

# Combination of epidural stimulation, serotonergic agonist, and rehabilitative training promotes forelimb recovery in cervical spinal cord injured rats circuits

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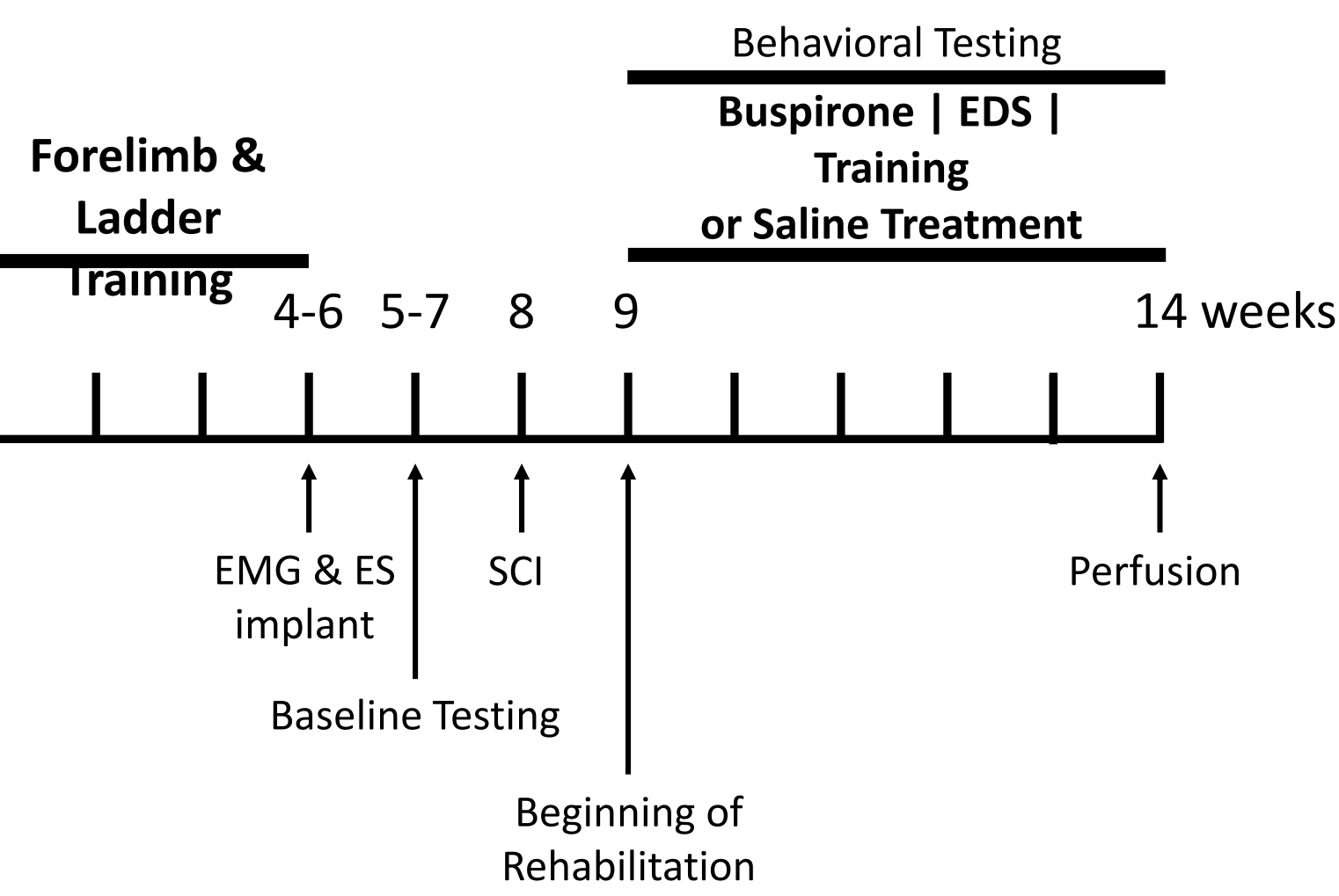
## Introduction

**Cervical spinal cord injury limits and impedes forelimb dexterity**, reducing independence and quality of life. Therefore, it is important to develop new therapies to facilitate fine forelimb movement after injury. A central question is whether the cervical spinal segments can be neuromodulated to improve motor forelimb motor function similar to that previously observed with lumbosacral spinal network modulation which facilitates lower limb function.

