Review Article

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Effects of Cranial Nerve Non-Invasive Neuromodulation (CN-NINM) Technology on Various Neurological Disorders

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Abstact

This article discusses the benefits of Cranial-nerve non-invasive neuromodulation (CN-NINM), which is a multi-targeted rehabilitation therapy that initiates the recovery of multiple damaged or suppressed brain functions affected by neurological disorders. Various Previous works has shown the feasibility of using the tongue as a route to deliver non-invasive electrical signals to the brain though the cranial nerves with afferent glossal innervation. In addition, the anatomy of cranial nerve nuclei within the brainstem allows for possible interaction of the incoming neurostimulatory signal with other anatomical or functional pathways and the possibility of neuromodulation within these and higher centers of the central nervous system (termed Cranial Nerve Non-Invasive Neuromodulation or CN-NINM). CN-NINM appears promising for treatment of full spectrum of movement didorders, and for both attention and memory dysfunction associated with traumatic brain injury.

Keywords: Neurorehabilitation; Neuroplasticity; Neurostimulation; Cranial Nerve; Brainstem; Tongue.

Introduction

First of all, although conventional physical rehabilitation therapy does employ retraining with the intention to return the patient to normal function, this occurs primarily during the acute and postacute period after trauma (typically up to 1 year). CN-NINM technology is oriented primarily on reha-bilitation during chronic stages (years after traumatic inci-dent), when conventional thinking assumes that there is no further capacity for change. It is deployable as a simple, home-based device (portable tongue neurostimulator, PoNSTM) and targeted training regimen following initial patient training in an outpatient clinic. It may be easily combined with all exist-ing rehabilitation therapies, and may reduce or eliminate need for more aggressive invasive procedures or decrease the total medication intake. CN-NINM uses sequenced patterns of electrical stimulation on the tongue. CN-NINM induces neu-roplasticity by noninvasive stimulation of two major cranial nerves: trigeminal, CN-V, and facial, CN-VII. This stimula-tion excites a natural flow of neural impulses to the brainstem (pons varolli and medulla), and cerebellum, to effect changes in the function of these targeted brain structures.

Integrated CN-NINM therapy intends to restore physi-ological and cognitive functions affected by brain injury beyond traditionally expected limits, by employing both newly developed and novel therapeutic mechanisms for pro-gressive physical and cognitive training, while simultane-ously applying brain stimulation through a device we call the Portable NeuroModulation Stimulator. Based on our previous research and recent pilot data, we believe a rigorous in-clinic CN-NINM training program, followed by regular at-home exercises also performed with PoNS, simultaneously enhances, accelerates, and extends recovery from multiple impairments from brain injury (e.g., movement, vision, speech, memory, attention, mood), based on divergent, but deeply interconnected neuro-physiological mechanisms[1-4].

Conceptual Framework

Long term potentiation is the phenomena of synaptic structural remodeling and formation of new synaptic contacts that is acti-vated by high frequency stimulation [5-8]. After 10–40 minutes of high-frequency stimulation (50–400 Hz, range of

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frequencies used in animal research) the number of synapses and proportion of multiple spine boutons can increase the efficiency of neural connections. [9]. Effects of LTP can continue during several hours and even days [10,11]. Using the PoNS device, prolonged and repetitive activation (20 minutes or more) of functional neuronal circuits (balance, gait) can initiate long-lasting pro-cesses of neuronal reorganization (similar to LTP), that we can see and measure in subjects' behaviour. The functional improvement after initial training sessions continues for sev-eral hours. Multiple regular sequential train-ing sessions lead to consistent increase of improved symptom duration and cumulative enhancement of affected functions.

This regular excitation may also increase the receptiv-ity of numerous other neural circuitries and/or affect inter-nal mechanisms of homeostatic self-regulation, according to contemporary concepts of synaptic plasticity. We cannot exclude also that this induces simultaneous activation of serotoninergic and noradrenalinergic regulation systems of the brain as well. The result of this intervention is essentially brain plastic-ity on demand—a priming or upregulating of targeted neural structures to develop new functional pathways, which is the goal of neurorehabilitation and a primary means of func-tional recovery from permanent physical damage caused by stroke or trauma.

Purposeful Neurostimulation

The PONS device was designed to provide optimized neurostimulation via the tongue specifically to induce neu-romodulation as part of CN-NINM therapy. In this sense it belongs to two broad categories of technologies. The first category includes devices that electrically activate the ner-vous system.

