**Wendy Chen**

PGY2 Scholarly Project Proposal

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**Mentors:**

Dr. Amy Nau, Dr. Valeria Fu.

**Project Title:**

Investigation of cortical plasticity using VEP measurements before and after training on the BrainPort™ Vision Device.

**Clinical Significance:**

Epidemiologic data indicate that blindness (20/200 best corrected acuity) affects nearly one million adults older than 40 years old in the United States (http://www.nei.nih.gov/eyedata). Age-related macular degeneration, cataract, glaucoma, and diabetes are among the leading causes of blindness, and the prevalence of these conditions increase significantly with age. Owing to the aging of the U.S. population, it is estimated that the number of blind persons will increase to 1.6 million by the year 2020 and result in an increase in morbidity as well as health care costs. Therefore, the development of vision-assist devices which help the blind to gain functional independence is crucial. The BrainPort™ Vision Device, which is based on the principles of sensory substitution, has shown excellent potential for providing surrogate vision to blind persons. Although it is hypothesized that adult plasticity plays an important role in visual rehabilitation, there has not been a systematic study that directly demonstrates plasticity over a period of training with the BrainPort™ Vision Device (or other artificial vision prototypes). The goal of this project is to investigate whether cortical plasticity is demonstrated over the course of training on the BrainPort™ Vision Device by measuring visually evoked potentials (VEPs) before and after training. If VEP waveforms are found to be more robust after a period of training, this would provide strong evidence that adult plasticity does in fact occur and play an important role in visual rehabilitation. This finding would also support the use of VEP recordings as a low-cost, objective measure of efficacy of the BrainPort™ Vision Device and provide a screening tool with which to identify potential candidates that may benefit from use of the device.

**Hypothesis:**

Training on the BrainPort™ Vision Device results in a measurable change in the VEP waveform of blind, but not sighted subjects.

**Specific Aims:**

1. To show that prior to training, control sighted subjects and blind subjects have little to no visual cortical activation by tongue stimulation mediated by the BrainPort™ Vision Device as measured by VEPs.
2. To show that after >40 hours of training on the BrainPort™ Vision Device, the resultant VEP waveform differs from the pre-training VEP waveform.
3. To compare differences in pre- and post- training VEP waveforms between study groups – control (sighted), congenitally blind, and congenitally blind.

**Background:**

How experience modifies the brain is a central question to neurobiologists. Over the course of development, the visual system gradually matures under the influence of sensory experience. That is to say, normal visual experience is crucial for correct wiring of the visual system. We know this is the case because disrupting normal visual experience during a critical period of postnatal development can profoundly alter the development of visual cortical properties such as refinement of receptive fields, orientation/direction selectivity, and visual acuity. It was once thought that visual cortical neurons were susceptible to this type of refinement only during the critical period, when neurons are “plastic”. However, there is a growing body of evidence that visual cortical neurons actually remain plastic even past the critical period, well into adulthood. These findings are intriguing and have great clinical relevance, particularly in the restoration of neurosensory function lost either through congenital defects or acquired injury [1].

Human subjects that have lost vision due to interruption of the visual pathway provide a remarkable means to study adult plasticity. Numerous anecdotal reports indicate that blind individuals have a heightened sensation through other modalities, particularly touch and hearing. This notion has been confirmed by studies showing enhanced tactile spatial resolution [2], auditory pitch discrimination [3], and spatial sound localization [4] in blind subjects. However, the mechanisms by which these individuals develop heightened sensorium have not been fully elucidated. One prevailing hypothesis is that the normal architecture of primary visual cortex (V1) in humans receives input from multiple sensory modalities. In normal sighted individuals, the predominant input to V1 comes from the traditional visual pathway comprised of neural connections from the retina to the lateral geniculate nucleus (LGN) to V1. However, this pathway is disrupted in blind patients; inputs to V1 bypass the retina-LGN-V1 route and arrive via alternative cortico-cortical or thalamo-cortical inputs from the remaining senses. Evidence for these alternative connections come from anatomical tracing studies [5] and electrophysiologic studies [6] in primates. Evidence for cross-sensory input to V1 in humans comes from less invasive studies using PET imaging and transcranial magnetic stimulation [7]. Whether the strengthened cross-sensory input reflects unmasking of previously existing anatomical connections versus growth of new anatomical connections has yet to be determined and remains an active area of investigation.