Here, we also ask whether **epidural stimulation and a broad serotonergic agonist, buspirone, combined with a task-specific rehabilitation program can open a window of opportunity for facilitating the recovery of forelimb function greater than that which occurs with one treatment alone following a bilateral cervical dorsal hemisection.**

## Skilled reaching in Rodents

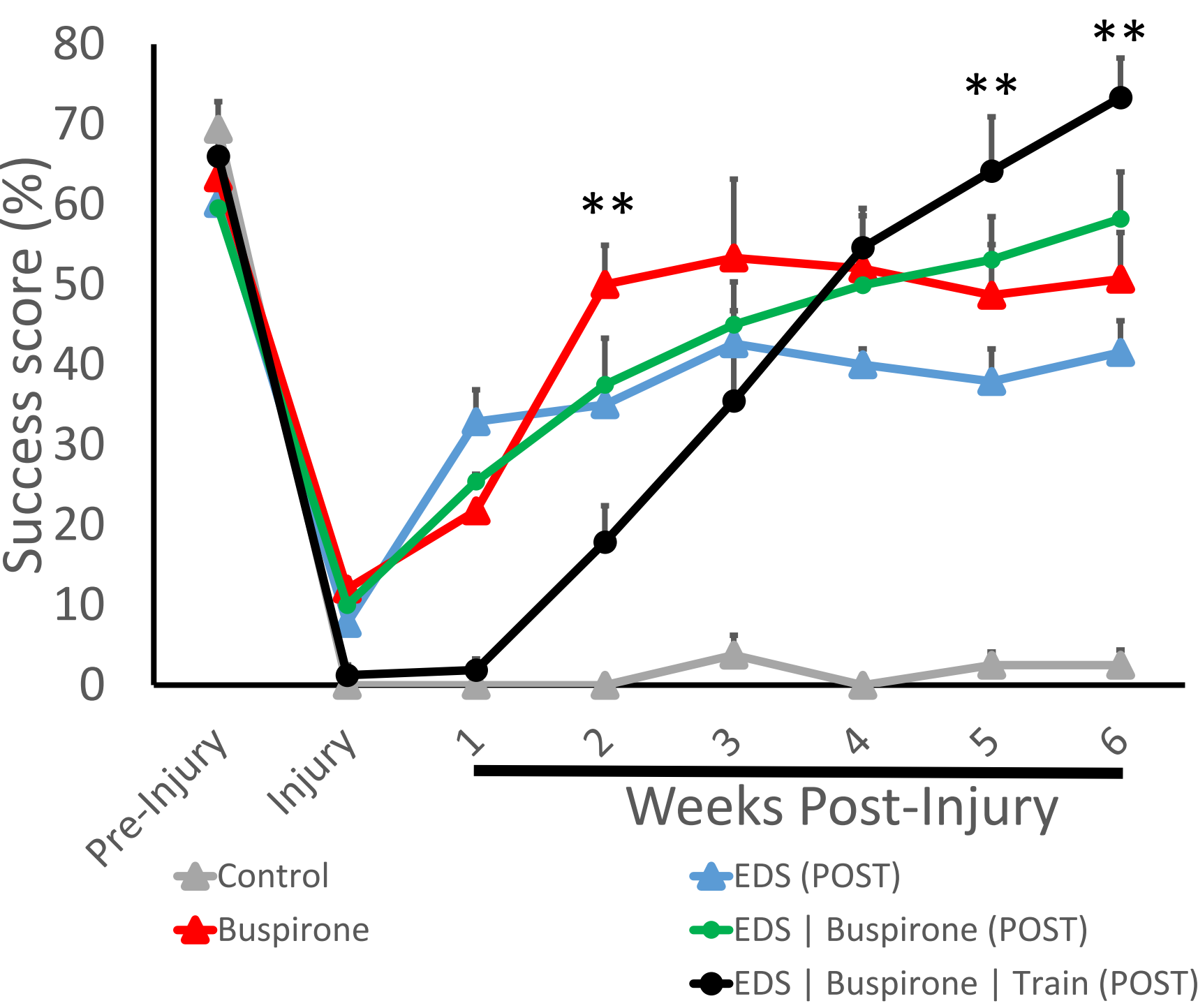
**Rats were trained to reach and grasp a pellet to receive a sugar reward<sup>1</sup> or a similar task on RUE.** The trained rats were implanted with electrodes on selected muscles (EMG) on their dominant forelimb and cervical spinal cord (ES). Baseline testing involved EMG recordings during the skilled reaching task and spinal motor evoked potentials (sMEPs).



