Non-Invasive Multi-Channel Neuro-Stimulators In Treatment Of The Nervous System Disorders

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Abstract: Approaches of non-invasive neuromodulation organization for rehabilitation brain injuries outcomes and psycho-emotional disorders are discussed. One of technologies based on electrocutaneous stimulation of the tongue (CN-NINM), and other technology based on transcutaneous stimulation of the neck (SYMPATHOCORRECTION). Currently, two portable devices were developed and introduced in clinical practice: PoNS^{TM} and SYMPATHOCOR. Both technologies are complement each other and demonstrate perspectives in various applications for purpose of neurorehabilitation and neurological symptoms management in such difficult for rehabilitation areas, as traumatic brain injury, stroke, Parkinson's disease, multiple sclerosis and many other neurological disorders.

1 INTRODUCTION

The brain injuries and psycho-emotional disorders are among the leading causes of severe human neurological disabilities and high mortality rate. The most common approach to treat such disorders is the neuroprotective therapy. Indeed, such a therapy facilitates, in some extent, the normalization and strengthening the physiological activity of the brain tissues. It is also can help to repair the system damages inflicted by various kinds of pathogenic impacts (traumatic, inflectional, inflammatory, vascular, degenerative, etc.).

In general, the neuro-protective therapy is based on the combinations of drug therapy with another kind of therapies (physical, cognitive, speech, etc.) that oriented on different symptoms, have an impact on different mechanisms and affect various physiological mechanisms and biochemical pathways. Eventually, all these means affect various components of a pathogenic process under treating (Greenberg, 2009).

Recently, the low effectiveness of the traditional methods has stimulated the development of new approaches and methods of the neuroprotection, which should be less dangerous, more effective and non-invasive. During last decade, the whole family of such methods have been discovered, based on various forms of physical impact on the neural system. All these methods were called the neurostimulation methods. Multiple studies demonstrate the efficiency of such neurostimulation methods and the perspective in use of non-invasive technologies for rehabilitation of the full spectrum of neural disorders. It has become especially important for age-related disorders, considering the growth of the human life span and the wave of retirement of "baby-boomers" generation.

2 PATHOPHYSIOLOGICAL PECULIARITIES OF THE NERVOUS SYSTEM DISORDERS

Any damage of the central nervous system leads to many pathological processes and affects numerous structural parts, pathways and physiological mechanisms. In clinics, these phenomena appear in multiple neurological, psychological, vegetative, and regulatory damages. The "multidimensional" damage needs the "multidimensional" treatment. Apparently, instead of one "universal," fit-for-all" medical mean, the complex therapy should be applied, as a combination of different methods and technologies that applied simultaneously can facilitate each other.

However, in case of drugs, such combination can become very dangerous, because simultaneous use of several medications can lead to summation of drug side-effects, lead to the increasing adverse effects. In this case, the positive treatment effects become slower. The treatment becomes ineffective and even harmful for the patient's life.

This situation becomes even more dangerous when the treatment interferes with the natural regulatory and adaptive processes of the nervous system, and, essentially, these interventions become the stress factors. As a result, the corresponding systems are reacting properly, initiating the stress adaptation mechanisms. It is initiating a composite regulatory complex that plays the main role in activation and coordination of all changes in the patient's organism in a response to the stress.

Such system, so-called stress-system, is based on mechanisms both self-regulation and outer-regulation. The self-regulation of the stress-releasing system is built on the feedback principle, where the main role is played by the adrenal-corticotrophin hormone, cortisol, and several other components of the brain (Davis, 2008). The outer-regulation mechanisms are released by the so-called stress-limiting system that limits activity of the stress-system and excessive stress-reaction on the central and periphery levels. The central levels are consisted of the GABA-ergic, opioid-ergic, and serotonin-ergic systems. The peripheral level includes the adenosine, prostaglandins, and antioxidant systems, and, additionally, the nitrate-oxide generation system (Stahl, 2008).

