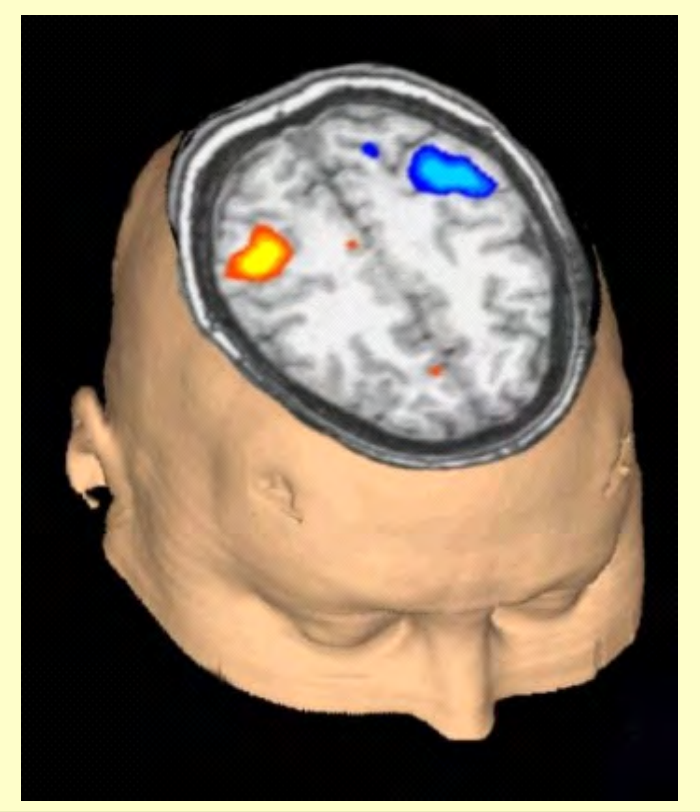

Neural pathways in cranial nerve non-invasive neuromodulation (CN-NINM)

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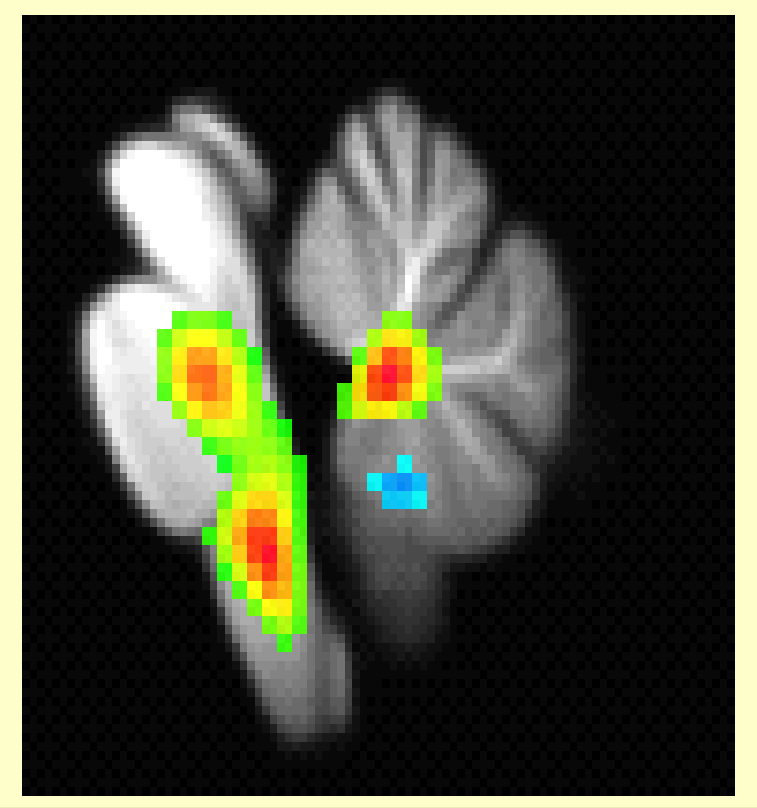


PURPOSE

To investigate the clinical efficacy of a new form of neurorehabilitation technology that we have developed, called cranial-nerve non-invasive neuromodulation (CN-NINM) by performing behavioral tests before, during and after training with the device

To develop a therapeutic training regimen for application of NINM to specific neurological symptoms

To develop and test new fMRI signal processing methods to improve image resolution specifically for the human brainstem and cerebellum

To use the improved fMR imaging technique to investigate possible functional changes in these neural structures for evidence of induced brain plasticity and neurorehabilitation in response to CN-NINM.

METHODS

Subjects:

Three women and three men (mean age 48.7±9.8 years) with various balance etiologies (two traumatic brain injury, two peripheral and one central vestibular dysfunction, and one spino-cerebellar ataxia) underwent one week of training with CN-NINM (3).

All patients had an MRI scan within three days of the start of the training week and another MRI scan within three days after completing training. Five age and gender-matched normal controls (three men, two women, mean age 56.0±5.0) also underwent an MRI scan but did not receive any CN-NINM training.

Patients **DID NOT** receive CN-NINM during the MRI scans.

Tests

The tests used fall into 3 categories:

1) Standardized self-assessment surveys of their perceived dizziness and loss of stability, specifically the Dizziness Handicap Inventory (DHI) and Activity-specific Balance Confidence scale (ABC);

2) Standardized Dynamic Gait Index (DGI) that is administered by a kinesiologist or physical therapist, and our own digital head postural stabilography (HPS - similar to standardized force platform posturography) that focuses specifically on head orientation and motion because this is the locus of spatial orientation information, and,

3) Inferential measurements of neural activity as it relates to regulation of balance, gait, and visual processing using a new method of functional magnetic resonance imaging (fMRI) and signal processing that we specifically developed for this study to observe changes in the cerebral cortex, cerebellum, pons varolli and brainstem.

Visual Stimuli:

The vestibular system was stimulated with motion in the visual field (optical flow). Three visual stimuli were used – a static checkerboard, a checkerboard that appeared to process/recess due to a sinusoidal change in the size of the squares, and a checkerboard that processed/recessed and rotated (Figure 1).

The rotation was produced by the sum of two sinusoids to prevent prediction of the motion by the subjects. The two dynamic stimuli had three versions that differed only in the phases of the sinusoids. Subjects were shown visual stimuli for 12 seconds alternated with 6 seconds of fixation in a block-design paradigm. The order of the visual stimuli was randomized with the requirement that each of the three types were presented nine times during each functional scan. Visual stimuli were displayed to subjects on fMRI-safe goggles at 800x600 resolution.

***Imaging Parameters*:**

All MRI scans were collected on a clinical 3T GE Signa HDx scanner. T1-weighted, three-dimensional, spoiled gradient recalled echo (SPGR) anatomical scans were collected with TR/TE = 10/3, 94 axial slices, and a 256x256 in plane resolution (0.938 x 0.938 x 1.5 mm). Functional images were collected with a T2*-weighted gradient-echo echo-planer imaging sequence (TR/TE = 2000/30, flip angle = 75) to acquire BOLD signal in a 64 x 64 matrix over a 24 cm field of view and 28 axial slices (3.75 x 3.75 x 5 mm resolution). Subjects underwent two functional scans, each 504 seconds in duration.

Image Processing:

All images were pre-processed with AFNI including slice-time correction, motion correction, and low-pass filtering at 0.15 Hz. GLM estimation was performed in SPM. All presented data is from individual subject contrasts of the rotating checkerboard and the static checkerboard (Figure 1). Due to the difficulty in accurately normalizing the cerebellum and brainstem to standard spaces, the SUIT template was used to normalize these structures into a restricted ICBM152 brain space. Whole brain normalization was performed with SPM. The resulting images were smoothed with a 8 mm FWHM isotropic Gaussian filter (the SUIT normalized images were smoothed with a 5 mm FWHM filter). Results were displayed using AFNI.