Trained rats received a bilateral dorsal funiculi crush at spinal level C4 (SCI), ablating the dorsal CST<sup>2</sup>. At 1-6 weeks post-injury, rats received one of the five treatments:

1. **Control** (sham EDS and drug)
2. Epidural stimulation (**EDS**) at spinal levels C6 and C8<sup>2</sup>
3. Serotonin agonist drug (**Buspirone**, 1 mg/kg/day)
4. **EDS and Buspirone**
5. **EDS, Buspirone, and task-specific rehabilitation (Training)**

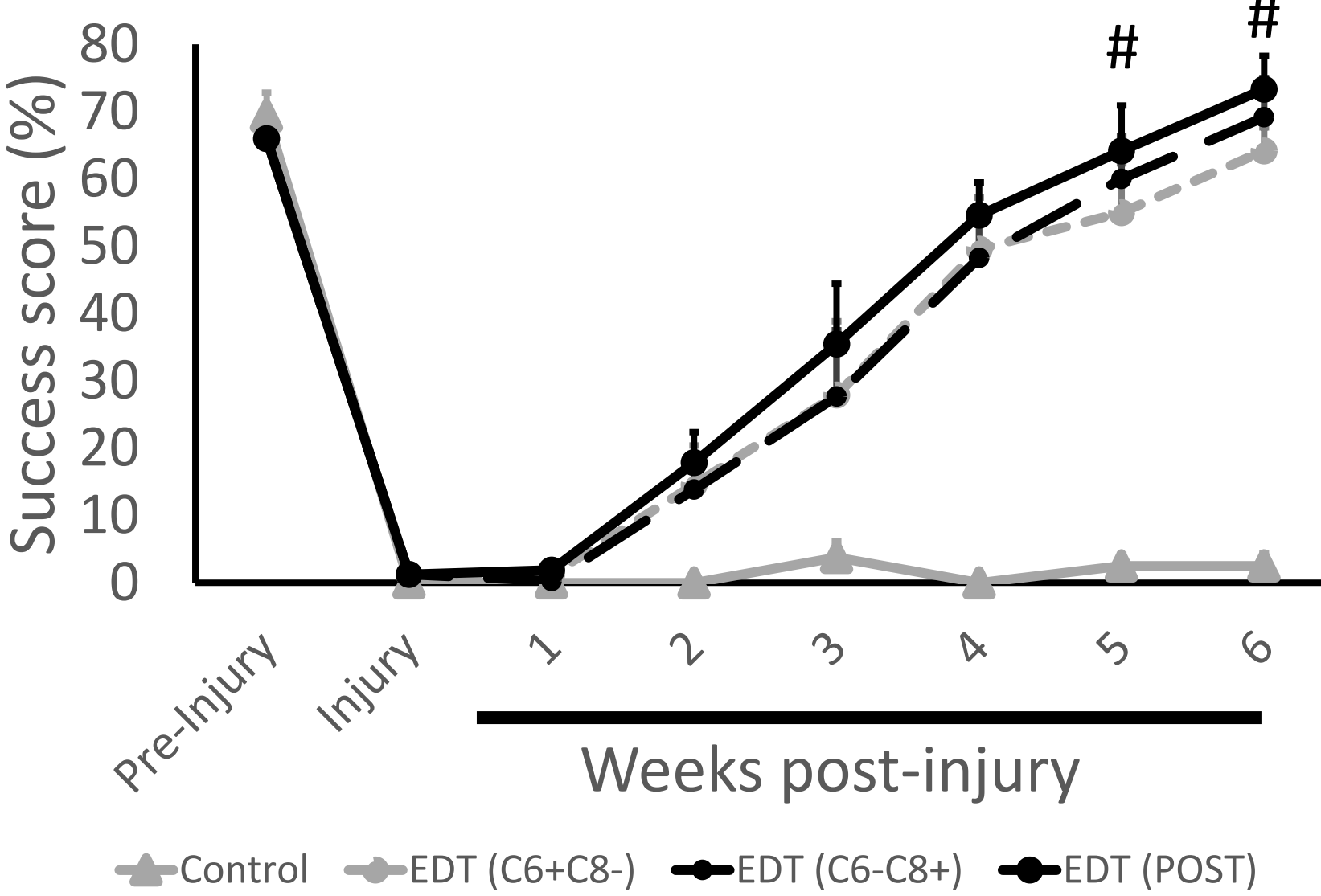
## Buspirone facilitated forelimb recovery when paired with task-specific rehabilitation and epidural stimulation