Moreover, there are also other factors that play an important role in the stress-reaction regulation. Those are the endogenous neuropeptides (the substance P), the brain growth factors, and some others (Dupont, 1981; Rothman, 2012). Therefore, the organization of complicated multi-phase adaptation reaction (during the stress) is provided by complex neurohumoral mechanisms of interaction between the stress-releasing and stress-limiting systems (Holaday, 1983; Knapman, 2012).

Considering, that the stress is caused by both the disease itself and the combination of direct and side effects of several applied drugs, there is a high probability of the immune system damages that can lead to, so called, secondary immune-deficit state, abnormal condition of the neurogenic origin (Turnbull, 1999; Kronfol, 2000).

If adaptation performance of the neural regulation is exceeded the natural limits, then the central regulatory mechanisms should be initiated. It includes the direct control of the endocrine, immune, cardio-vascular, and digestive systems. This new level of activation is implemented by complex communication networks, including the neurohumoral interactions, hormones, neuromediators, and immunotoxic agents (McEwen, 2009; Dedovic, 2009).

Such natural basic and fundamental regulation systems eventually become the primary target for development of new neurostimulation methods.

3 SPECIFICITY OF NEUROSTIMULATION SYSTEMS

The non-medication methods of neuro-stimulation can be classified by the following key features:
Depending on the part of nervous system involved in activation, different clinical effects of the neurostimulation can be obtained. Therefore, the non-medication neurostimulation can modulate various processes in the human body.

In contrast to the traditional pharmacotherapy, the neurostimulation methods do not change directly the balance of neurochemical and molecular compounds in the regulatory, biochemical, and immune processes in the organism. As a result, the non-invasive neurostimulation (if applied properly) does not have unwanted side effects and do not cause evident additional stress-reaction of the organism. It is an open wide spectrum of application of the neurostimulation methods in the rehabilitation of many kinds of pathologies.

To solve particular medical problems, it is necessary to find the appropriate "targets" and conditions for technical implementation of adequate neurostimulation, based on the pathophysiology of disorder and the knowledge of anatomy and physiology of the CNS and pattern of innervation of affected organs and systems.

In our investigations, the specific regions of the neck and the dorsal surface of the tongue were chosen as new targets for the transcutaneous electrical neurostimulation.

There are several reasons why these areas were selected as perspective targets:

Both the neck and tongue regions are located in the close proximity of the major structures of the CNS (brainstem, cerebellum and cranial nerve ganglia) and its main sensory, motor and autonomic control systems, i.e., close to structures of the vegetative nervous system (VNS, both the sympathetic and parasympathetic) on the level of its over-segmental and segmental sections.

Regulating and controlling many functions of the organism, these structures of the VNS essentially control intimate mechanisms of compensation and adaptation to various damaging factors of the outer and internal environment. This determines importance of the VNS in creating the prerequisites and development of disorders. Therefore, the malfunctioning in the work of the VNS can be represented by its own nosologic forms, and at the same time. The abnormal functions of VNS can go together with many wide-spread disorders. Considering, that even the treatment of pathological processes in the VNS itself is rather problematic, it is not surprising, that the vegetative disorders as accompanied symptoms frequently are not the targets of the major treatment at all.

Indeed, during stimulation of the neck and tongue regions it is possible to impacts both the parasympathetic and sympathetic structures of the VNS and to affect the ascending afferent conductive pathways, and correspond centers in the brainstem, subcortical and cortical areas of the brain.

The neck section of the sympathetic stem consists of three nodes and inter-node connection branches that are located in the deep neck muscles behind the pre-spinal plate of the neck fascia. Incoming afferent fibers are coming from the vegetative cores of the lateral intermediate (gray) substance of the eighth neck and six-seven upper pectoral segments of the spinal cord through the inter-node branches of the pectoral section of the sympathetic stem.

