Non-invasive vagal nerve stimulation modulates the nociceptive withdrawal reflex in healthy subjects: a cross-over placebo-controlled study

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OBJECTIVE

The aim of this study is to evaluate whether non-invasive Vagal Nerve Stimulation (nVNS) can modulate pain transmission.

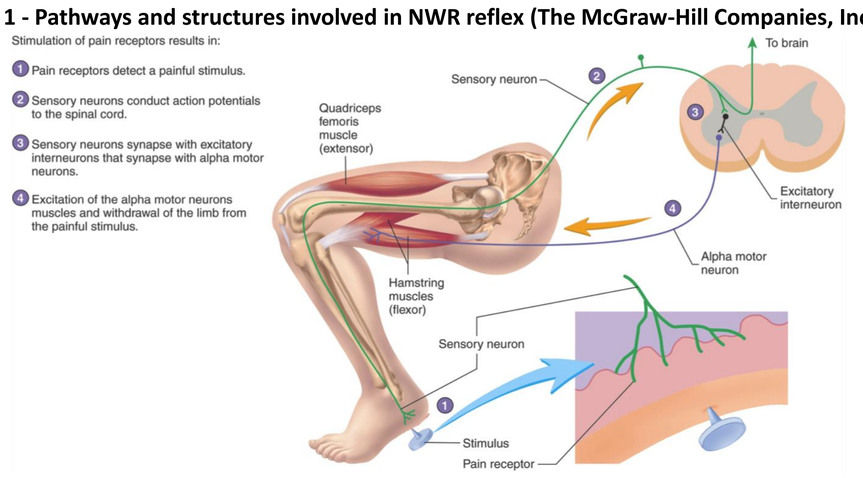
INTRODUCTION

Vagal Nerve Stimulation (VNS) is a promising method for chronic pain relief.[1] GammaCore is a portable device for non-invasive VNS (nVNS) at the neck level that has shown encouraging results in the treatment of cluster headache and chronic migraine.[2-4]

The neural networks involved in the analgesic effect of nNVS are still being elucidated. Analgesia is potentially mediated by vagal afferents that inhibit spinal nociceptive reflexes and transmission and have strong anti-inflammatory properties. No neurophysiological data is available regarding the modulation of pain with nVNS.

The paradigm of nociceptive withdrawal reflex (NWR) is a neurophysiological tool widely used to investigate the modulation of nociception. Since the threshold of the reflex has been shown to correspond to the pain threshold and the size of the reflex to be related to the level of pain perception, it has been suggested that the NWR might constitute a useful tool to objectively investigate pain processing at the spinal and supraspinal levels.[5]

Figure 1 - Pathways and structures involved in NWR reflex (The McGraw-Hill Companies, Inc., 2012)



MATHERIAL AND METHODS

Seven healthy subjects (4 males, 3 females, mean age 26.14±2.5) with no history of headache or chronic pain diseases, were evaluated in a cross-over placebo-controlled study as shown in Figure 2. All subjects were randomly assigned to:

a)nVNS: one 120-s electrical stimulation, with an individualized intensity, of the vagal nerve on each side of the neck over the carotid artery using gammaCore and applying its standard treatment protocol (Figure 3);

b)active placebo stimulation (PS): one 120-s electrical stimulation of the median nerve at 1 cm proximal to each wrist crease, using gammaCore. The intensity of the stimulus was individually set on the minimal intensity able to induce a contraction of the abductor pollicis brevis muscle with a painless hand twitching.

Electrical stimuli of increasing intensity were delivered at the sural nerve while recording NWR from the biceps femoris/tibial anterior muscle.

Figure 2 - Study design.