Success score **increased** with each **additional** treatment – reflecting combinatory effects.

EDS-treated animals were stimulated during testing and then tested again a few minutes after stimulation (POST).

Success score significantly **increased after stimulation** – reflecting acute dynamic modulation via EDS.



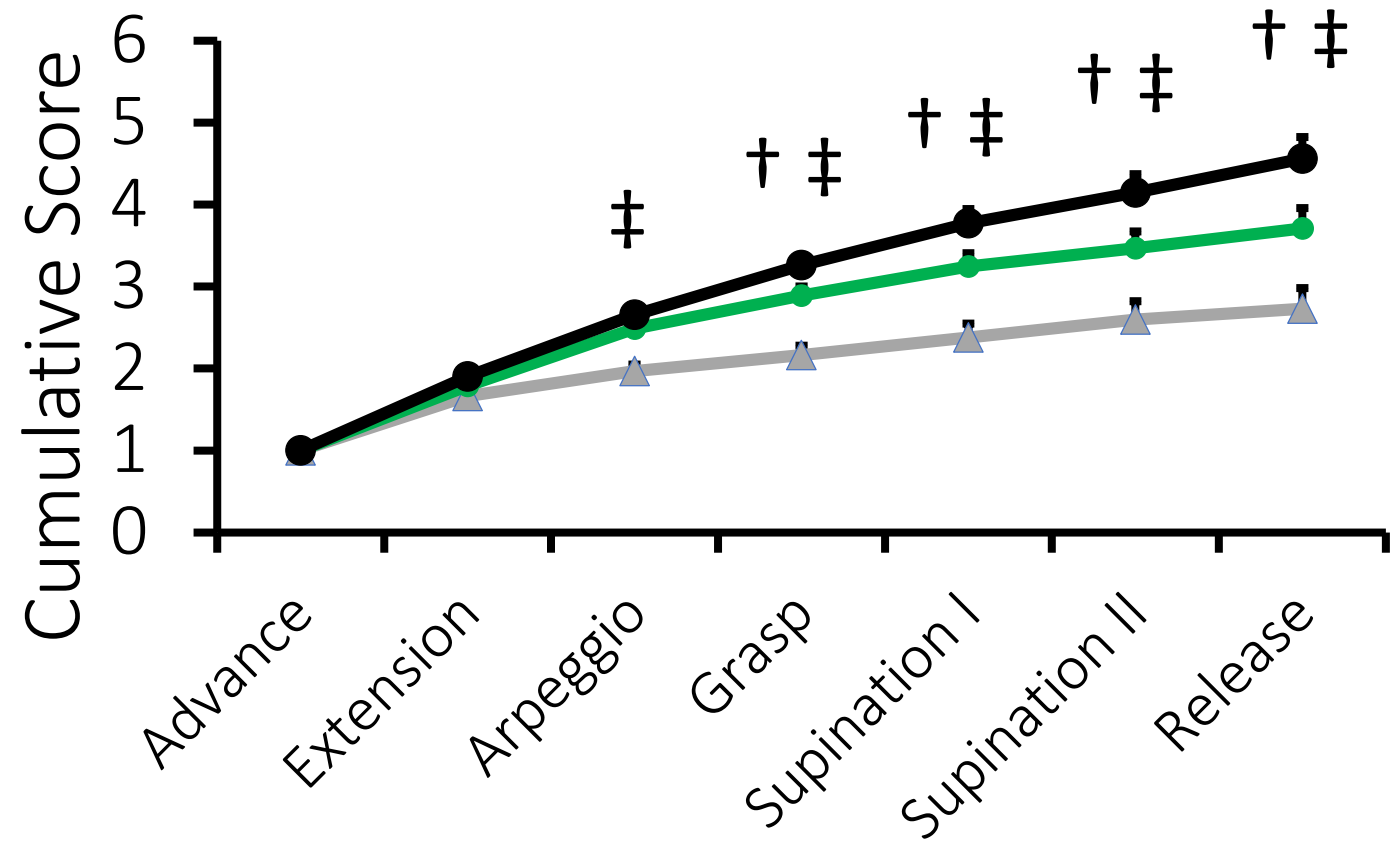
\*\*  $p < 0.05$ , EDS | Buspirone vs. EDS | Buspirone | Training  
#  $p < 0.05$ , EDS (C6-C8+) vs. EDS (POST)