The efferent branches (coming out of the neck node) contain the post-ganglion sympathetic fibers passing close to the upper nerves of spinal cord and cranial nerves (glossopharyngeal, vagal, additional, and hypoglossal) and next to the outer and internal carotid arteries and other near located blood vessels.

The parasympathetic nervous system in the neck region is represented by components of the pneumogastric or vagal nerve. Moreover, on the neck level from this nerve came out pharyngeal, laryngeal, and heart branches that participate in innervations and regulations of muscles and mucous membrane of the pharynx, larynx, trachea, esophagus, tongue root, thyroid and near-thyroid glands, thymus, myocardium, and lungs (by creating the lung plexus).

The oral cavity, including the tongue, is intensively innerved by the motor, sensory, and secretion control fibers. The motor, sensory, and taste fibers are parts of the cranial nerve system. The multiple glands of oral cavity are controlled by VNS fibers divided into sympathetic and parasympathetic ones. In total, five out of twelve cerebral nerves participate in innervations of the tongue and oral cavity. Those are the following nerves: trigeminal, facial, hypoglossal, glossopharyngeal and pharyngeal ones. The mentioned above five nerves (that innerve the walls and organs in the oral cavity) have nuclei in the brainstem just under the rhomboid fossa. These cores are divided into motor, sensory, and vegetative (autonomic) ones.

Both non-invasive multichannel neurostimulation methods allow directly affect VNS for purpose of neurorehabilitation. It is well known, that in control of complex objects, the effectiveness of control is increasing proportionally to degree of freedom of the control system (McEwen, 2009). Considering the neuro-stimulation problems, this rule can be applied by extension of the control abilities by increasing the number of specific ways of the neural structure's activation. The stimulation effectiveness can be also improved by using bio-tropic parameters of stimulation signals similar to parameters of internal processes.

In neurostimulation systems, the application of low-frequency impulse series of one polarity current seems to be perspective, especially in combination of the multi-channel neuro-stimulation with computerized process control.

In this article, we are presenting two original multi-channel portable systems for noninvasive stimulation of the tongue (PoNS device) and the neck area (SYMPATHOCOR device) for purpose of neurorehabilitation of sensory, motor and autonomic functions.

Block diagram of the engineering feasibility of multi-channel neurostimulation systems is shown in Fig.1.

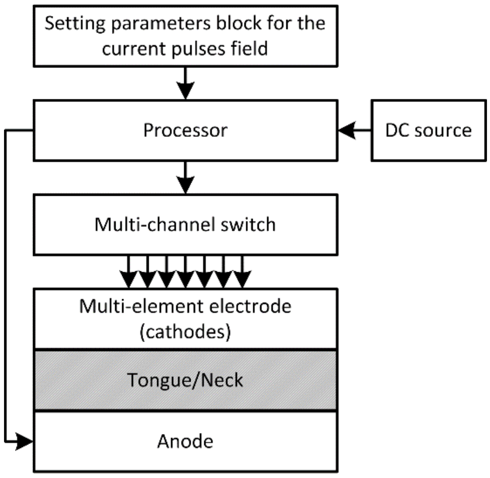

Figure 1: Block diagram of the engineering feasibility of multi-channel neurostimulation systems.

3.1 CN-NINM Technology

The portable neuromodulation stimulator (PoNS™) is an electrical pulse generator that delivers carefully-controlled electrical stimulation to the tongue. The pulses are generated and controlled by commercially available counter, timer, and wave-shaping electronic components. The components are mounted on a single printed circuit board (Fig. 2). The circuit board contains 143 gold-plated electrodes that contact the tongue. A rechargeable lithium-polymer battery with built-in charge safety circuitry provides the power.