Vision assist devices such as the BrainPort™ Vision Device (Wicab, Madison WI) take advantage of cross-sensory input to enhance independent functioning in blind individuals. The premise behind this device is to use sensory substitution in the form of tactile stimulation to the tongue as a surrogate representation of objects within the visual field. To do so, the BrainPort™ Vision Device translates visual information detected by a digital camera into tactile stimulation to the tongue by gentle electrical pulses presented in a topographically oriented pattern [8]. Remarkably, test subjects have been shown to have increased acuity when tested with the tumbling E chart after just 7-9 hours of training on this device [9], suggesting that it has excellent potential for providing surrogate vision to blind individuals within a short period of training. Furthermore, test subjects have increased regional cerebral blood flow in the visual cortex following training [10]. Therefore, one may hypothesize that the visual cortex is recruited via cross-modal activation during training on the BrainPort™ Vision Device and that this recruitment is an important mechanism for gaining benefit from the device. To investigate whether this may be true, I propose to examine activation of the visual cortex using clinical recordings of visually evoked potentials (VEPs) before and after training on the BrainPort™ Vision Device.

Measuring VEPs from test subjects would be a non-invasive and objective method to interrogate the potential of the visual cortex for functional reorganization after training on the BrainPort™ Vision Device. Analogous to these experiments, data from auditory substitution for vision devices show that auditory events evoke measurable activity of the visual cortex after training on a sound localization task in blind, but not sighted individuals [11]. If blind individuals also show more robust activation of the visual cortex following training on the BrainPort™ Vision Device, these findings would support cross-sensory activation as a mechanism of visual adaptation. Furthermore, this would be strong evidence that adult plasticity does in fact occur and play an important role in visual rehabilitation. Finally, this study would provide an important basis for using VEP recordings as a low-cost measure of efficacy of the BrainPort™ Vision Device. This will be advantageous as the BrainPort™ Vision Device becomes more widely available as a vision assist device, and it may assist the ophthalmology community in identifying candidates that may benefit from the device [12].

**Methods:**

1. Study Design

The primary aim of the study is to compare VEP recordings from the occipital cortex before and after training on the BrainPort™ Vision Device in five groups of study subjects – control (sighted), congenitally blind, and acquired blind. The acquired blind group can be further subdivided based on the duration of blindness – blind < 1 year, blind 2-5 years, blind 6-10 years, and blind > 10 years. The study subjects will be recruited through the patient population at the UPMC Eye Center and the Blind and Vision Rehabilitation Services of Pittsburgh based on the following inclusion and exclusion criteria. Note that the inclusion and exclusion criteria listed include criteria based on a larger study protocol where the same study subjects will undergo additional testing other than VEP recording; the criteria not immediately relevant to VEP testing are denoted by an asterisk (\*):

Inclusion criteria

Volunteer subjects enrolled and treated in this study must meet all of the following criteria:

a. Over 18 years of age

b. Male or female

c. Blind (documented visual acuity of light perception or worse) or not blind (normal sighted controls)

d. Able to read (or have read to him or her), understand and sign the Informed Consent form

e. Able to provide valid feedback regarding use of the Brainport device

f. Able to tolerate functional neuroimaging tests (PET) \*

g. Able to walk and stand independently (previous training) \*

Exclusion criteria

Subjects will be excluded from the study if they meet any of the following criteria:

a. Current oral health problems as determined by the subject’s history and an examination of the oral cavity performed by a member of the study team, including:

- A history of injury to the tongue resulting in impaired sensation or use of the tongue,

- Visible open lesions, cold sores, abrasions, blisters, or rash on the tongue,

- Numbness or lack of feeling of the tongue,

- Oral surgery or dental work in the past 3 months or anticipated to occur for the duration of participation in the study (does not include routine dental health exams/cleanings).