## EDS and 5HT intervention assists pellet retrieval

### Task-specific rehabilitation further facilitates forelimb recovery with EDS and buspirone at 6 weeks post-injury

Skilled reaching task was divided into 7 stage components and scored on a qualitative score of 0-1. Points were accumulated and averaged across the task.

EDS and buspirone improved behavioral components **throughout** the task, facilitating skilled movement during reach, grasp, and retrieval in the task.



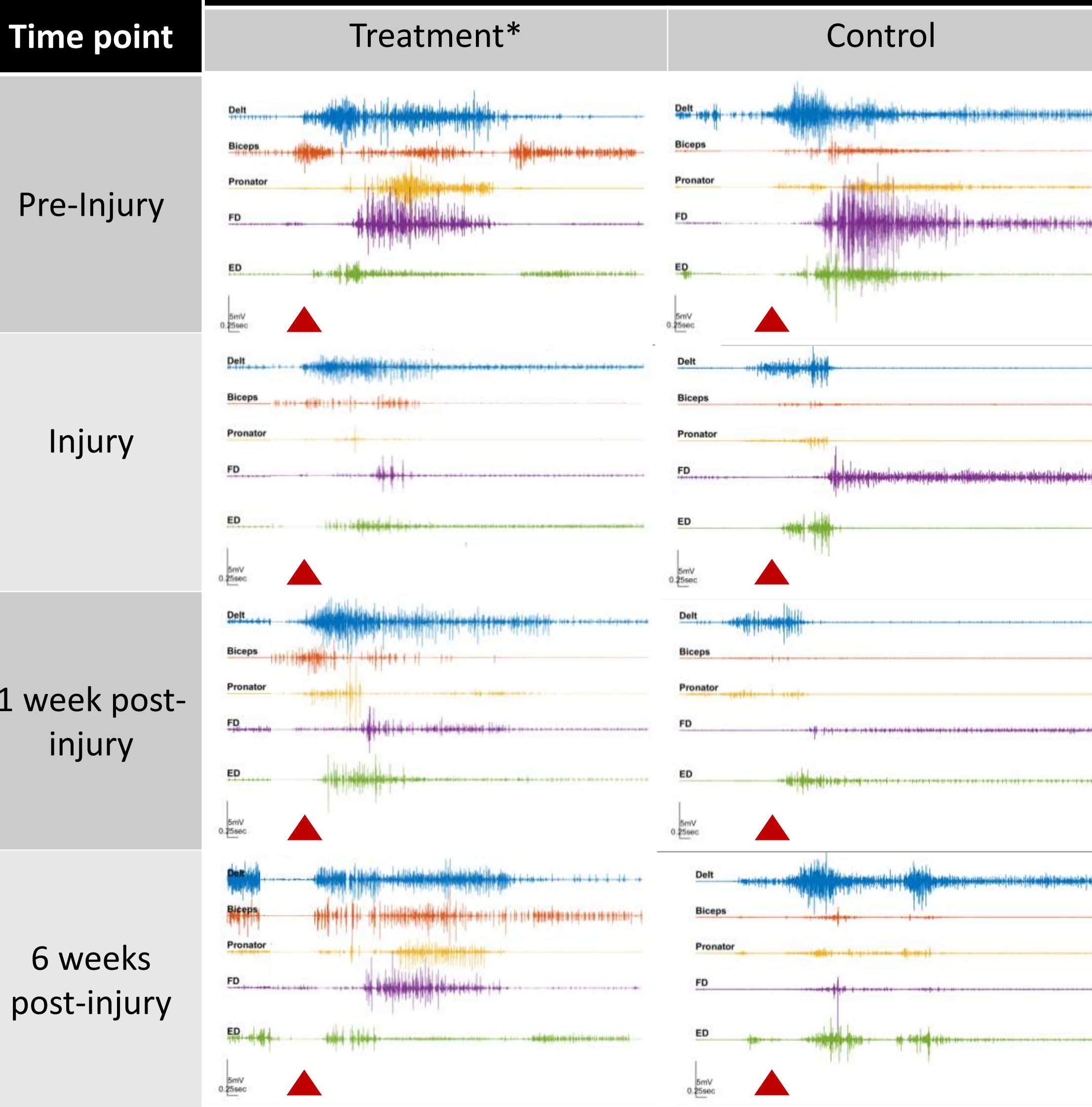
Qualitative score **increased** with task-specific rehabilitation – reflecting combinatory effects.