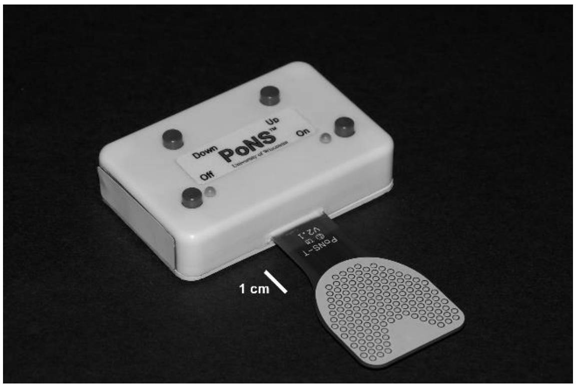

Figure 2: PoNS device.

The PoNS™ device is placed in the mouth and has been investigated in conjunction with physical therapy for treatment of balance and gait disorders caused by a variety of etiologies, including the traumatic brain injury, multiple sclerosis, central and peripheral vestibular disorder, migraine-related balance disorder, chronic Meniere's disease, spinocerebellar ataxia, gentamicin ototoxicity, idiopathic cerebellar ataxia, idiopathic vestibular disorder, and cerebellar infarction (Danilov, 2007; Wildenberg, 2010; Tyler, 2014).

The device is easily held at the place by the lips and teeth around the neck of the tab that goes into the mouth and rests on the anterior superior part of the tongue. The paddle-shaped tab of the device has a hexagonally patterned array of 143 gold-plated circular electrodes (1.50 mm diameter, on 2.34 mm centers). The array is created by a photolithograph process used to make printed circuit boards. It uses the low-level electrical current to stimulate the lingual branch projections of at least two cranial nerves in the tongue anterior through the gold-plated electrodes. Device function is user-controlled by four buttons: On, Off, Intensity 'Up', and Intensity 'Down'. The system delivers triplets of 0.4 – 60 µs wide pulses at 5 ms intervals (i.e., of 200 Hz) every 20 ms (50 Hz) that has been designed to achieve a balance of stimulus dynamic range and sensation quality. The sensation produced by the array is similar to the feeling of drinking a carbonated beverage. The system has operational limits of 19V (max) on the tongue (a nominal 5–7 kOhm load). The biphasic waveform is specifically designed to ensure zero net DC current to minimize the potential for the tissue irritation.

The current hypothesis for the underlying mechanism by which the PoNS™ Cranial Nerve Noninvasive Neuromodulation (CN-NINM) stimulation leads to sustained neuromodulation (and subsequent therapeutic effect) comes from previous FMRI studies using optokinetic visual stimulation to activate regions involved in processing balance information (Wildenberg, 2010). Cortical procession of the motion is performed primarily by the motion sensitive visual cortex (hMT+).

Previous work from our group investigating network behavior after the CN-NINM (Cranial Nerve Noninvasive Neuromodulation) showed hypersensitivity of the balance-processing network in individuals with balance dysfunction compared to healthy controls. The network behavior normalized after the CN-NINM therapy. A high-resolution study of activity within the brainstem suggested that the trigeminal nucleus, the point at which afferents from the tongue enter the central nervous system, had altered neural responses to motion in the visual field after stimulation.

We hypothesize that spatio-temporal trains of spikes induced in the trigeminal and facial nerves by electrical stimulation of the tongue produce changes of activity in corresponding nuclei of the brainstem, namely, at least in the sensory and spinal nuclei of trigeminal nuclei complex (the largest nuclei in the brainstem, extending from the midbrain to the nuclei of the descending spinal tracts), and in the nucleus tractus solitarius where both stimulated nerves have direct projections. We postulate that intensive activation of these structures initiates a sequential cascade of changes in neighboring and/or connected nuclei by direct collaterals, interneuron circuitry, or passive transmission of biochemical compounds in the intercellular space. Accordingly, electrotactile stimulation of cranial nerve endings, particularly in the lingual tract of the trigeminal and the facial nerve, initiate activity in the corresponding nuclei similar to long-term potentiation/inhibition, which, in the turn, increases the receptivity of multiple neural circuitries and/or affect internal mechanisms of homeostatic regulation.