- Piercing on the tongue.

- Current smoker (anecdotal evidence that sensation of the tongue is impaired in smokers).

- Presence of any foreign metal in the body with the exception of dental fillings will need to be screened by radiology prior to enrollment \*

- Breastfeeding \*

b. Any medical condition that would interfere with performance on mobility evaluation tests \*

c. Known neuropathies of tongue or skin tactile system

d. Prior exposure to the BrainPort™ Vision Device

e. Unwilling or unable to adhere to all study requirements, including completion of the training period and evaluation tests

f. Implanted electrical medical devices such as pacemakers \*

g. Pregnancy \*

h. Cortical blindness from any cause

i. Claustrophobia that would prevent functional neuroimaging \*

j. Severe depression

Training and testing schedule

Enrolled study subjects undergo a baseline ophthalmologic exam, including detailed history of the condition leading to blindness. Baseline VEPs are then recorded from the study subject. Each study subject will undergo an initial training and orientation session followed by 5 separate 2.5 hour formal training sessions on the BrainPort™ Vision Device. The training will proceed in a step-wise fashion. After a brief introduction to the use of the device (how it is worn and operated by the user) the study subject will first be trained to use the device to perceive high contrast objects that they are allowed to explore with their hands (i.e. a white foam bar held against a black background). Second, the study subject will be trained to view a 2-dimentional high contrast objects against a black background and asked to identify and determine the orientation of the object. Third, the study subject will be trained to locate and identify high contrast objects (both static and dynamic) in space and asked to retrieve these objects with their hands. Fourth, the study subject will be trained to recognize distinguishing features of objects presented in the visual space. Fifth, the study subject will be trained to use the device to help recognize obstacles, doorways, and hallway intersections during a supervised walking task. Next, the study subject will be trained to use the device to incorporate object feature detection while maneuvering in an indoor and outdoor environment during a supervised walk. Finally, the study subject will be trained to use the device to actively explore the environment during a “hide and seek” task, incorporating all parts of the previous training. Following these sessions of intense training, VEPs are again recorded. All training and testing sessions are to be completed within a 3-4 week time frame.

2. BrainPort™ Vision Device

The BrainPort™ Vision Device (Wicab, Madison WI) is a vision assist device designed to translate visual information detected by a digital camera into tactile stimulation to the tongue by gentle electrical pulses [8]. The aim of the device is to provide information about object location, size, and shape to subjects who are blind or have very low vision. Visual information is detected by a digital camera mounted to a pair of glasses that can be worn by the subject and relayed to a controller device. The controller device converts the visual information into a black/white “image” that is output to a 3 cm X 3 cm intraoral device that provides electrical stimulation pulses to the subject’s tongue at the points of contact with an array of 400 stainless steel electrodes. The controller device allows the subject the ability to control the stimulus intensity up to 17V. The design of the device also allows the subject to zoom in on objects within the visual, adjust the field of view (range 3 to 90 degrees), and invert contrast of the images. However, for experimental testing purposes, the zoom and field of view are held constant during testing. Contrast is fixed at the highest contrast level during stimulus presentation. The patient is allowed to adjust the stimulation intensity to detect a threshold level of stimulation reliably with each stimulus presentation while minimizing discomfort associated with electrical pulses to the tongue. Additionally, an external BrainPort™ Monitor can be used by the test administrator to monitor detection of external visual stimuli by the digital camera to ensure reliable and faithful detection of visual stimuli presented.