ROI Analysis: *A priori* regions of interest (ROI) were drawn for the dorsal pons and flocculus in ICBM152 space using a neuroanatomical atlas and AFNI's draw dataset plugin. ROI results are the average and standard deviation of the measured activity across all voxels in an ROI. Statistical analyses were performed with paired t-tests for comparison of patients before and after training, and with 2-sample t-tests for comparison of patients with normal controls.

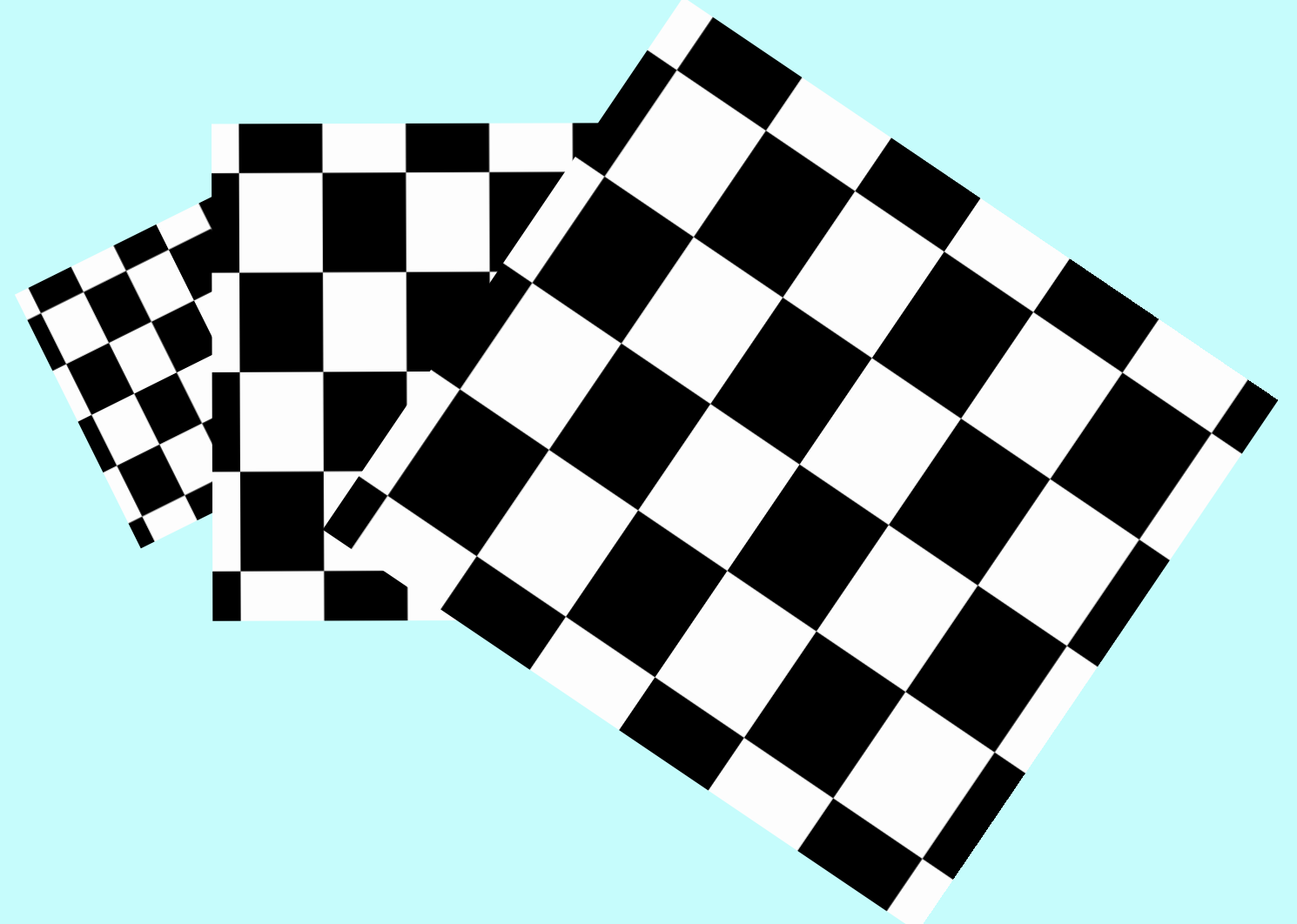


Figure 1. Three visual stimuli designed to activate the subject's balance processing centers were presented to subjects. One was an image of a static checkerboard as shown above.

A) The second included apparent procession/recession of the board by varying the size of the squares following the equation:

$edge = 170\sin(2\pi 0.2t+\Phi e)+230$.

B) The third added rotation about the central point given by a sum of two sinusoids:

$\theta = 60(\sin(2\pi 0.2t+\Phi 1)+\sin(2\pi t 0.35+\Phi 2))+180$

to prevent prediction of motion by the subjects. The two dynamic stimuli had three versions which differed only in the phases of the sinusoids.

WHY THE TONGUE?