This, in the turn, causes radiating therapeutic neurochemical and neurophysiological changes affecting both neural and glial networks affecting information processing of afferent and efferent neural signals involved in the motion control, including the cerebellum and nuclei of spinal motor pathways. PET scans study on the blind subjects before and after training with the visual sensory substitution system via the tongue stimulation (electrotactile feedback) system demonstrates massive activation in cortical and subcortical levels of the brain (Kronfol, 2000). It may also increase the receptivity of multiple neural circuitries and/or affect internal mechanisms of homeostatic regulation according to the contemporary concept of synaptic plasticity. We as well cannot exclude also that this induces simultaneous activation of serotoninergic and noradrenalinergic regulation systems components located in the brainstem.

In the course of testing and training numerous persons having a primary indication of balance and gait disorder using the balance recovery therapeutic method we developed, we observed therapeutic benefits well beyond balance (attention, memory, multitasking, vision, fine motor control, sleep, tremor, tinnitus) regardless of their etiology (peripheral vestibular, central or idiopathic vestibular loss, cerebellar stroke, Meniere's, Parkinson's, MS).

3.2 SYMPATHOCORRECTION Technology

The portable corrector of activity of the sympathetic nervous system (SYMPATHOCOR) is an electrical pulse generator that delivers the spatially-distributed field of the carefully-controlled current pulses in the neck (Kublanov, 2008). The general view of the SYMPATHOCOR device is presented in Fig. 3.

Figure 3: The general view of the SYMPATHOCOR device.

The spatially-distributed field of the current impulses in the SYMPATHOCOR device is formed between two multi-element electrodes. Each electrode comprises a cluster of thirteen partial current-conducting elements with galvanic isolation of each other. The multi-element electrodes are arranged on the neck into left and right arrays. In the working state, the central element of one array plays the role of the anode. Electrodes on the other side become the cathodes. If it is necessary, the arrangement can be reversed in opposite direction.

Placing the multi-element electrodes on the subject neck, the anodes have to be located in projections of the neck ganglia of the sympathetic nervous system (Fig.4).

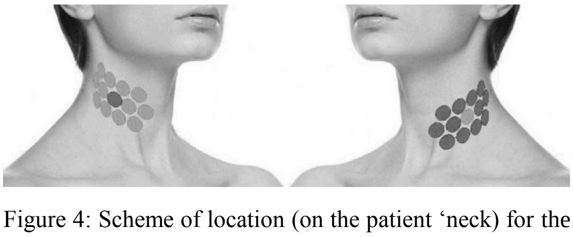

Figure 4: Scheme of location (on the patient 'neck) for the partial current-conducting elements of the multi-element electrodes.

The electric current impulses are delivered to the partial elements of the multi-element array from the processor through the multi-channel switch. At each instant moment, the impulse of current is formed only between only one partial cathode element and the anode partial element on the opposite side of the neck. Therefore, the current flows between the opposite multi-element electrodes across the neck. The spatio-temporal pattern of stimulation is controlled by processor, using specially developed software. Such control provides the necessary input information on variation of structure of the spatially-distributed field of the current and implements pre-calculated pattern for activation the partial cathodes. Pre-calculated pattern was designed to manipulate continuously changing vectors of the current and provide the maximum current density (onto the volume unit) in the active anode zone.

Note the following basic bio-tropic characteristics of the field: the current partial impulse length is from 20 to 60 -sec. The number of partial impulses in the period (impulse group) is 12. The frequency of impulse group is from 10 to 150 Hz. The partial electrodes are switched accordingly to each given rule (for example, a pseudo-random with the clockwise or counterclockwise direction of switching, and so on). The current impulse amplitude can be up to 20 mA.

