

# Effects of Cranial-Nerve Non-Invasive Neuromodulation (CN-NINM) on neural activity as measured by BOLD-fMRI

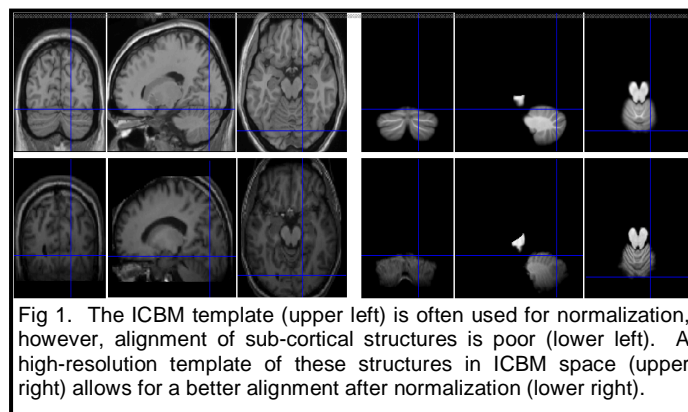
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**Introduction:** Direct electrical stimulation of the nervous system is successfully used in the treatment of neural disorders such as Parkinson's disease (DBS), epilepsy (VNS), and sensory-neural deafness (cochlear implants). Previous work has shown the feasibility of using the tongue as a route to deliver non-invasive electrical signals to the brain through the cranial nerves with afferent glossal innervation (1). 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). A previous study on sensory-substitution in vestibular patients revealed an unexpected result: unlike in other uses of vestibular feedback or neurostimulation such as DBS, the effects of CN-NINM through the tongue persist after the stimulation has been removed (2). Behavioral and subjective measures remain elevated compared to baseline days and even weeks after therapy.

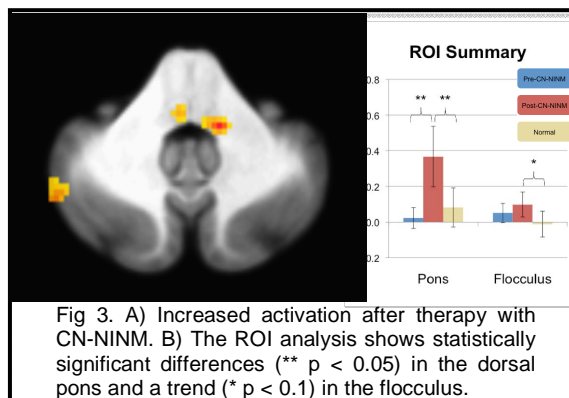
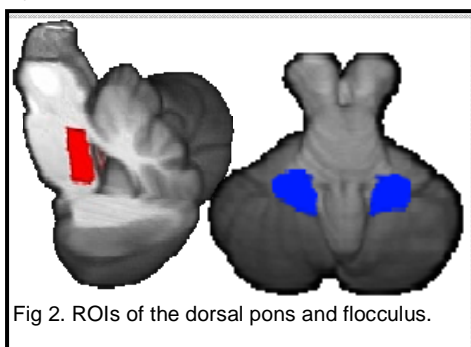
**Purpose:** Here we present the results of a functional magnetic resonance imaging (fMRI) study intended to reveal local changes in neural activity after therapy with CN-NINM as measured by blood oxygen level dependent (BOLD)-fMRI. Using optical flow designed to induce the sensation of self-motion through stimulation of the balance integration centers, patients with balance disorders were scanned before and after therapy with CN-NINM to detect changes in neural activity. We also scanned healthy controls without any exposure to CN-NINM to compare the neural activity before and after therapy to people without balance dysfunction.

**Methods:** Six patients with various balance dysfunction etiologies 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. Patients DID NOT receive CN-NINM during the MRI scans. Optical flow was presented in the scanner during EPI acquisition to activate the vestibular system. The SUIT template (3) was used to normalize the sub-cortical structures separately as these small structures do not align well using standard normalization procedures (Figure 1). Data was processed with AFNI and SPM5 and corrected for motion, heart and respiratory measures. A region of interest (ROI) was drawn over the dorsal pons and flocculus (Figure 2).



**Results:** ROI analysis reveals increased activity in the dorsal pons in response to optical flow in every patient after therapy with CN-NINM compared to before therapy. A paired t-test of these changes is significant ( $p < 0.05$ ), and a 2-sample t-test shows a significant difference between patients after therapy compared to controls (Figure 3). The ROI analysis of the flocculus shows a trend toward increased activity in patients after training compared to controls ( $p < 0.1$ ). Voxelwise analysis also shows decreased activity in the primary visual cortex and increased activity in pre-motor areas and the anterior cingulate gyrus after therapy with CN-NINM.

**Conclusions:** CN-NINM modulates neural activity in the dorsal pons, and this modulation remains even when stimulation has been removed. The behavioral and neural changes seen after CN-NINM therapy can be explained by improved processing of sensory input to the dorsal pons. Cortical activity changes mirror expected changes due to this improved sensory processing. Finally, this study confirms previous work showing decreased activation of the visual cortex in response to optical flow in patients with vestibular dysfunction(4,5).



## References:

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