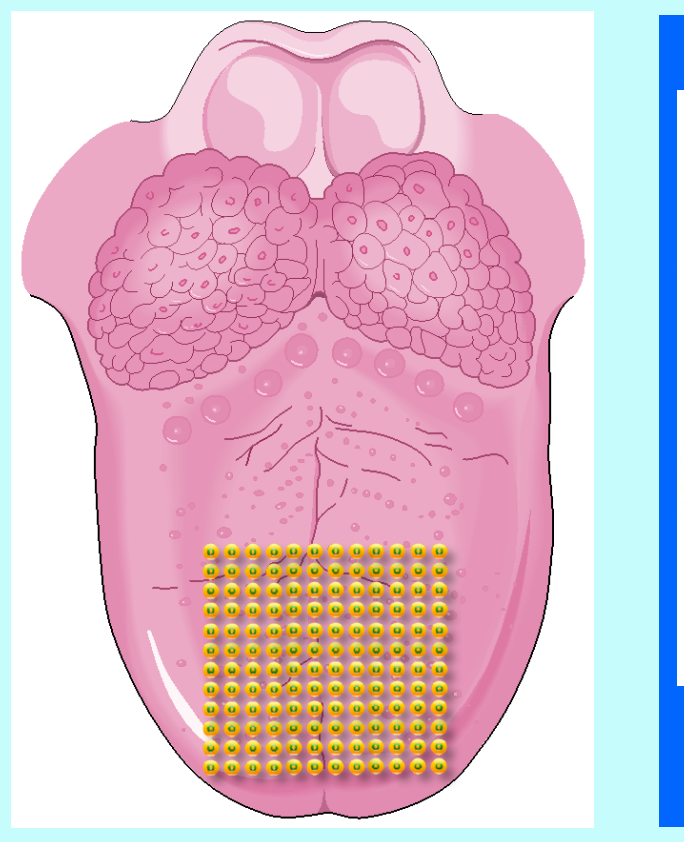


Figure 2. Tongue stimulation

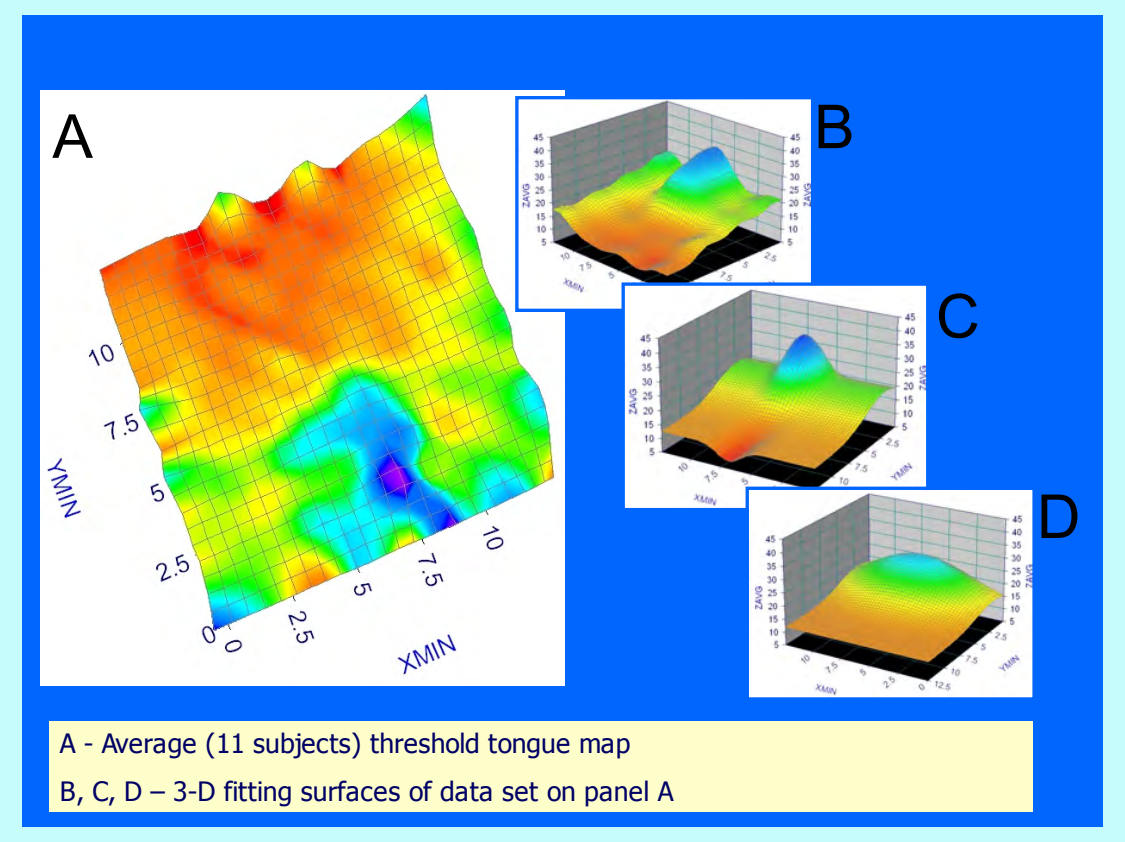


Figure 3. TONGUE SENSITIVITY MAP

High density of sensory nerve endings of:

Lingual nerve, branch of trigeminal nerve (CN-V) and ***Chorda tympani*** branch of facial nerve (CN-VII)

Saliva is excellent electrolyte

Tongue stays at constant ***pH+*** and **t°**

Electrode array is non-invasive

Discreet protected environment

Sensation "feels like Champagne bubbles"

CN-NINM CONCEPT

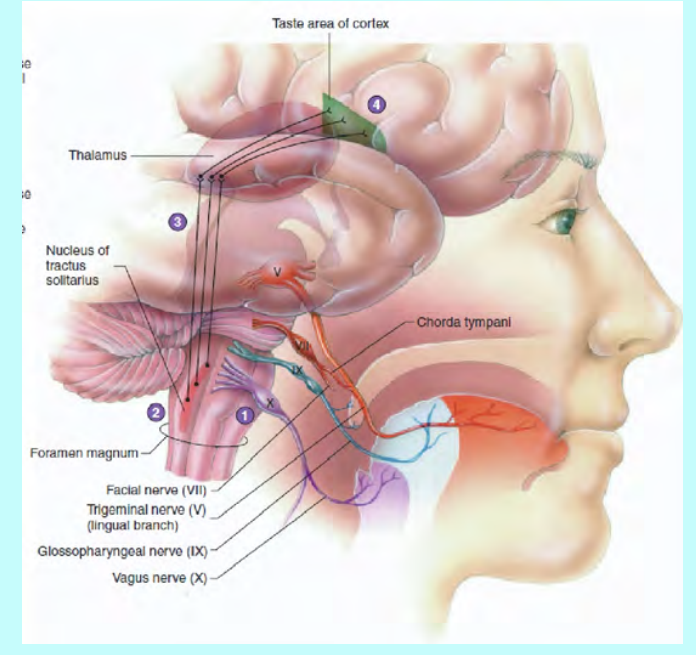


Figure 4. Tongue Innervation

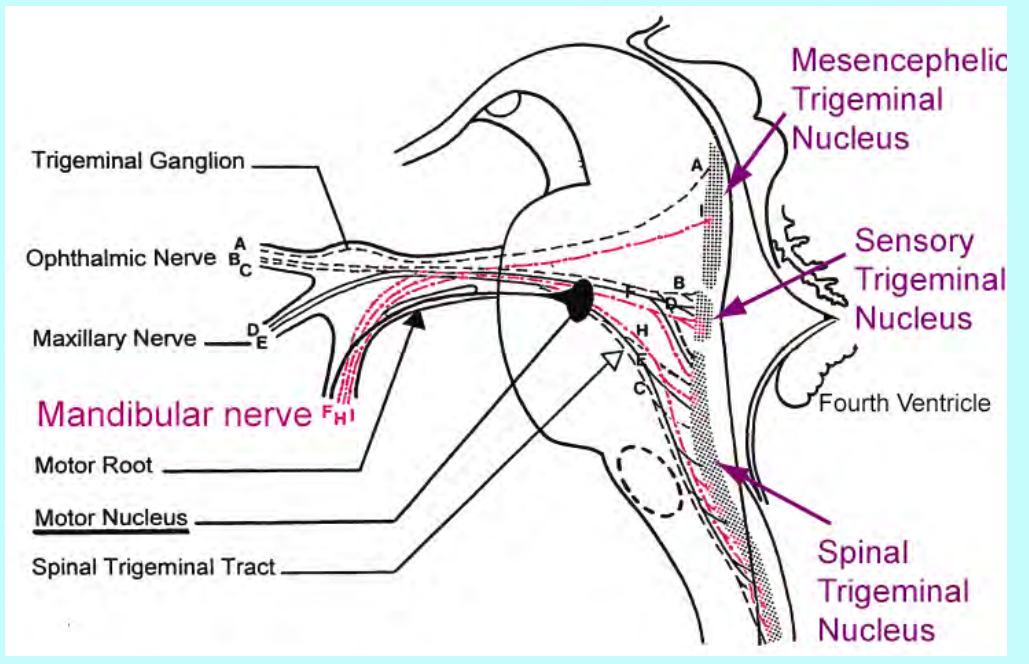


Figure 5. Trigeminal nerve input in brainstem

Cranial Nerve Non-Invasive Neuro-Modulation (CN-NINM) uses sequenced patterns of electrical stimulation on the tongue, transmitted to the brainstem (pons) and cerebellum via the lingual branch of the cranial nerve (CN)-V, and chorda tympani branch of CN-CII, to effect changes in the function of these targeted brain structures.

The spatio-temporal trains of spikes induced in these nerves eventually produce changes of neural activity in corresponding nuclei of the brainstem—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 nucleus tractus solitarius—where both stimulated nerves have direct projections.

Consequently, that intensive activation of these structures initiates a sequential cascade of changes in neighboring and/or connected brain stem nuclei by direct collateral connections, interneuron circuitry or passive transmission of biochemical compounds in the intercellular space. First of all that include the activation of vestibular nuclei complex, cochlear, facial and hyppoglossal nerve nuclei, and vermis of cerebellum. Prolonged activation (20 minutes or more) of neuronal circuits can initiate long lasting processes of neuronal reorganization(similar to long-term potentiation / inhibition). It is also can increase the receptivity of multiple neural circuitries and/or affect internal mechanisms of homeostatic regulation, according to contemporary concept of synaptic plasticity.

RESULTS

We developed a new cranial nerve non-invasive neuromodulation (CN-NINM) device that excites and entrains neural activity in the brain, and tested its efficacy with 5 patients having moderate or severe balance, gait, and visual tracking deficits.

All patients exhibited improved performance on all functional measures of postural and gait behavior as a result of NINM training, and patient scores in self-assessments of dizziness and mobility also uniformly improved.

The new fMRI signal processing techniques we developed afforded improved resolution of the brainstem and cerebellum, allowing observation of functional changes in activity in the areas that correspond to the improvements in the sensory-motor behavioral measures.

These images provide the first evidence of how and where CN-NINM is apparently changing brain function.