SYMPATHOCORRECTION Technology is a method of the dynamic correction of the activity sympathetic nervous system is used for the neck neuro-stimulation in limits of the “homeostatic corridor," under which the vegetative regulation is not violated (Kublanov, 2010).

Depending on pathogenesis of the peripheral or central dysfunctions of the vegetative nervous system, the dynamic correction of the activity sympathetic nervous system algorithm has two different branches. Decision of which branch should be executed is based on nature of the VNS dysfunction. The bio-tropic parameters of the implemented current impulse field (the field structure, impulse amplitude, frequency, and length) are calculated from the analysis of the heart rhythm variability. In particular, in the case of the abnormal hyperactivity of sympathic innervation, it is necessary to block or suppress the activity of the sympathetic nervous system. In contrast, sympathic innervation should be increased, if the hyperactivity of the parasympathic innervation is observed.

In case of central dysfunctions, the bio-tropic parameters of the stimulation field are calculated, based on analysis of the main activity rhythms of the cerebral cortex and its deviation from the norm.

The first model of the SYMPATHOCOR unit is certified for fabrication, marketing, and application on the Russian Federation territory. In clinic practice, the SYMPATHOCOR device and the dynamic correction of the activity sympathetic nervous system technology are efficiently applied to treatment (Kublanov, 2010):

- Diseases involving organic and / or functional disorders of the CNS and / or the VNS: consequences of trauma or stroke, epilepsy, chronic headache, somatoform disorders, anxiety and depressive spectrum disorders, attention-deficit hyperactivity and tic disorder, consequences of alcoholism, disorders of autonomic nervous system, hypertension and its consequences;
- Diseases associated with impaired visual, auditory and vestibular function.

4 CONCLUSIONS

Analysis of topological structures of the neural network of the neck and tongue shows that the structures affected by neurostimulation are organized in the similar way. The primary activation targets have several common components (e.g. solitary nucleus) and spectrums of observed effects for both neurostimulation systems are significantly overlapped. Therefore, both presented technologies are complimentary to each other. The CN-NINM technology primarily affects sensory-motor integration in CNS and partially autonomic system. The DCASNS technology is affecting primarily VNS and partially sensory-motor integration. Both technologies can affect cognitive (memory, attention) and psychosocial (depression and anxiety) functions as well.

Considering the complimentary nature of both systems, the results of pilot research and experience in the clinical applications of the PoNS and SYMPATHOCOR units, we can recommend the parallel use of the neck and tongue neurostimulation in the rehabilitation process. It has become especially important in cases of the brain polytrauma or multiple functional damage after stroke, moderate traumatic brain injury or in advanced stage of multiple sclerosis. Moreover, it can be the only way, non-invasively, to recover various autonomic functions – bladder and bowl control, GI motility, hypertension, etc.

The result of this transcutaneous non-invasive neurostimulation is essentially brain plasticity on demand, i.e., a priming or up-regulating of targeted neural structures to develop new working pathway that is the goal of neurorehabilitation and a primary means of functional recovery from permanent physical damage caused by a stroke or trauma, by neurodevelopmental or by neurodegenerative disorders.

We believe on the theoretical grounds that both neurostimulation systems activate and synchronizes several large brainstem nuclei and the cerebellum, neck ganglia and VNS centers enabling the beneficial neuroplastic changes in multiple CNS and VNS control circuitries. We envision the application of these technologies to functional recovery to the broad range of sensory, motor, cognitive, autonomic and mood disorders.

REFERENCES

Danilov, Y.P., Tyler, M.E., Skinner, K.L., Hogle, R.A., Bach-y-Rita, P., 2007. Efficacy of electrotactile vestibular substitution in patients with peripheral and central vestibular loss. *Journal Vestibular Research*. 17(2-3), 119-130.

Davis, M.C., Zautra, A.J., Younger, J., Motivala, S.J., Attrep, J., Irwin, M.R., 2008. Chronic Stress and Regulation of Cellular Markers of Inflammation in Rheumatoid Arthritis: Implications for Fatigue. *Brain*, *Behavior*, and *Immunity.* 22 (1), 24-32.

