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Functional MRI of Sensory Substitution in the Blind

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Abstract

Visual cortex functionality in the blind has been shown to shift away from sensory networks toward task-positive networks that are involved in top-down modulation. However, how such modulation is shaped by experience and reflected behaviorally remains unclear. This study evaluates the visual cortex activity and functional connectivity among congenitally blind, acquired blind, and sighted subjects using blood-oxygenation-level-dependent functional MRI during sensory substitution tasks and at rest. We found that primary visual cortex activity due to active interpretation not only depends on the blindness duration, but also negatively associates with behavioral reaction time. In addition, alterations in visual and task-positive functional connectivity progress over the duration of blindness. In summary, this work suggests that functional plasticity in the primary visual cortex can be reshaped in the blind over time, even in the adult stage. Furthermore, the degree of top-down activity in the primary visual cortex may reflect the speed of performance during sensory substitution.

I. Introduction

Vision loss is an increasingly serious public health problem. According to the American Community Survey by the Bureau of the Census, 25 million American adults age 18 and

older reported significant vision loss. In addition, about 485,000 children age 18 or younger in the United States reported experiencing difficulty seeing. It is known that blindness causes alterations in the structure and function of regions of the brain devoted to vision by a process termed neuroplasticity. However, development of the visual system is highly dependent on experience, and how this prior experience impacts neuroplasticity and behavior following visual deprivation remains unclear. Understanding plasticity of the visual system and developing biomarkers to non-invasively measure its effects are critical for vision restoration devices. For example, sensory substitution devices can provide indirect visual perception to blind patients using alternative, intact senses and existing neural connections including the visual cortex [1, 2]. However, little is known about the neural mechanisms through which multisensory processes interact with one another to influence perception and behavior in the blind.

Visual plasticity can be observed through alterations in brain activity and connectivity as measured by magnetic resonance imaging (MRI) [3, 4]. Recently, we used functional MRI with a sensory substitution task to investigate plasticity due to blindness, and observed increased top-down influence in the visual cortex in both congenitally and acquired blind subjects [5]. In addition, functional connectivity of the visual cortex appeared to shift away from sensory networks toward task-positive networks that are involved in top-down modulation [5, 6]. While visual cortex functional remodeling may differ between congenitally blind subjects and those who lose vision later in life [5], whether these brain changes and the corresponding top-down influence accrue over time in congenital and acquired blindness remains uncertain. In this study, we aim to model the effects of prior visual experience on training-induced visual cortex modulation by measuring brain activity and connectivity along with behavioral outcomes in the blind across duration of blindness.

II. Methods

A. Subjects

Four congenitally blind subjects (age= 50.8 ± 17.5 years), 7 acquired blind subjects (age= 45.4 ± 16.6 years), and 11 sighted controls (age= 49.9 ± 16.2 years) were examined for this sensory substitution functional MRI study (mean $\pm$ standard deviation, $p = 0.82$ for ANOVA on age), whereas 7 congenitally blind subjects (age= 55.4 ± 13.7 years), 11 acquired blind subjects (age= 53.8 ± 16.0 years), and 18 sighted controls (age= 54.4 ± 14.3 years) were examined for the resting-state functional connectivity study (mean $\pm$ standard deviation, $p = 0.97$ for ANOVA on age). All studies were performed using a 3 Tesla Siemens Allegra MRI scanner (Siemens, Erlangen, Germany) after obtaining informed written consent. Sighted subjects wore a blindfold for all scans and training. Complete demographic information and methodological details on functional MRI experimental settings have been previously described [5]. All studies were approved by the University of Pittsburgh Institutional Review Board.

B. Task-based functional MRI experiment

Subjects who were naïve to the vOICE auditory sensory substitution device [7] were presented a series of soundscapes that represented bars moving across the image in one of

four directions (left, right, up and down). In order to examine top-down influence on the visual cortex during sensory substitution, each subject underwent two block-design blood-oxygenation-level-dependent (BOLD) functional MRI scans with identical sound stimuli within the same experimental session in the scanner. Subjects first passively listened to soundscapes without any prior knowledge of the vOICe (Pre-training). Immediately after the pre-training scan, subjects were instructed on how images are encoded as soundscapes and asked to actively interpret the sounds as images during the second scan (Post-training). They also responded with a keypad placed in their right hand as soon as they could discern the direction of motion. E-prime software (Psychology Software Tools, Inc. Sharpsburg, PA, USA) was used for presenting the stimuli and recording keypad responses while subjects were in the scanner, and sounds were played through a pneumatic headphone system (Avotec, Inc., Stuart, FL, USA). Reaction time was recorded by the E-prime software.