PREVIOUSE RESULTS

Figure 6. Short and Long Term Retention Effect

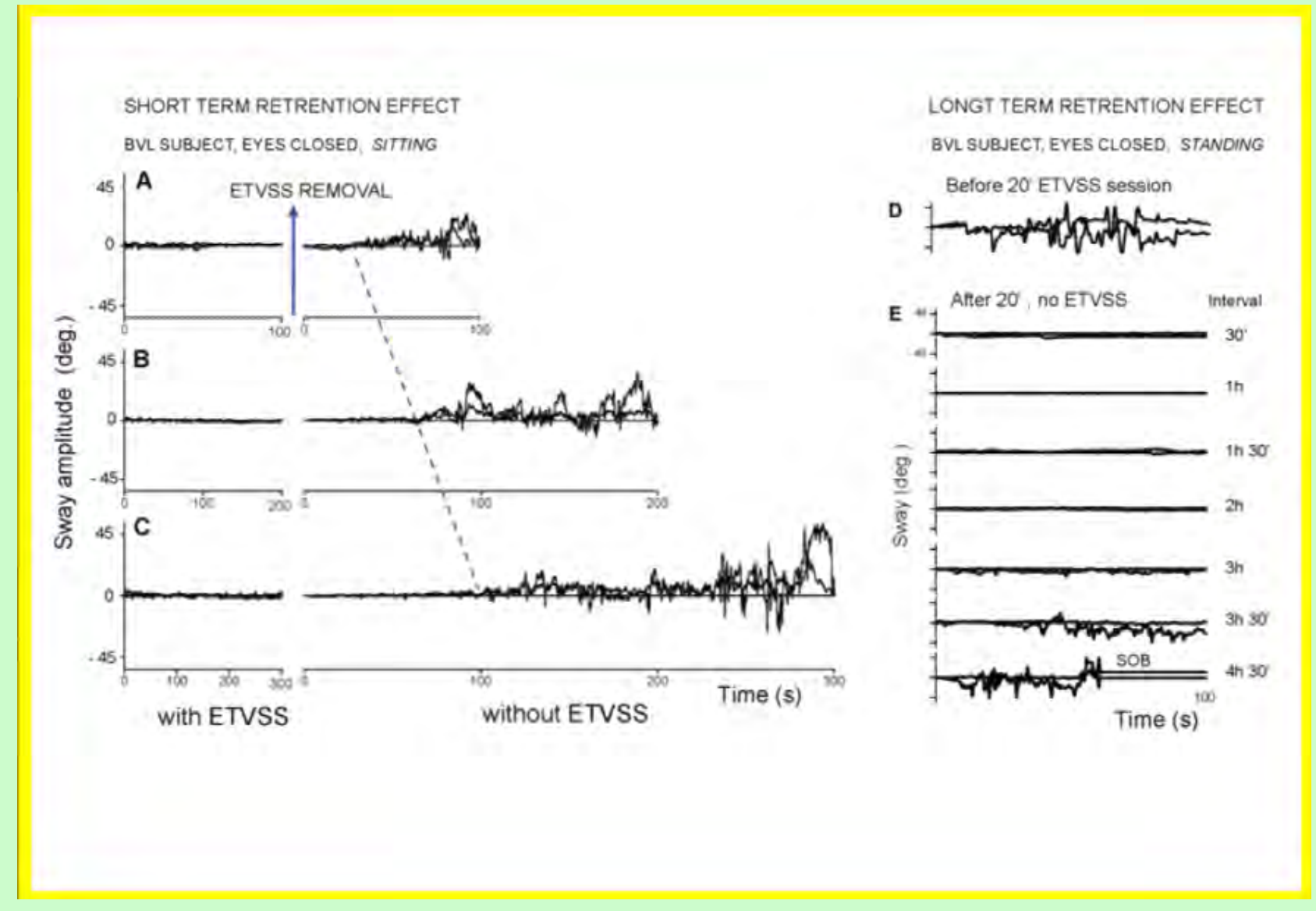


Figure 7. Age Independent Effects

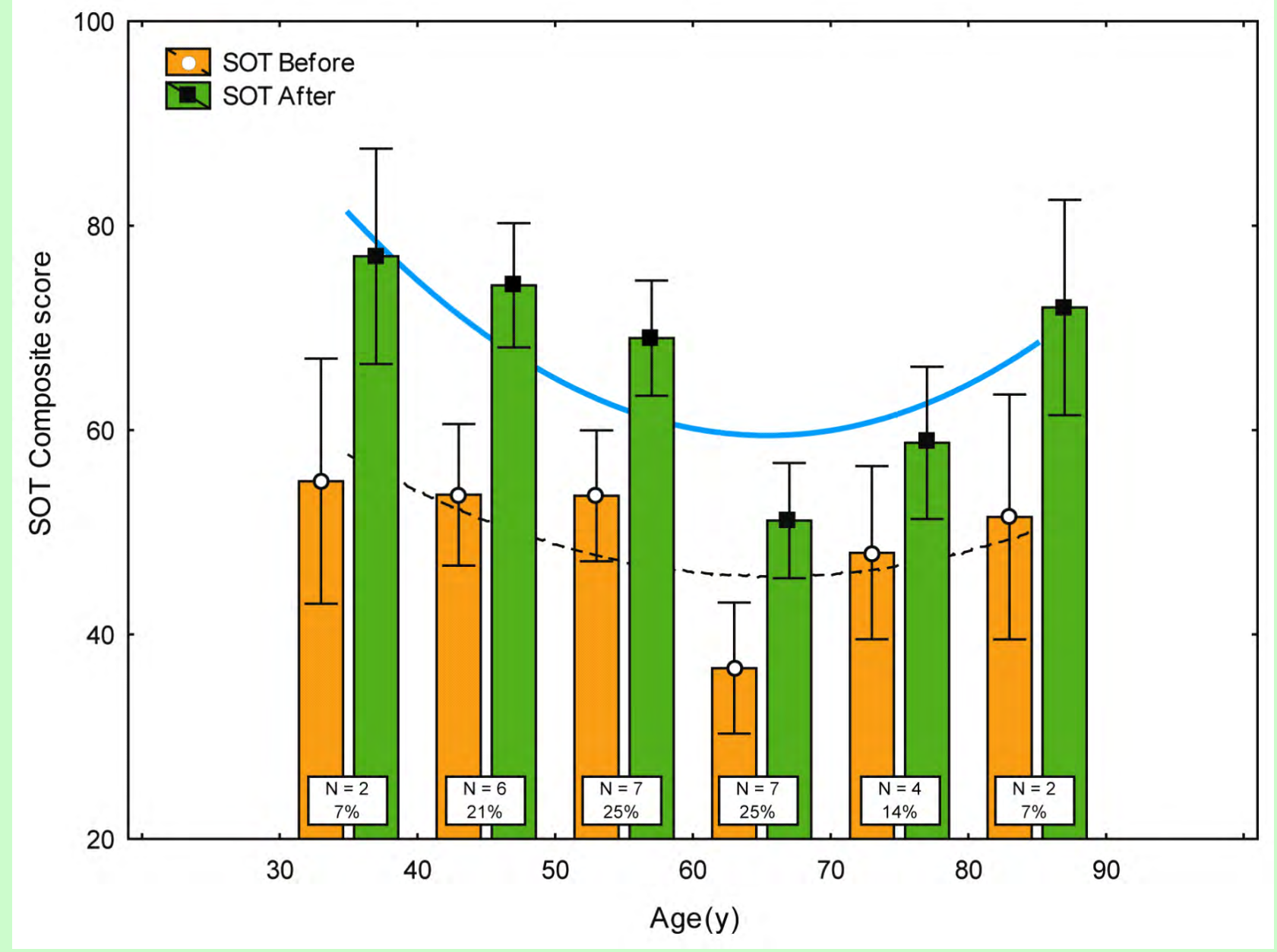


Figure 8. Scope of Patients
N=50

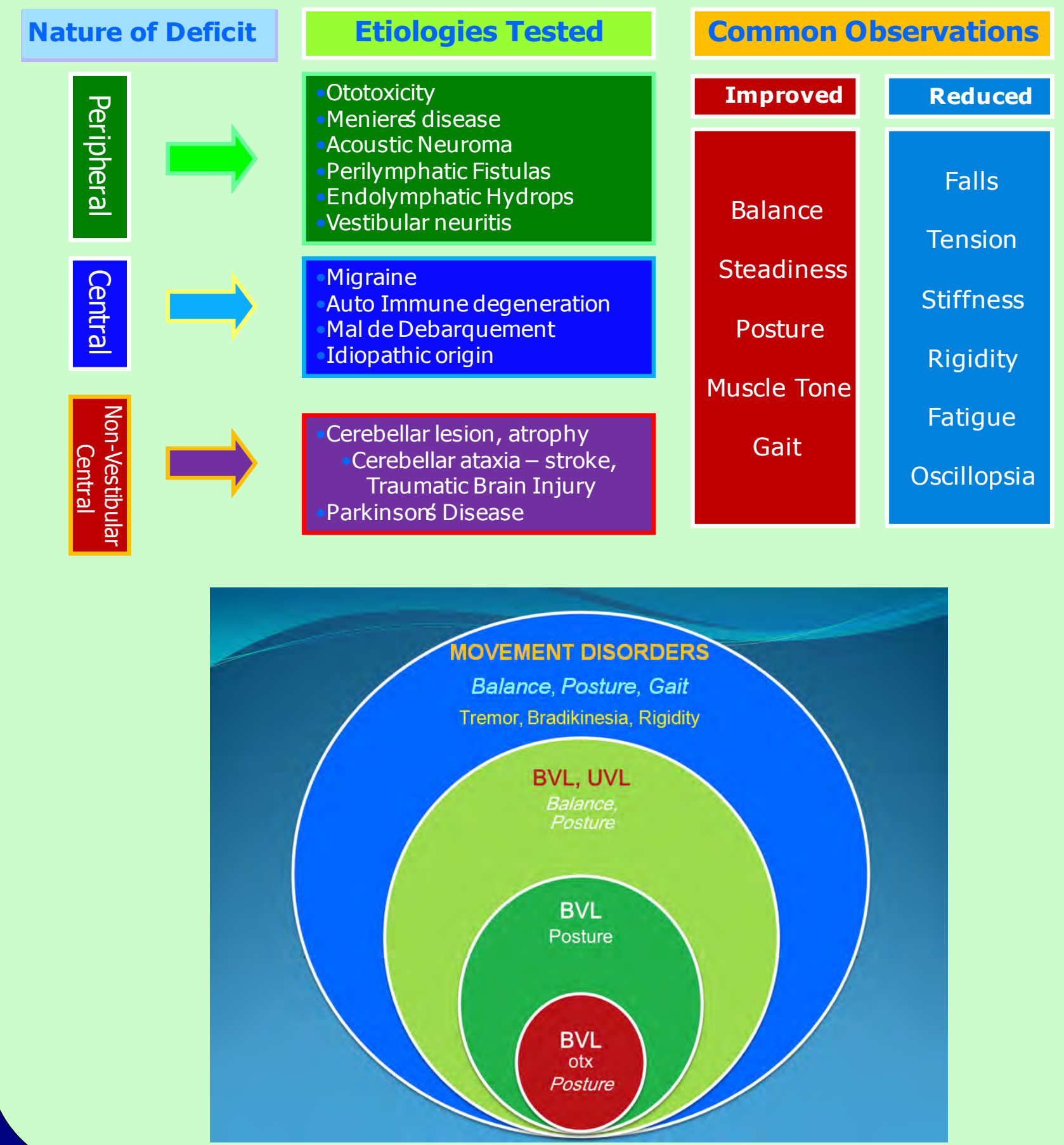
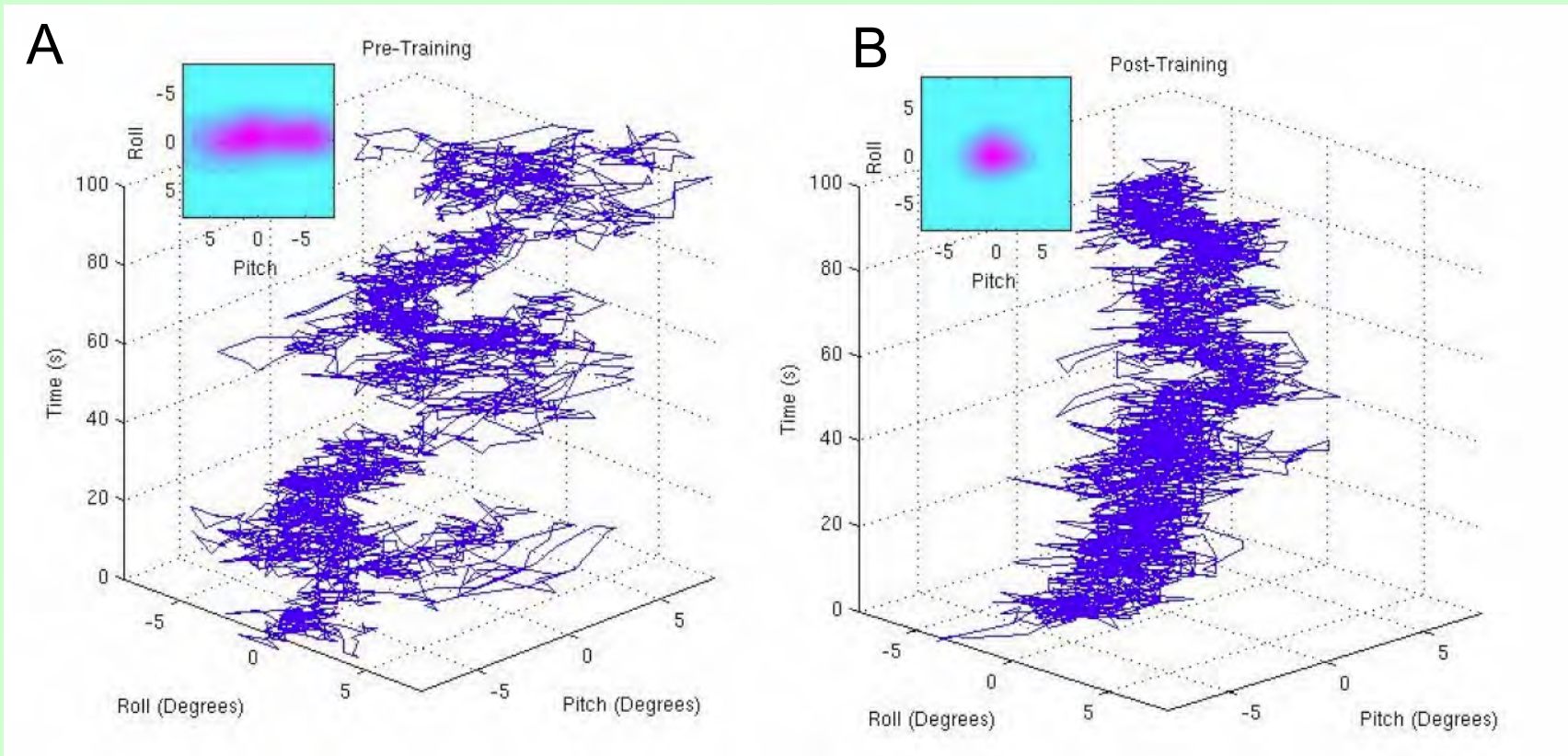


Figure 9. Head-Postural Stabilograms



Before CN_NINM Training

After CN-NINM Training

Head-Postural Stabilograms for one subject while standing, feet together, eyes closed, at

A - Baseline (no training), and

B - After 5 days of twice-daily CN-NINM training. Inset is a density plot of mean head position over trial. Both pitching and drifting in the Fore-Aft plane are significantly reduced, indicating greater postural stability.

