Tempo-Spatial Inhibitory Mechanisms in the Human Spinal Cord – Insights From the Nociceptive Withdrawal Reflex

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Introduction

- A noxious stimulus applied in the arch of the foot produces dorsal flexion and inversion of the ankle joint [1]. Eversion is evoked when the stimulation is delivered in the lateral side of the foot' sole [1].
- Spatial summation has previously been observed in the NWR, although when stimulating the medial and lateral side of the sole of the foot, the magnitude of the NWR was inhibited [2]. A spinal inhibitory mechanism seems to play a major functional role in the defensive strategy of the NWR [2].
- Temporal features of this spinal mechanism remain unclear and are important to elucidate nociceptive processing at spinal level.

Aim

To investigate whether a temporal delay introduced on a paired stimuli applied in the medial and lateral side of the sole of the foot, modulate the size of the NWR.

Methods

Subjects: Fifteen healthy participants were included in the study.

Stimulation:

- Two stimulating sites: Arch (A) and Lateral (L) side of the sole of the foot.
- Stimulus delivered as single (in either site), simultaneous (both sites), and sequentially (in either site and as a combination of both).
- Sequential stimulation with different inter-stimulus intervals (ISI: 50, 100, 150, 200 and 500 ms) (Fig 1).
- Stimulation intensity (St_i) defined for each site based on Pain threshold (P_{th}) and NWR threshold (NWR_{th}), as: $St_i > 1.2 \times P_{th}$ and $St_i > 1.2 \times NWR_{th}$.

NWR quantification: EMG in Tibialis Anterior (TA) and Biceps Femoris (BF). NWR quantified by the root mean square (rms) value in the reflex window (80-150ms post stimulus), five repetitions of each stimulus type were averaged. NWR normalized dividing the NWR due to single stimulation.

Perceived intensities: Numerical rating scale anchored at 0: "No sensation", 5: "Pain threshold", and 10: "Worst pain imaginable".

Methods (cont.)

Experimental protocol

Single session. Stimulus type randomized throughout the experiment. Perceived intensity rated after each stimulus. Five minutes break every 25 stimulations.

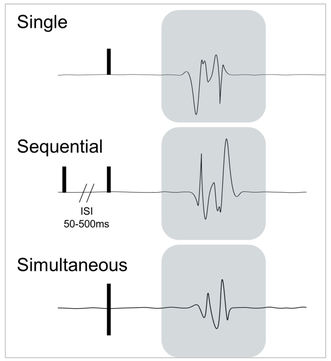

Figure 1: Three different stimulus type were delivered: Single, Sequential with varying ISIs (between 30-500ms), and simultaneous. Black bars indicate stimulus artifact. The NWR was quantified in the reflex windows defined between 80 and 150ms after the last stimulus artifact.

Data and statistical analyses

- Quantified NWR due to single stimulation compared to simultaneous stimulation in both TA and BF muscle (Wilcoxon signed ranked test)
- NWR due to different ISIs was compared (RM-ANOVA) Planned comparison between two extreme conditions with Bonferroni correction.
- Pain intensity ratings due to varying ISIs was compared (RM-ANOVA).

Results

- Simultaneous stimulation elicited larger NWR than single stimulus in both A or L.
- With sequential stimulation, a main effect of the ISD was found regardless of stimulus site and recorded muscle (RM-ANOVA, p<0.05).
- For TA muscle, larger NWR with larger ISI (Fig 2. *:p<0.05) .
- For BF muscle, larger NWR with shorter ISI (Fig 2. *:p<0.05).
- Perceived intensities were not affected by different ISI.

Results (cont.)

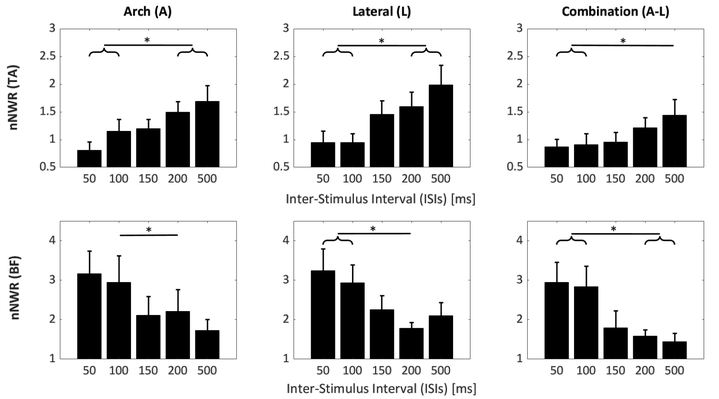

Figure 2: Results showing magnitude of the NWR when delivering sequential stimulation normalized by dividing to the single stimulation. Regardless of stimulation site, there was a tendency of larger NWR for longer ISI in TA, and larger NWR for shorter ISIs in BF. * p<0.05

Conclusions

- The inhibition observed in a previous study when the same two sites (A and L) were simultaneously stimulated (NWR recorded in TA), is reduced when a larger ISI is introduced, suggesting a functional principle underlying the tempo-spatial integration.
- Larger ISI produced significantly larger motor responses in TA, while the opposite occurred in BF. This differential modulation between proximal vs distal muscle suggests the presence of **spinal circuits controlling the optimal behavioral response** to the specific tempo-spatial characteristics of a dangerous stimulus. .
- No effect of ISI on NRS.
- Larger NWR with simultaneous stimulation (vs single) indicate spatial summation at spinal level.

References

[1] Andersen OK, Sonnenborg FA, Arendt-Nielsen L. Modular organization of human leg withdrawal reflexes elicited by electrical stimulation of the foot sole. Muscle and nerve 1999;22:1520–1530.
[2] Henrich MC, Frahm KS, Andersen OK. Spinal spatial integration of nociception and its functional role assessed via the nociceptive withdrawal reflex and psychophysical measures in healthy humans. Physiol. Rep. 2020;8:11–20

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