BOLD functional MR images were collected with a single-shot gradient-echo echo-planar-imaging pulse sequence with the following parameters: 2 s repetition time, 26 ms echo time, 104×104 imaging matrix over a 20.5×20.5 cm² field-of-view, and 28 contiguous 3.24 mm thick axial slices to cover the entire occipital lobe. The block design consisted of 15 trials with alternating 14 s of rest and 10 s of task. We calculated activation maps for each subject using a combination of SPM8 subroutines (<http://www.fil.ion.ucl.ac.uk/spm>) and in-house software implemented in MATLAB (Mathworks, Natick, MA, USA). Images underwent slice timing correction and realignment, were normalized to Montreal Neurological Institute (MNI) space [8], masked with a subject-specific gray matter mask, and smoothed with a Gaussian kernel [full-width half-maximum (FWHM)= 8 mm]. The time course of each voxel was fitted with a general linear model with predictors including the stimulus paradigm convolved with a canonical hemodynamic response function, the temporal derivative of this predictor, realignment parameters, the average time courses from the white matter and the cerebrospinal fluid to control for physiological noise, and a constant. BOLD activation maps were calculated by dividing the coefficient of the stimulus paradigm predictor by the coefficient of the constant term. To display the average activation maps within each group both before and after training, all of the individual activation maps were modeled with a general linear model with 6 predictors (one for each combination of group and pre- versus post-training), and average activation maps were tested with the corresponding t-test. T score maps summarizing the results of the voxel-wise testing were thresholded at a family-wise error (FWE) corrected $p < 0.05$ (uncorrected $p < 0.01$, cluster size > 213 voxels). The average BOLD% change was calculated in 3 regions of interest (ROIs) corresponding to the primary visual cortex [Brodmann area (BA) 17], secondary visual cortex (BA 18), and tertiary visual cortex (BA 19) with reference to a publicly available atlas in the MRICron software package. To determine the degree of top-down modulation in the visual cortex, we subtracted the pre-training BOLD% change from the post-training BOLD% change (BOLD%) for each of the 3 ROIs in each subject. The relationships between BOLD% and duration of blindness or behavioral reaction time were then tested by non-parametric Spearman correlations. $P < 0.05$ was considered significant.

C. Task-free functional connectivity MRI experiment

We collected 8 min of BOLD functional images at rest using a single-shot gradient-echo echo-planar-imaging pulse sequence with the following parameters: 2 s repetition time, 25 ms echo time, 64×64 imaging matrix over a 20.5×20.5 cm² field-of-view, and 36 contiguous 3.24 mm thick axial slices. Images were preprocessed using a standard pipeline [5], and a visual functional connectivity map was then constructed for each individual by computing the average correlation coefficient between the visual cortex (using either striate or extrastriate cortex as the seed ROI) and each voxel in the brain. We then modeled the effects of visual experience by fitting these functional connectivity maps with a general linear model with predictors including duration of blindness, a dummy variable for congenital blindness, and the interaction of these two effects. T score maps of these effects were thresholded at a family wise error (FWE) corrected $p < 0.01$ (corrected at the cluster level). We also computed the average functional connectivity for each individual using voxels where significant effects were detected by voxel-wise analysis. We used 5 ROIs, which represent large modules of functional connectivity networks as provided by a previously published atlas [9]. These modules include somatosensory/motor, auditory/insula/limbic, task-positive, task-negative, and visual networks. Finally, we plotted functional connectivity versus duration of blindness in each of these ROIs by group and tested for correlation using a Spearman correlation to ensure results were not overly influenced by outlying blindness durations. P values of less than 0.05 were considered significant.

III. Results

A. Top-down activity in the visual cortex varies with duration of blindness and negatively associates with reaction time

Figure 1 shows the BOLD activation maps in the brains of sighted, acquired blind and congenitally blind subjects in response to a visual-to-auditory sensory substitution task before and after 10 min of training in the MRI scanner. While our sensory substitution task showed similar levels of negative BOLD response in the occipital visual cortex of sighted subjects before and after training likely due in part to cross-modal inhibition or deactivation [10, 11], both acquired blind and congenitally blind subjects showed increased positive BOLD responses in the visual cortex after training. Such findings indicate increased top-down modulation of the visual cortex in the blind but not sighted subjects following the short duration of training. When comparing the degree of top-down modulation in the visual cortex with behavioral performance and across duration of blindness (Fig 2), our further analyses showed a decreasing BOLD activity change in the primary visual cortex with increasing reaction time during sensory substitution. The degree of top-down modulation in the primary visual cortex of acquired blindness also negatively associated with increasing blindness duration.

B. Relationship between visual functional connectivity and duration of blindness depends on onset of visual deprivation

In addition to task-induced brain activity changes, we observed the plasticity of the visual system based on alterations in functional brain connectivity that accrue over time in congenital and acquired blindness using BOLD functional MRI at rest. The results of voxel-

wise statistical testing using a general linear model and the extrastriate cortex as the seed region of interest (ROI) are shown in Figures 3 and 4. When comparing congenitally and acquired blind subject, we found a statistically significant relationship between visual functional connectivity and duration of blindness (Fig 4). To observe these relationships more directly, we summarized visual functional connectivity in different brain networks for each subject and plotted the results against duration of blindness. In general, the correlations between visual functional connectivity and duration of blindness observed in congenitally blind subjects were opposite than those in acquired blind subjects. For example, the visual and task-positive functional connectivity showed a negative association with duration of blindness in acquired blindness but positive association in congenital blindness (data not shown). Similar findings were observed when using the striate cortex instead of the extrastriate cortex as the seed ROI.