TEST RESULTS

Table 1. Summary of Results from Various Tests of Stability and Gait on 5 Subjects. Changes greater than 5% are considered clinically significant improvements in performance.

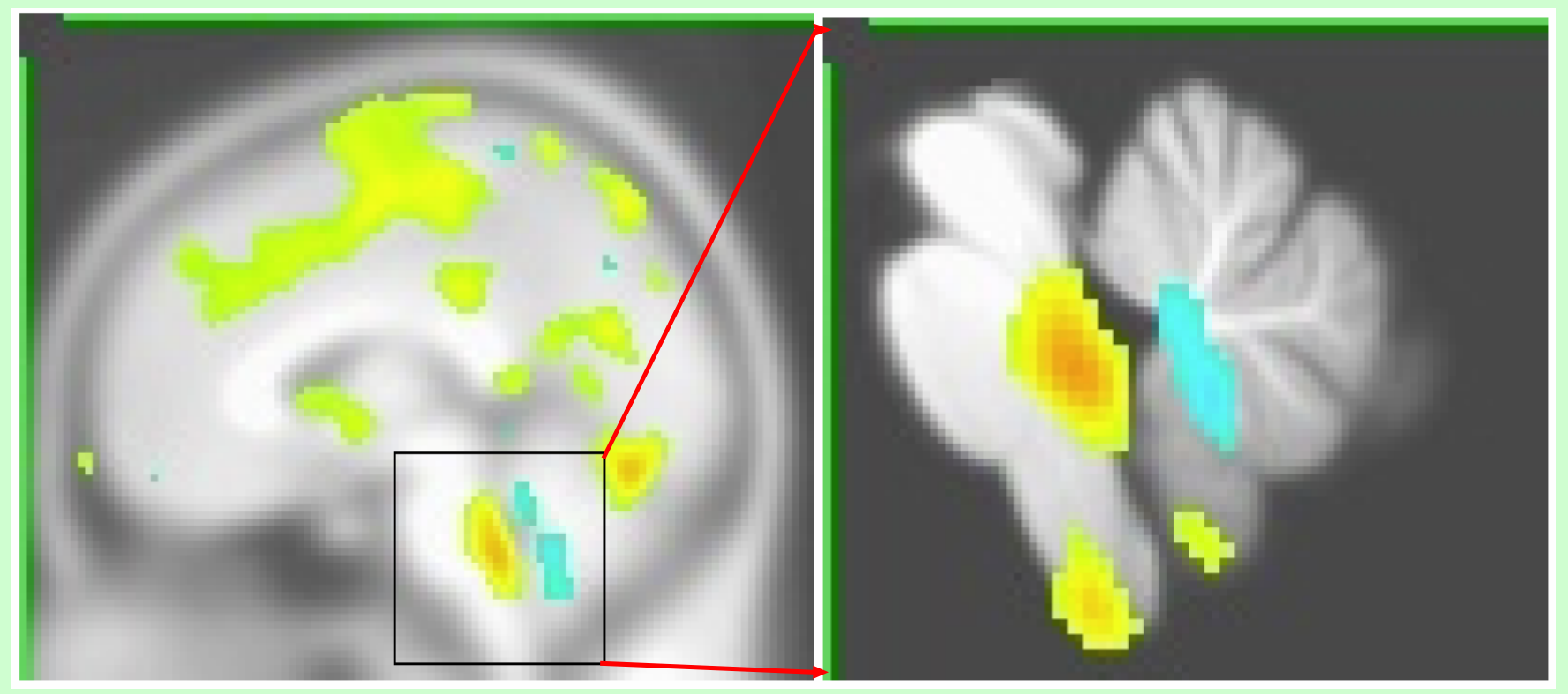
	Subject #						
Calculated % Improvement After CN-NINM Training	01	02	03	04	05	Mean	SD
Activity-Specific Balance Confidence (ABC)	3	12	49	10	16	**18.0**	16.1
Dizziness Handicap Index (DHI)	130	154	81	41	71	**95.4**	41.0
Dynamic Gait Index (DGI)	4	2	52	8	5	**14.2**	19.0
Head - Postural Stabilogram (HPS)	58.1	33.8	22.9	45.4	57.1	**43.5**	15.2

As can be seen in the results of these tests (Table 1), all subjects exhibited improved scores on both theself-assessment (ABC & DHI), and functional measures of postural and gait behavior (DGI and stabilography)as a result of NINM training. Scores on the standardized tests exhibiting changes greater than 5% are considered clinically significant improvement in performance.

The results indicate that while individual differences varied widely, and are dependent on both the subjects' initial condition and unique symptoms,every subject improved their postural control.

The results also indicate that subjects perceived themselvesas being more stable and less 'dizzy' after CN-NINM training (ABC & DHI), and in fact were more stable asindicated by the stabilography scores. They also indicate that the DGI is not a particularly sensitive metricfor this relatively ambulatory population.

Figure 10. Results of fMRI imaging



Diagrams of ensemble differential neural activity

[After CN-NINM training – Before training] from 5 subjects while viewing dynamic visual stimuli.

A - Saggital view of whole brain with head facing to left.

B - Enlarged & enhanced section showing detail activation of thebrainstem, pons, midbrain, and cerebellum. Color map indicates relative difference in the magnitude of activation after CN-NINM ($p<0.10$). Red represents the highest increase, occurring in the posterior aspect of the pons varolli, and in the primary visual area of the occipital lobe.

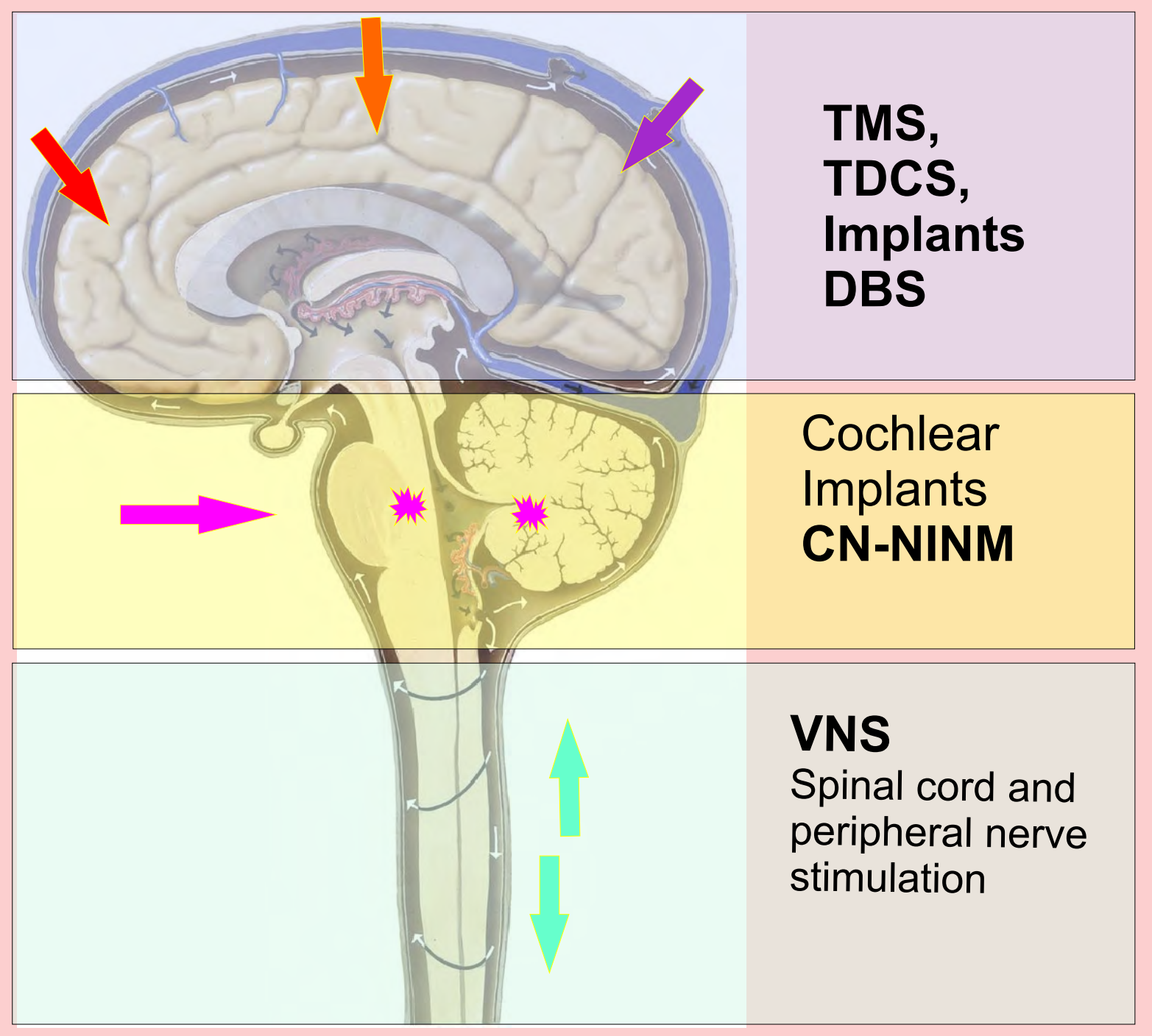
Teal indicates decreased activation in the cerebellum following CN-NINM.