The elec-trode array of the PoNS device induces an electric field in the tongue epithelia that based on the relevant anatomy and sensory percept, activates sensory fibers (pre-dominantly mechano, thermo, and free nerve endings) to a depth of approximately 300–400 ìm. This creates a massive flow of action potentials that are perceived by the subject. as a "buzzing" or "champagne bubble" sensation. Here, the stimulation is a flow of neural impulses filling the brain-stem nuclei through the trigeminal and facial nerve fibers. Activation of primary targets—these brainstem nuclei neurons—happens through existing synaptic connections, initiating a cascade of activation through multiple neural circuitries.

Pons Device

The current-generation PoNS device achieves localized electrical stimulation of afferent nerve fibers on the dorsal surface of the tongue via small surface electrodes. Because of the resulting tactile sensation, which, depending on stimulation waveform, typically feels like vibration, tin-gle, or pressure, it is certain that tactile nerve fibers are acti-vated. Taste sensations are infrequently reported, although it is not known whether gustatory afferents are in fact stimu-lated, given the nonphysiological patterns of activation likely to result from PoNS-induced stimulation of these fibers.

Physical Construction

The PoNS device is held lightly in place by the lips and teeth around the neck of a tab that goes into the mouth and rests on the anterior, superior part of the tongue. The paddle-shaped tab of the system has a hexagonally patterned array of 143 gold-plated circular electrodes (1.50-mm diameter on 2.34-mm centers) that is created by a photolithographic process used to make printed circuit boards. The board is an indus-try-standard polyimide composite that is USP Class VI com-pliant and meets ISO 10993 biocompatibility standards. The edges and nonelectrode surface of the array tab are coated with a rugged USP Class VI biocompatible epoxy. Therefore, the only materials that contact oral tissues are the gold elec-trodes and the biocompatible polymers. The remainder of the PCB and all electronic components, including battery, are in a sealed Delrin (USP Class VI compliant) enclosure that remains outside the mouth. Although the PoNS device is built using biocompatible materials, it is investigational and not approved by any regulatory agency. Device function is user-controlled by four buttons: On, Off, Intensity "Up," and Intensity "Down." The PoNS device is powered by an inter-nal battery that may be recharged via an external power sup-ply that plugs into a 120-V or 240-V AC electric mains outlet, similarly to a mobile phone.

Electrical Stimulation

The tongue electrodes deliver 19-V positive voltage-con-trolled pulses that are capacitively coupled both to limit maximal charge delivered under any rare circuit failure and also to ensure zero DC to the electrodes, minimizing poten-tial tissue irritation from electrochemical reactions. Tongue sen-sitivity to positive pulses is greater than that for negative pulses. The pulse width is adjustable in 64 unequal steps from 0.3 to 60 ìs by the intensity buttons. This intensity control scheme takes advantage of the steep section of the strength–duration relationship for electrical stimulation of neural tissue [12].

These pulses repeat at a rate of 200 per second, within the typical physiological firing rate for tactile afferents. Because of the neural refractory period, and extrapolated from earlier single-fiber median nerve response to similar electrotactile stimuli on a rhesus mon-key fingerpad (Kaczmarek et al., 2000), it is presumed that at most one action potential results in any given afferent fiber for each stimulation pulse. To minimize sensory adaptation [13] and to ensure a good quality of sensation[14] , every fourth pulse is removed from the pulse train, so that each electrode deliv-ers a burst of three pulses every 20 ms . This combination of pulse amplitude and width results in an elec-trotactile stimulus that may be varied by the user from well below sensory threshold to a perceived sensation at the upper limit of comfortability.

Electrode Array and Pulse Sequencing

The PoNS electrode array, irregularly shaped to take advan-tage of the most sensitive regions of the tongue, comprises 143 electrodes nominally organized into nine 16-electrode sec-tors. Within each sector, one electrode is active at any moment (pulse beginnings staggered by 312.5 ìs), with unstimulated electrodes serving as the return current path. The nine sectors present simultaneous stimulation, with the intensity of each sector adjusted to compensate for the variability of tongue sensitivity to electrotactile stimuli[15].

The sensation produced by the array has been described as similar to the feeling of drinking a carbonated beverage. The electrode size and geometry were chosen to achieve a reasonable balance between number of electrodes that may be packed into the array area and the comfortability and control-lability of the electrotactile percept [16]. The overall result of this stimulation is the comfortable and convenient presentation of almost 26 million stimulation pulses to the tongue during a typical 20-minute therapy ses-sion. How many action potentials are propagated to the brain as a result of this surface stimulation is at this point unknown.