1, Normal movement; 0.5, abnormal movement; 0, absent movement  
†  $p < 0.05$ , Control vs. EDS | Buspirone  
‡  $p < 0.05$ , Control vs. EDS | Buspirone | Training

Injured rats demonstrated impaired reaching, characterized by incomplete pronation and pellet retrieval. In contrast, treated animals **recovered in precision and accuracy of retrieval** movements.

## Treatment improves forelimb motor activity and intralimb coordination

### Representative forelimb muscle activity during RUE task



Legend: Deltoid (blue), Biceps (orange), Pronator (yellow), Flexor (purple), Extensor (green)

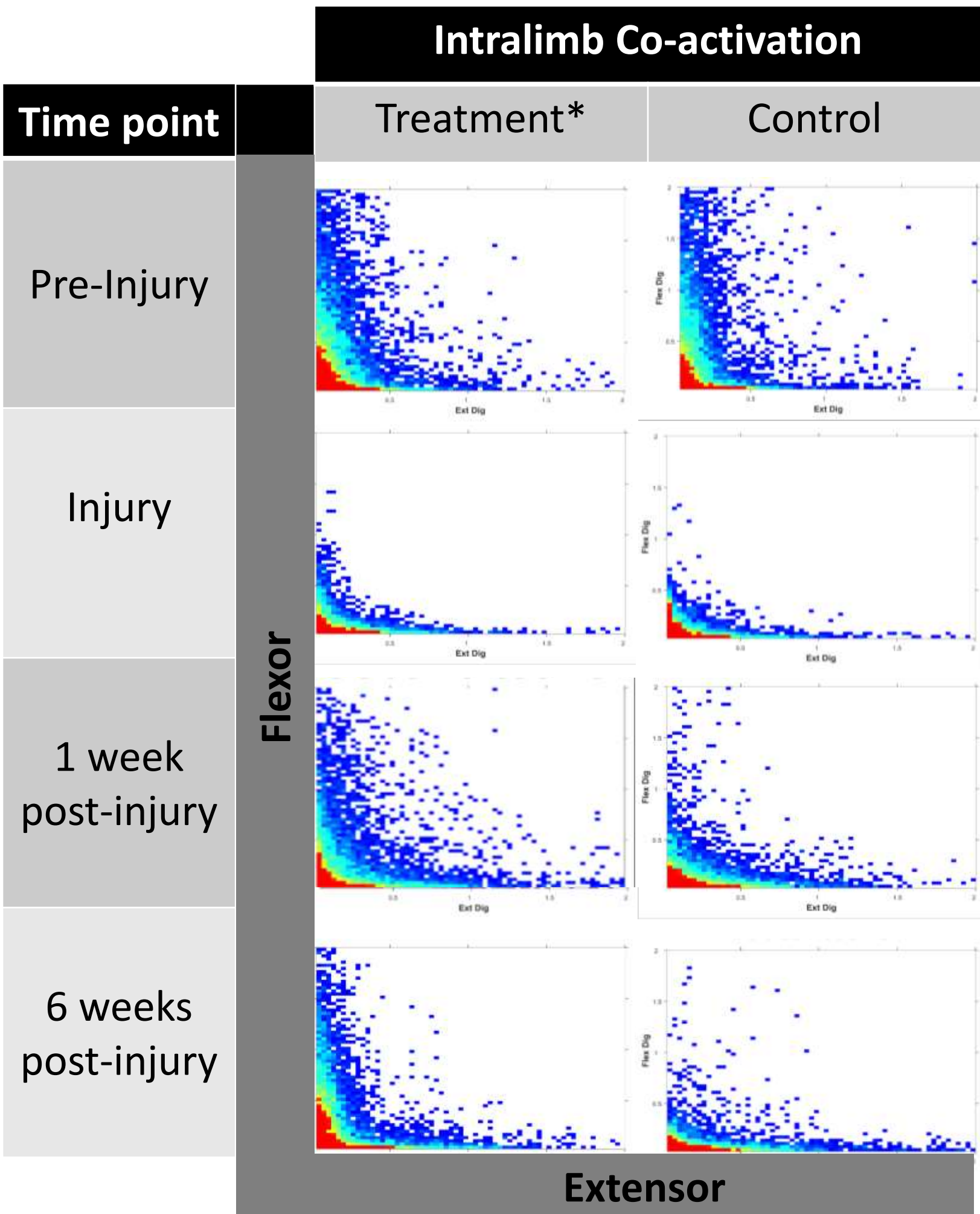
\*Treatment = EDS | Buspirone | Training  
Reach onset ( ).

To evaluate intralimb coordination following injury and treatment\*, joint probability distributions of the EMG amplitudes of the flexor and extensor muscles were taken from each attempt within a 2 second period during the RUE task of control and treated rats.

**Injury diminished EMG amplitude.** The extensor was generally more active than the flexor during the RUE task.

**Note higher amount and incidence of coactivation of the antagonistic muscles after sham compared to treatment at 1 and 6 weeks post-injury.**

\*Treatment = EDS | Buspirone | Training.  
Note decrease in incidence of degrees of co-contraction with treatment



Overall forelimb activity decreased after injury, particularly in the more distal flexor and extensor muscles.