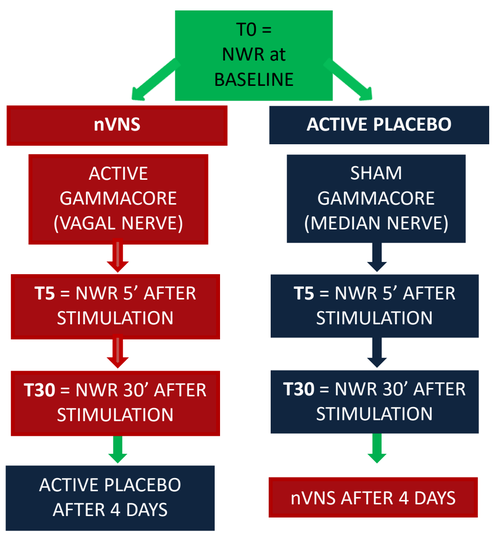
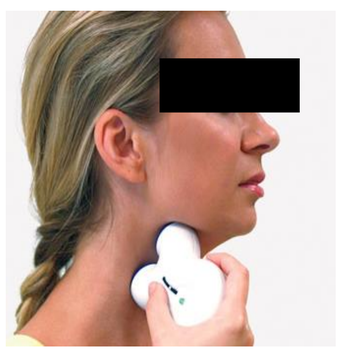


Figure 3 - gammaCore in treatment position.