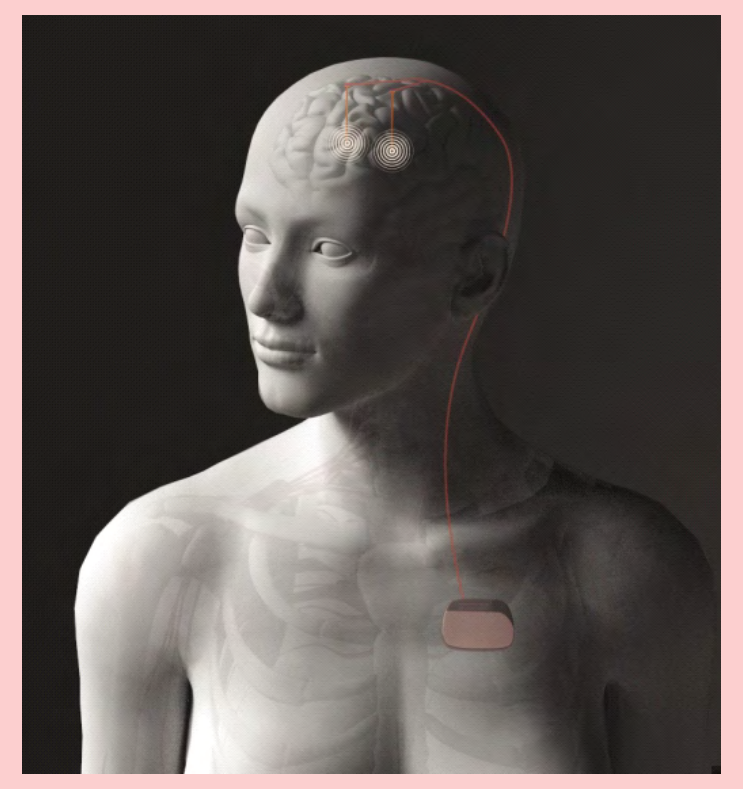
MORE ABOUT fMRI IMAGING RESULTS ON POSTER 454.9

"CRANIAL NERVE NON-INVASIVE NEUROMODULATION (CN-NINM) EFFECTS ON CORTICAL aND SUB-CORTICAL ACTIVITY AS MEASURED WITH BOLD-FMRI"