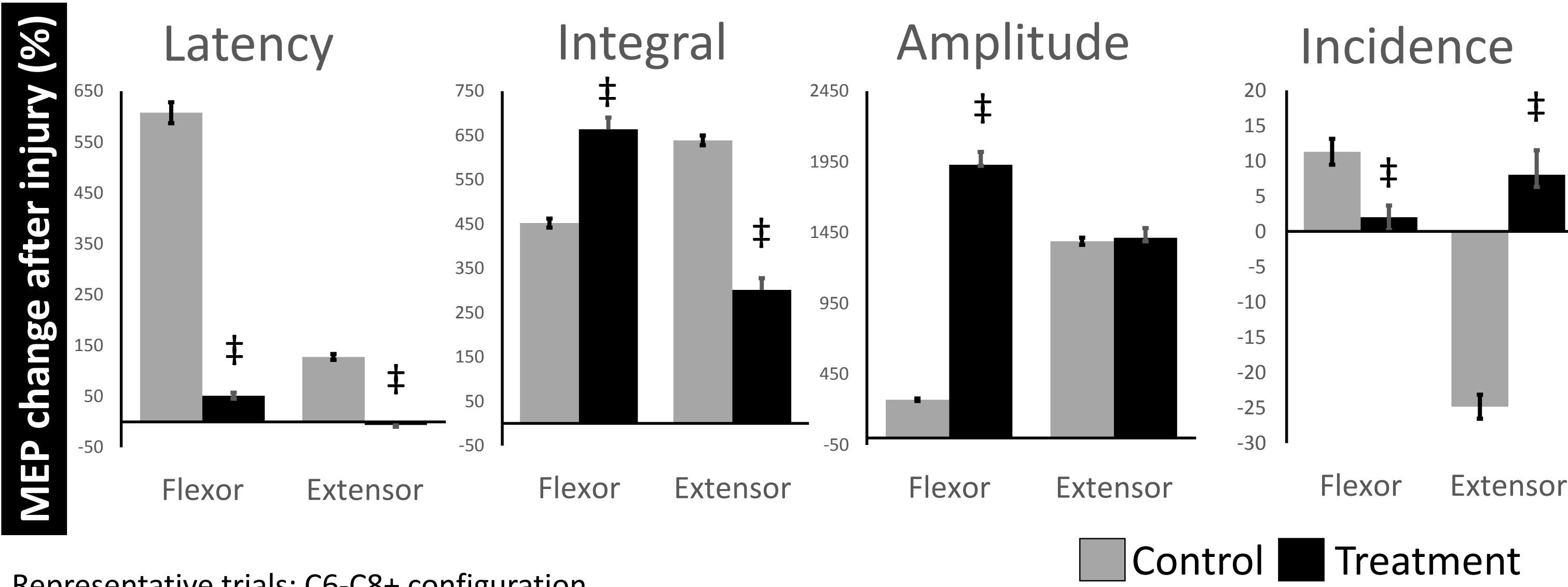
Diminished muscle activity persisted in control at 6 weeks post-injury.

Flexor activity acutely increased 30 minutes after buspirone and EDS intervention at 1 week post-injury.

Muscle activity and pattern trends during RUE task at 6 weeks post-injury were similar to that of pre-injury.

## Dynamic sMEP after injury and treatment

### Treatment\* modulated late responses in distal muscles by 6 weeks post-injury



Representative trials: C6-C8+ configuration

\*Treatment = EDS | Buspirone | Training  
sMEP recordings for -100ms to 300ms after stimulation pulse.

‡  $p < 0.05$ , Control vs. EDS | Buspirone | Training

Muscle	Latency	Amplitude	AUC	Bursts after onset
Flexor	↓	↑	↑	↓
Extensor	↓	=	↓	↑

By 6 weeks post-injury, **treatment\* modulated late sMEP responses**, particularly in the flexor and extensor muscles.

sMEPs evoked by monophasic stimulation pulses at 2Hz under a constant current-paradigm for bipolar configurations at spinal levels C6 and C8.

Within a single pulse, the early response was defined as the first **1-10ms** and late response as **10-30ms**. sMEP parameters were compared between animals with and without treatment\*: response *latency*, *integral* of the EMG signal (area-under-the-curve), peak-to-peak *amplitude*, and the *incidence* of activity responses (number of EMG bursts) after pulse onset.

## Summary

- EDS, Buspirone **OR** task-specific rehabilitation<sup>3</sup> promotes forelimb dexterity after spinal cord injury paralysis.
- EDS, Buspirone **AND** task-specific rehabilitation ...
  - Further increased** reaching and grasping ability. By 6 weeks post-injury, success rates were **greater than pre-injury values**.
  - Facilitated pellet retrieval** after ablation of the corticospinal tract at spinal level C4.
  - Improved muscle activity and intralimb coordination** during reaching and grasping
  - Modulated spinal cord excitability** as shown in sMEPs

EDS and buspirone most likely adapt sensorimotor networks to form a de novo functionally significant supraspinal-spinal connectome that can be guided and further facilitated by motor training.

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