CN-NINM Training with the Pons Device

The goal of CN-NINM training is to recover normal movement control. By combining brain activation with tar-geted physical training, we believe we are affecting neural pathways directly related to the task. Through experimenta-tion in multiple studies with various populations (TBI, stroke, multiple sclerosis, Parkinson disease), we have found that the most effective way to train using this technology involves five main components:

1. Movement training
2. Balance training
3. Gait training
4. Cognitive training
5. Breathing and awareness training (BAT)

Individuals are trained in the clinic initially for 1 to 2 weeks (Monday through Friday). As they improve, they are challenged with harder tasks in order to progress. After the clinical training period, they continue training at home, performing the same components of CN-NINM train-ing that they learned in the clinic. Individuals return to the clinic approximately at weekly and monthly intervals to review training

Daily Training Session Sample

Morning	**Movement training—warm-up exercises**
Balance training with PoNS	20 minutes
Gait training with PoNS	20 minutes
Cognitive training with PoNS	20 minutes
Break	3–4 hours
Afternoon	
Movement control exercises with PoNS	20 minutes
Balance training with PoNS	20 minutes
Gait training with PoNS	20 minutes
Cognitive training with PoNS	20 minutes
Evening	
BA Twith PoNS	20 minutes

Various Studies

Gait

Four Subject TBI Cohort Dynamic Gait Index Results

The results presented below represent the changes over a 5-day period of CN-NINM intervention in subjects with a TBI. Four female subjects (mean age:

48.3) presented with sustained and significant balance and gait deficits from mod-erate closed-head, nonpenetrating, concussive TBI (9–13 on Glasgow Coma Scale) at initial diagnosis. All were approxi-mately 5 years postinjury and had previously completed rehabilitative therapy programs at their respective primary care facilities. The Dynamic gait index scores indicate significant improve-ments in stability and gait that are retained for as much as 6 hours after completion of the second intervention session of the day.

Single TBI Subject Electromyelogram Results

Additional quantitative gait analysis using electromyography was performed on one of these subjects . At baseline, it revealed desynchronization of muscular activity—early acti-vation of the left soleus during stance, and delayed activation of the left vastus lateralis, creating an abnormal gait pattern. After 1 week of CN-NINM rehabilitation, much more normal phasing of both these mus-cles is present when the subject walked at the same speed. The medial hamstrings and medial gastrocnemius were not substantially affected, exhibiting similar phasing both before and after treatment.

Stroke Subject DGI Results

Careful analysis of gait improvement in a stroke subject revealed a very important feature of CN-NINM training. The training protocol included balance, gait, and movement train-ing (see previous section) during the initial 2 weeks in the laboratory, and an additional 5-day retraining and adjustment every month. In between the laboratory training sessions, the subject was instructed to continue the training at home. In this particular case, measurements of gait performance were conducted before and after every in-laboratory training period. Results are presented in Figure 44.7, which shows that the subject's gait performance improved 48% over 6 months. However, development of such performance was not smooth and continuous, but looks stepwise.

Balance

1. The four TBI subjects were tested on the NeuroCom CDP Sensory Organization Test (SOT) before and after the week of twice-daily interventions. A composite score is calculated and compared with a database normalized for age and height. It was found that greatest functional improvement occurred in the most dynamic and challenging tasks
2. A study was done in 6 patients with various balance dysfunction etiologies who underwent one week of therapy with CN-NINM. All patients had an MRI scan on the day before the start of the therapy week and another MRI scan within three hours after completing the last therapy session. Five age and gender-matched healthy controls also underwent an MRI scan but did not receive any CN-NINM therapy. It has been concluded that CN-NINM modulates neural activity in the dorsal pons, and this modulation remains even when stimulation has been removed [17].

Cognitive Function

1. Additionally, TBI subjects C and D were tested for changes in cognitive function, memory, attention, and mood both before the 5-day intervention began, and within 24 hours of com-pleting the training. Their primary indications and scores on the Brief Repeatable Battery of Neuropsychological Tests showed improvement.

Eye Movement

1. Beginning with our first studies with rehabilitation of periph-eral and central balance disorders, we noticed striking effects of CN-NINM training on the recovery of visual dysfunctions (oscillopsia, abnormal nystagmus, color perception, visual acuity, light and dark adaptation, limits of visual field). Similar and even stronger effects were observed during studies with stroke, traumatic brain injury, multiple sclero-sis, and Parkinson subjects.

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