IV. Discussion

The developed primary visual cortex of sighted subjects is capable of differentiating objects based on edge detection, contrast, and spatial orientation, and is highly involved in visual attention, expectation and perceptual tasks [12]. Although vision loss may negatively impact spatial orientation and perception due to our reliance on our sense of sight, as theorized in the general loss hypothesis [13], some evidence shows support for the compensatory hypothesis, where blind individuals gain superior non-visual capabilities in a compensatory manner [13, 14]. In blind individuals, the visual cortex may respond to non-visual stimuli such as sound localization, auditory movement, and detection of sound changes [15]. However, the role of the visual cortex in interpreting such stimuli remains unclear. The amplitude and size of cortical activation in BOLD functional MRI have been shown to negatively correlate with reaction time in sighted subjects during visual tasks [16, 17]. Here, we demonstrated that stronger top-down activity in the visual cortex may reflect faster responses during auditory sensory substitution. Our results showing decreasing top-down activity in the visual cortex of acquired blindness over time also indicate that the plasticity of the visual system can gradually be reshaped after late onset of blindness beyond the sensitive period.

Our results for the distinct relationships in visual functional connectivity versus duration of blindness, when comparing congenitally and acquired blind individuals, highlight the differences in neural mechanisms underlying the visual plasticity between the two groups [18]. Such differences may be due in part to the contrasting processes of brain metabolism in congenital and acquired blindness [19]. Early neuroimaging studies revealed an increase in occipital glucose metabolism in congenitally blind individuals, whereas acquired blind individuals showed a decrease in glucose utilization [20]. Furthermore, while the immature visual cortex in congenitally blind individuals may offer strong capacity for cross-modal plasticity, the relatively mature visual cortex in acquired blind individuals could have a general reduction in such cross-modal recruitment [3]. Taken together, these findings indicate that age of blindness onset may be a determining factor for the functional changes within the visual cortex following blindness, and that there may be a sensitive period during which cross-modal brain reorganization will likely be more pronounced. Of note, the visual and task-positive functional connectivity showed a negative correlation with duration of

blindness in acquired blindness, which coincides with the negative trend of top-down visual cortex activity versus blindness duration during the sensory substitution task in Fig 2. Recent studies suggested that cognitive task activations can be predicted from resting-state functional connectivity networks [21, 22]. Future studies are envisioned that evaluate the relevance of resting-state functional connectivity changes between visual and task-positive networks to top-down activity during sensory substitution.

V. Conclusion

This work represents an early step toward understanding plasticity in the visual system, how it depends upon prior visual experience, and how it may reflect behaviorally. Our results suggest that alterations in top-down brain activity and functional connectivity due to visual deprivation progress as a function of time. However, the direction of these changes differs depending on whether a person was blind at birth or became blind later in life. Furthermore, the degree of top-down activity in the visual cortex may reflect the speed of performance during sensory substitution. In the long term, discovering biomarkers of visual plasticity could aid in the screening of patients who are candidates for vision restoration devices. Our study suggests that MRI-based measures may play a critical clinical role in this screening. Future studies may also determine if visual deprivation needs to be complete for these plasticity patterns to occur, or whether residual vision can still induce these changes with or without sight restoration. Moreover, longitudinal measures of brain activity and connectivity may be essential for characterizing the dynamic states of the visual system.

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Fig 1. Functional MRI of brain activity during a sensory substitution task.

The colored overlays on the anatomical brain images are the blood-oxygenation-level-dependent (BOLD) activation maps in response to a visual-to-auditory sensory substitution task for sighted (left column), acquired blind (middle column), and congenitally blind adult subjects (right column) before (top row) and after 10 minutes of training (bottom row), indicating increased modulation of the occipital visual cortex in the blind but not sighted subjects following the short duration of training in the MRI scanner. Each average activation map was tested with a t-test after modeling individual maps with a general linear model using 6 parameters for each combination of group and pre- versus post-training conditions. Green arrows: auditory cortex; white arrows: visual cortex.

Fig 2. Top-down brain activity vs. reaction time (left) and duration of blindness (right). The degree of top-down modulation in primary visual cortex negatively correlated with reaction time during sensory substitution, whereas decreasing BOLD activity change in the primary visual cortex of acquired blindness with increasing blindness duration.

Fig 3. Summary of voxel-wise statistical testing for sighted versus blind functional connectivity using the extrastriate cortex as the seed region-of-interest.

Top row: Average functional connectivity map in sighted subjects. Middle row: Average functional connectivity map in blind subjects. Bottom row: Difference in functional connectivity between groups (average blind map minus average sighted map).

Fig 4. Summary of voxel-wise statistical testing for visual functional connectivity versus duration of blindness using the extrastriate cortex as the seed region-of-interest.

Top row: Slope map in congenitally blind subjects. Middle row: Slope map in acquired blind subjects. Bottom row: Difference in slope between groups (average congenitally blind map minus average acquired blind map).