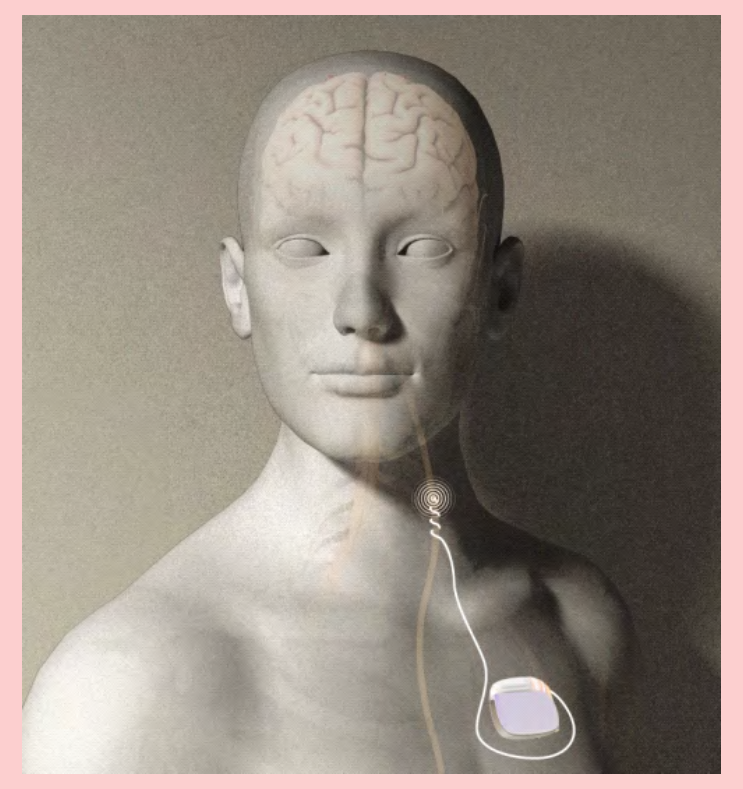
DISCUSSION

Figure 11. Levels of Neuromodulation



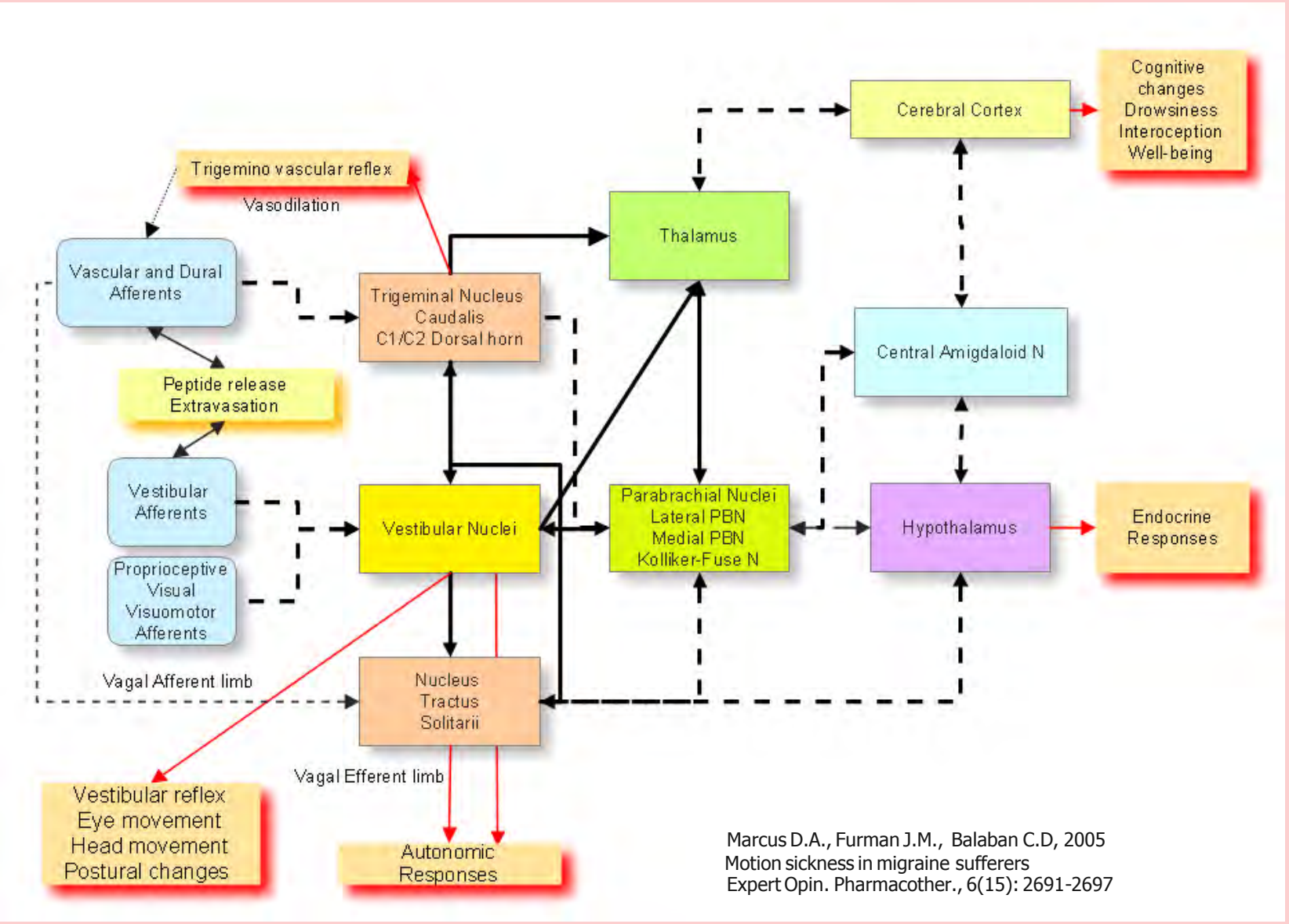


Deep Brain Stimulation (DBS)



Vagal Nerve Stimulation (VNS)

Figure 12. Potential targets of CN-NINM



TC&N Lab historically was deeply involved in development of theoretical and practical applications of brain rehabilitation.

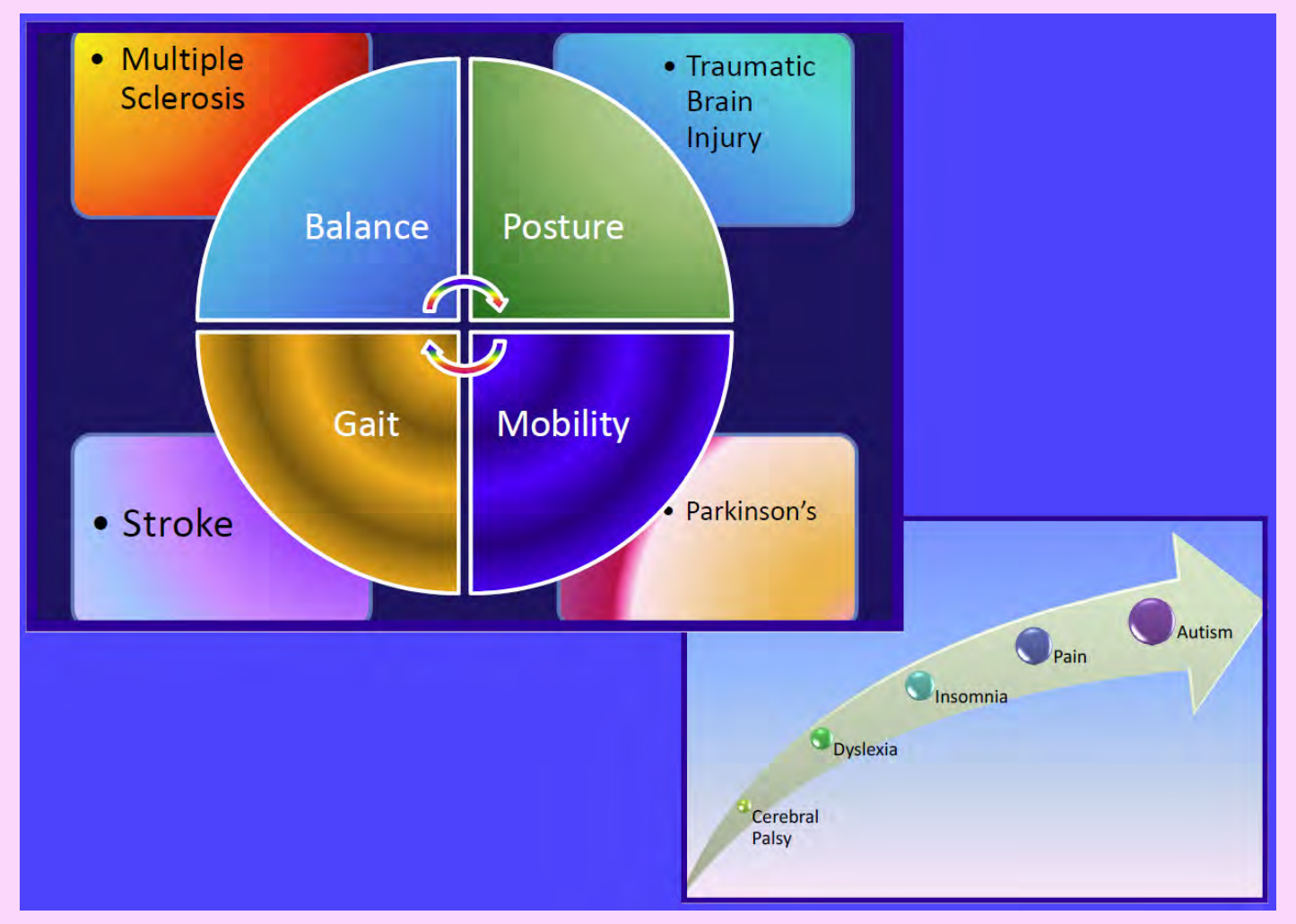
Founder and for many years leader of our laboratory, Professor Paul Bach-y-Rita was well known pioneer in discovery and introduction of brain plasticity concept in modern neuroscience. His research of sensory loss and cerebral damage in human lead him to concept of sensory substitution and new approach for development of neuroprosthetic devices.

In 2007, our group developed the new generation of neurorehabilitation technology, specifically oriented on targeted and controlled stimulation of the brain to induce neuroplasticity and actively initiate neurorehabilitation processes in traumatized brain. These induced changes may be targeted to specific brain regions, structures, or functions, or they may be more global in nature.

So far, our suggested method is the only method of neuromodulation applied from outside the body and primarily targeted on subcortical levels of brain, namely brainstem and cerebellum. Physically and physiologically CN-NINM is oriented on targets, that laying in between points of application of known invasive DBS and VNS stimulation methods.

A new technology called cranial-nerve non-invasive neuromodulation (CN-NINM) has been developed to improve the brain's ability to reorganize and "normalize" its activity during special physical and occupational therapy exercises. CN-NIMN is related to an existing successful, commercially-available technology for treating balance disorders, but is designed specifically for movement disorders beyond balance and is being optimized for faster, longer-term reduction of symptoms.

Future Development



- The non-invasiveness and ability to control the neurostimulation is a critical component, and may be optimized to treat disease-specific symptoms and be customized for each patient.
- The CN-NINM is not a substitute for existing therapy, but rather extends and enhances it by activating and facilitating brain plasticity via mechanisms that are as yet not well understood.
- CN-NINM stimulation may be combined with regular PT and OT techniques to achieve an optimal therapeutic regimen for each disease of group of symptoms.
- CN-NINM stimulation can also work together as an assistive tool for all current neuromodulation methods such as DBS, VNS, or pharmaceutical techniques.
- CN-NINM could also work as a preventive procedure in the early stages of diseases such as Parkinson's, Alzheimer's, or dementia.
- Furthermore, CN-NINM could be applied to children, whose brains are still in a highly developmental stage and are therefore most sensitive to modulation for treatment of the identified symptoms of autism or sensory integration hypofunction.

CONCLUSION

Based on our prior research, we postulate that NINM induces resynchronization of sensory-motor coordination of both head and body control, leading to improved functional balance and gait.

We believe that neuromodulation of the brainstem and cerebellum via cranial nerves that enervate the tongue (CN-V and CN-VII), exciting primarily the trigeminal nuclei complex, nucleus tractus solitarius is principally responsible for the observed this functional neurorehabilitation.

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