatment sessions. A recent review addressed this issue by comparing the short-term effects of rTMS on motor recovery after stroke with the long-term effects [38]. The review suggested the session-number-dependent effect of rTMS on UE paresis recovery after stroke but that increasing the session number to five produced the most benefits before a plateau is reached. Subsequently, the therapeutic effect was rapidly lost after the use of more than 15 sessions. Similarly, after the initial five sessions of t-DCS were administrated to chronic stroke patients, the more sessions of t-DCS were performed, the less effective they became over time [49]. It remains unclear how or why this phenomenon occurs. In spite of our efforts, we have not found any studies that address the above issues concerning NMES and rPMS. It is likely that ceiling effects of NMES and rPMS may also exist. Further study is required.

4.9. Other Possible Factors: Gender Difference

Some reports have pointed out the gender difference in functional outcomes after a stroke [50], as well as the influence of gender on functional reorganization after a stroke [51]. The former suggested that females experienced worse functional recovery than males. Furthermore, gender difference in functional outcome was significantly modified by stroke severity, with the differences being prominent for mild and moderate but not for severe stroke. The latter study estimated gender differences in brain excitability in the acute phase of stroke, demonstrating gender differences in the functional asymmetry of inter-hemispheric excitability in an opposite manner. Therefore, it is plausible that the beneficial effect of NMES or other neuromodulations, such as rTMS and t-DCS, on motor recovery might be influenced by gender difference. However, to the best of our knowledge, there no study has focused on gender difference in terms of the benefits of neuromodulation. Further studies are required.

4.10. Neural Basis for the Benefits from Neuromodulators

There is increasing evidence that motor recovery after stroke is associated with reorganization of the damaged brain [52,53]. Specifically, Nudo et al. demonstrated that, during intensive rehabilitative training, monkeys recovered from UE paresis after infarction in association with enlargement of the motor map representing the disabled forearm [52].
How do neuromodulators at the periphery regain motor recovery? It is speculated that the administration of NMES or rPMS to affected UE muscles could induce cortical reorganization of the affected hemisphere [23, 45, 54, 55]. Some studies have proposed the possible neural mechanism underlying UE function recovery mediated by NMES. A near-infrared spectroscopy study suggested the association of the ipsilateral sensorimotor cortex with the improvement in UE function by EMG-triggered NMES in chronic-phase stroke patients [23]. Seventeen patients in the chronic phase of stroke underwent NMES applied to affected UE once or twice a week for 5 months. After this period, UE function improved and hemodynamic responses in the sensory-motor cortex (SMC), measured by NIRS, were altered to be bilaterally activated in a hemisphere-dominant way during affected wrist/finger extension with EMG-triggered NMES relative to voluntary of wrist/finger extension. This activation shift to the affected SMC may be related to cortical plasticity induced by NMES, in conjunction with motor recovery. This view is supported by a previous study [53] (Figure 7). Another neuroimaging study demonstrated that the contralateral SMC was activated when administering NMES to the wrist extensor and flexor muscles [54]. In addition, a previous animal study addressed the effect of forepaw electrical stimulation during a 90 min period of right middle cerebral artery (MCA) occlusion on neurological and tissue outcomes in a rat model of reversible focal forebrain ischemia [56]. The cortical and striatal infarct volume were both significantly reduced in the group with stimulated forepaw contralateral to the occlusion relative to the ipsilateral stimulated group (48% total reduction). This suggested the neuroprotective effect of peripheral electrical stimulation contralateral to the ischemic hemisphere in the rat ischemic model. It remains unknown how this protection takes place, but it is most likely related to the contribution of NMES to neuronal reorganization. Altogether, NMES could produce cortical reorganization associated with motor recovery. A previous PET activation study [45] delineated the reorganization of the motor map induced by rPMS. The authors demonstrated that regional cerebral blood flow (rCBF) increases in the superior posterior parietal cortex and that the premotor cortex is associated with an improvement in spasticity in the paretic arm following rPMS treatment. The use of rPMS might produce cortical neuroplastic changes in conjunction with motor recovery. Another study of corticospinal excitability tested by means of transcranial magnetic stimulation demonstrated that rPMS generated an increase in motor-evoked potential (MEP) amplitude and a decrease in MEP latency [55]. In other words, higher MEP amplitudes represent the recruitment of a larger volume of residual pyramidal neurons in the M1 area after stroke [57]. Shorter MEP latencies can be interpreted as two potential changes: (1) better synchronicity of multiple descending volleys (I-wave) arising from rPMS, thus leading to a more efficient depolarization of spinal motor neurons [58] and (2) better recruitment of short-latency corticocortical projections from premotor areas to primary motor cortices (area 4) [59]. In other words, rPMS-induced proprioceptive inflows can be conveyed to the affected hemisphere mediated by thalamocortical and corticocortical fibers, resulting in the potentially enhanced synaptic connectivity of premotor and residual M1 cells [44].

4.11. Limitations

To date, NMES studies have included several considerations. Because of the small sample size, the results should be interpreted with caution. We need to accumulate a larger sample size to provide stronger evidence. Further study exploring the causal relationship between motor recovery and factors such as time to intervention, intensity, dose, duration, stroke severity, or gender are required. Furthermore, we need to investigate whether the long-term effects of NMES or rPMS differ from short-term effects, or how long NMES or rPMS benefits endure. At least, both responders and non-responders to NMES or rPMS application seemed to exist in our study. Some participants showed a prominently accelerated PR not only in the NMES intervention group but also in the standard care group. Understanding fully what causes patients to exhibit different responses to NMES
would be valuable; this knowledge might provide a crucial clue as to how to overcome motor recovery limits.

**Figure 7.** NMES setting (placement of electrodes applied to FDS) and neural basis underlying the beneficial effect of NMES on motor recovery. The scheme illustrates that NMES, when applied to affected forearm muscles, can facilitate motor recovery as shown by augmented PR and subsequently generate cortical reorganization of affected SMC activation, revealed by f-NIRS. FDS: flexor digitorum superficialis; SMC: sensory-motor cortex.

5. Conclusions

This review identified factors influencing the benefits of NMES, such as target muscles, stroke severity and time post-stroke. In addition, other factors, such as dose, duration and NMES modes need to be considered to optimize the NMES effects. Further exploration of specific treatment parameters is required to establish a definitive approach to the improvement of severe UE paresis immediately after stroke onset. Simultaneously, we need to further understand the precise neural mechanisms underlying how neuromodulators act beneficially in motor recovery. Such a comprehensive approach should be integrated to produce new strategies, resulting in the overcoming of recovery limits.

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