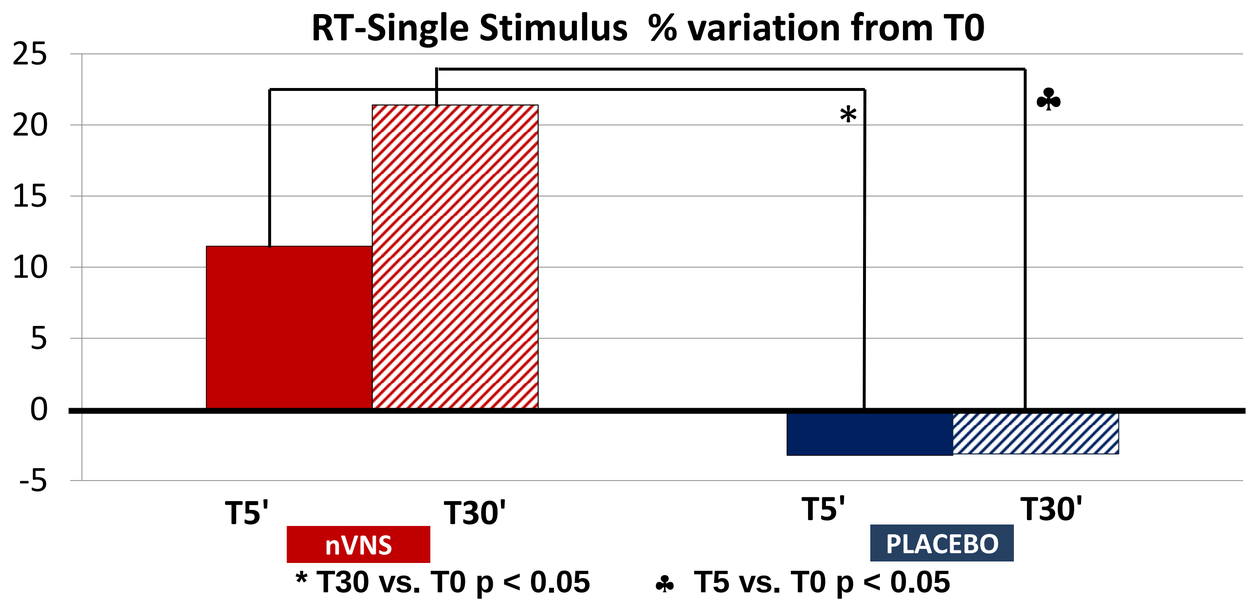


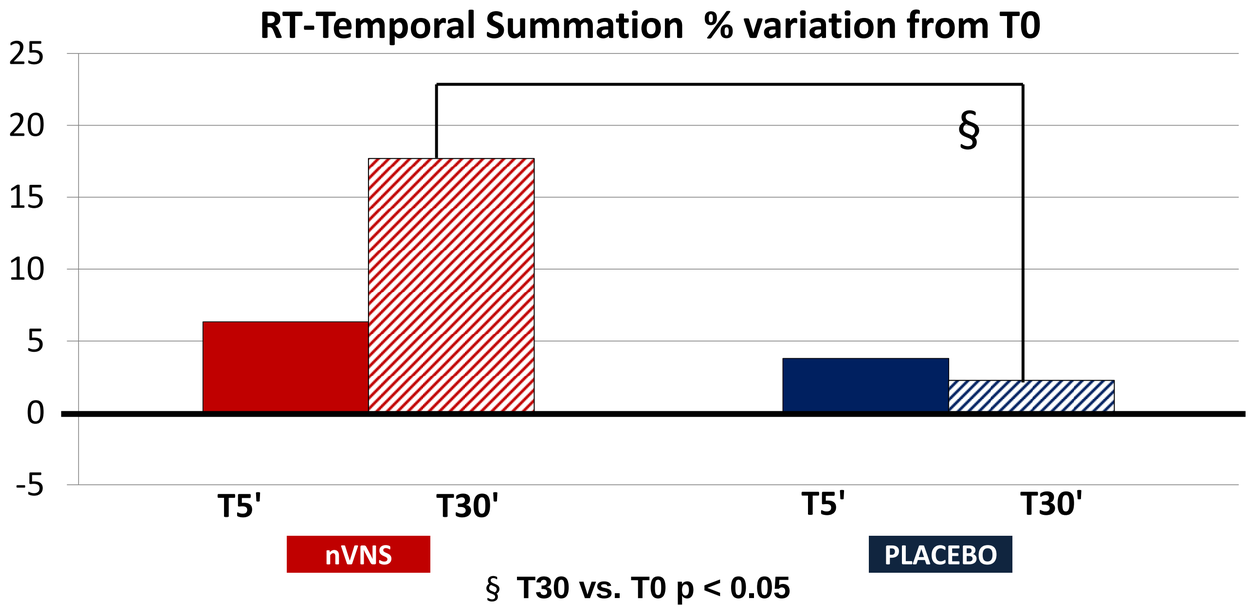
The threshold of NWR was defined as the lowest current intensity needed to evoke a stable EMG response with a single stimulus (RT-SS). We also investigated temporal summation (TS) by means of a train of 5 consecutive stimuli (2Hz): the lowest intensity that evoked the NWR was considered the TS reflex threshold (RT-TS). TS allows evaluation of the perception of increasing pain in response to repeated noxious stimuli, and it is the perceptual correlate of "wind-up" in the spinal dorsal horn.

RESULTS

In the nVNS group we detected a significant increase in RT-SS 30 minutes after the stimulation: T0 14.5±3.2 mA; T30 17.3±3.1 mA, p=0.043. The same pattern was observed for RT-TS: T0 11.4±2.4 mA; T30 12.96±2.3 mA, p=0.041. At variance, PS did not cause any significant modification on the reflex parameters.

When comparing percent changes from baseline induced by the 2 types of stimulation, we observed that nVNS caused a significant increase in RT-SS already at 5' as compared to PS: nVNS +11.5±13.3%; PS -3.2±4.3%, p=0.044. The difference between treatments became even more evident at T30: nVNS 21.4±19.9%; PS -3.1±7.1%, p=0.048. At T30, nVNS also induced a significant increase in RT-TS as compared to PS: nVNS +17.7±16.2%; PS +2.3±8.7, p=0.046.





CONCLUSIONS

- nVNS has a rapid-onset inhibitory effect on the nociceptive withdrawal reflex in healthy subjects.
- The analgesic effect of nVNS is likely to affect pain facilitation mechanisms in the spinal cord, as suggested by the increase in the threshold of temporal summation.
- This effect represents one potential Mechanism of Action for nVNS in acute and prophylactic headache management.

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