Dedovic, K., Duchesne, A., Andrews, J., Engert, V., Pruessner, J.C., 2009. The Brain and the Stress Axis: The Neural Correlates of Cortisol Regulation in Response to Stress. *Neuroimage*. 47(3), 864-871.

Dupont, A., Sabord, P., Merand, G., et al., 1981. Age-related changes in central nervous system eukephalins substance P. *Life Science*. 29 (22), 2317-2322.

Greenberg, D.A., Aminoff, M.J., Simon, R.P., 2009. *Clinical Neurology*, Seventh Edition (LANGE Clinical Medicine). – McGraw-Hill Professional Publishing.

Holaday, J.W., 1983. Cardiovascular Consequences of Endogenous Opiate Antagonism. *Biochemical Pharmacology*. 32, 573-585.

Knapman, A., Kaltwasser, S.F., Martins-de-Souza, D., Holsboer, F., Landgraf, R., Turck, C.W., Czisch, M., Touma, C, 2012. Increased Stress Reactivity is Associated with Reduced Hippocampal Activity and Neuronal Integrity Along with Changes in Energy Metabolism. *European Journal of Neuroscience*. 35, 412-422.

Kronfol, Z., Remick, D.G., 2000. Cytokines and the Brain: Implications for Clinical Psychiatry. *The American Journal of Psychiatry*. 157 (5), 683-694.

Kublanov, V.S., 2008. A hardware-software system for diagnosis and correction of autonomic dysfunctions. *Biomedical Engineering*. 42 (4), 206-212.

Kublanov, V.S., Danilova, I.G., Goette, I.F., et al, 2010. Application of Spatially Distributed Field of Electric Impulses for Correction of Angiogenesis in Ischemic Muscular Tissue. *International Journal of Biomedical Science* 2010, Vol. 6, Issue 4, 310-315.

Kublanov, V.S., Shmirev, V.I., Shershever, A.S., Kazakov, Ya.E., Porshnev, S.V., Vasilijev, A.S., 2010. About innovative possibilities of the device “SIMPATOCOR” in management of functional disorders of vegetative and central nervous system in neurology. *Kremljovskaya Medicina. Clinichesky Vestnik*. 4, 60-64.

McEwen, B.S., 2009. The Brain is the Central Organ of Stress and Adaptation. *Neuroimage*. 47 (3), 911-913.

Rothman, S.M., Griffioen, K. J., Wan, R., Mattson, M.P., 2012. Brain-derived Neurotrophic Factor as a Regulator of Systemic and Brain Energy Metabolism and Cardiovascular Health. *Annals of the New York Academy of Science*. 1264, 49–63.

Stahl, S.M., Wise, D.D., 2008. The Potential Role of a Corticotropin-Releasing Factor Receptor-1 Antagonist in Psychiatric Disorders. *CNS Spectrums*. 13 (6), 467-483.

Turnbul,l A.V., Rivier, C.L., 1999. Regulation of the Hypothalamic-Pituitary-Adrenal Axis by Cytokines: Actions and Mechanisms of Action. *Physiological Reviews*. 79 (1), 1-71.

Tyler, M.E., Kaczmarek, K.A., Rust, K.L., Subbotin, A.M., Skinner, K.L., Danilov, Y.P., 2014. Non-invasive neuromodulation to improve gait in chronic multiple sclerosis: A randomized double blind controlled pilot trial. *Journal of NeuroEngineering and Rehabilitation*. 11 (1), Article number 79.

Wildenberg, J.C., Tyler, M.E., Danilov, Y.P., Kaczmarek, K.A., Meyerand, M.E., 2010. Sustained cortical and subcortical neuromodulation induced by electrical tongue stimulation. *Brain Imaging and Behavior*. 4, 199-211.