3. Visually Evoked Potentials (VEPs)

VEP recording is a non-invasive method to interrogate the integrity of the visual pathway from the retina to the visual cortex as well as measure visual cortical activity from potential non-retinal inputs. A modified VEP protocol used at the UPMC Eye Center will be utilized in this study, based on clinical standards recommended by the International Society for Clinical Electrophysiology of Vision [13]. Modifications to the standard protocol include a lower stimulation frequency (0.25Hz versus 1-1.5Hz) and an increase in number of presented stimuli (250 versus 60-80). Gold disc recording electrodes are placed on the scalp in relation to bony landmarks – the nasion anteriorly and inion posteriorly. The active electrode is placed at the midline over the visual cortex at position Oz (approximately 1 inch above the Inion) for the purpose of recording VEPs. A second active electrode is placed at position Pz (approximately 3 inches above the inion) to serve as a positive control for detection of the tongue stimulus presented by the BrainPort™ Vision Device. The reference electrode is placed at the midline over the frontal lobe at position Fp (approximately 1 inches above the nasion). The ground electrode is placed over the earlobe. The BrainPort™ Vision Device’s detection camera is placed directly in front of the Ganzfeld dome for detection of flash stimulus for full field illumination at a rate of 0.25Hz. The resultant VEP waveform is captured by the recording software (EM for Windows). VEPs from one trial of 250 stimulus presentations are averaged, and two total trials are run for each test subject. Test subjects who are sighted or have LP vision are blindfolded, and in all test cases, the Ganzfeld dome is covered with a black cloth to prevent activation of the retina-cortical pathway inadvertently. Pre- and post- training VEP recordings will be performed following >40 hours of training on the BrainPort™ Vision Device in accordance with the study protocol testing schedule.

4. Sample size

At present, 6 control sighted individuals have undergone baseline VEP recordings. Another 37 individuals with LP or worse vision are currently enrolled in the study based on the above inclusion and exclusion criteria and can be parsed out into either congenitally or acquired blindness based on their medical and ophthalmic history. Based on preliminary data from Wicab studies using the BrainPort™ Vision Device, an n = 6 for each study group is needed to achieve statistical power. However, the preliminary data from Wicab is based on visual function and radiology imaging studies rather than VEP data. Thus, an accurate power calculation cannot be performed at this time. It is certainly possible that n = 6 will be insufficient to attain statistical significance, particularly since the VEP is a crude measure of visual cortical activation. In that situation, the preliminary data gathered in this study will serve as pilot data to allow us to perform an appropriate power calculation based on VEP data. This information will help guide an increase in the number of enrolled subjects should additional subjects need to be recruited.

5. Outcome measures

The primary outcome measure of this study is the VEP amplitude and latency of study subjects in three groups of study subjects – 1) control sighted, 2) congenitally blind, and 3) acquired blind. VEP recordings will be analyzed by amplitude and latency of the N2 and P2 peaks, the most robust components of the prototypical flash VEP [13]. The amplitude and latency of N2 and P2 peaks will be calculated pre- and post- training, and these results will be compared across the three groups of study subjects tested. Statistical analysis will be performed using an analysis of variance (ANOVA). If statistical significance is detected, the data will undergo further post-hoc analysis to determine which group(s) resulted in significantly different VEP waveforms pre- and post- training. Furthermore, subgroup analysis can then be performed, including the effect of the duration of acquired blindness (blind < 1 year, blind 2-5 years, blind 6-10 years, and blind > 10 years).

The secondary outcome measure of this study is the correlation of pre- and post- training VEP amplitude and latency to the following test subject characteristics: 1) Age at the time of VEP recording, 2) Age of onset of blindness, and 3) Duration of blindness. The correlation coefficient for each of these sets of data will be calculated. However, the final statistical method employed will depend on whether the data are linearly or nonlinearly related.

**Resident role in the project:** XYZ

**IRB status:** approved. I plan to complete the appropriate research training modules by July 1, 2010 so that I may be added to the research group.

**References**

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