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Differences in the major fiber-tracts of people with congenital and acquired blindness

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Abstract

In order to better understand how our visual system processes information, we must understand the underlying brain connectivity architecture, and how it can get reorganized under visual deprivation. The full extent to which visual development and visual loss affect connectivity is not well known. To investigate the effect of the onset of blindness on structural connectivity both at the whole-brain voxel-wise level and at the level of all major white-matter tracts, we applied two complementary Diffusion-Tension Imaging (DTI) methods, TBSS and AFQ. Diffusion-weighted brain images were collected from three groups of participants: congenitally blind (CB), acquired blind (AB), and fully sighted controls. The differences between these groups were evaluated on a voxel-wise scale with Tract-Based Spatial Statistics (TBSS) method, and on larger-scale with Automated Fiber Quantification (AFQ), a method that allows for between-group comparisons at the level of the major fiber tracts. TBSS revealed that both blind groups tended to have higher FA than sighted controls in the central structures of the brain. AFQ revealed that, where the three groups differed, congenitally blind participants tended to be more similar to sighted controls than to those participants who had acquired blindness later in life. These differences were specifically manifested in the left uncinated fasciculus*, the* right corticospinal fasciculus*, and the* left superior longitudinal fasciculus*, areas broadly associated with a range of higher-level cognitive systems.*

Background

A powerful recent technique for understanding the effect of visual experience on brain organization is the Diffusion-Tensor Imaging (DTI). Visual deficits can lead to changes in both gray and white matter of the brain, and neurophysiological differences between these populations have long been used as a model for explaining the influence of visual experience on brain structure. Though much of this previous work has focused on brain function changes, past studies have also shown that there are differences in connectivity (both functional and anatomical) between blind and sighted individuals [1-5]. Additionally, there are differences in cortical activation and connectivity between congenitally blind participants who became blind later in life [6-13]. However, the extent of the differences between these two groups are not entirely clear; some studies find only minor atrophy of white matter tracts in late blind participants, while other studies show similar atrophy in the brains of congenitally blind and late blind participants (for review see Rokem et al. 2017 [14]). Because of the inconsistencies across results, the nature and extent of the differences in white matter structure across blind and sighted groups is still unclear, and in need of further investigations.

Additionally, previous studies have not looked at differences at the level of major white matter tracts. These tracts are associated with specific higher-level function, and thus defining changes for congenitally blind and acquired blind groups could give us important insights into neuroplastic changes potentially related to cognitive processes. Both functional and connectivity similarities and differences related to cognition across the whole spectrum of visual function development – from the congenitally blind (who have never had visual function), acquired blind (who lost vision function later in life), severe low vision and (temporarily) blindfolded-sighted participants - have been systematically studied in our laboratory. In particular, training-driven brain reorganization in function and connectivity was investigated by fMRI and Granger Causal connectivity [15-21]. The current work seeks to characterize the structural connectivity changes as a function of visual system development and status, that might be further associated with neuroplastic reorganization of higher-order cognitive systems, as well as to shine light onto the macro-level structural connectivity differences in these important clinical populations.

The goal of the current study is to address the questions: 1) does the effect of blindness on white matter structure depend on the onset of this condition? and 2) are these changes detectable at the structural level of major white matter pathways? In order to determine the effects of the time of onset of blindness, the present study used two advanced analysis methods to compare congenitally blind (CB) with acquired blind (AB) participants, as well as with sighted control participants (SC).

The first method used is known as Tract-Based Spatial Statistics (TBSS), a method allowing for whole-brain, voxel-wise comparisons. This method allowed us to make direct comparisons to previous work by Wang et al. [22] showing a more widespread decrease in white matter in late blind compared to congenitally blind participants. However, as opposed to our study, the Wang et al. study was restricted to classifying white matter properties at a local, rather than large-scale level. Some work has been done to attempt to classify changes at a larger scale - specifically thalamocortical structures - but failed to find differences [23].

We capitalized on recently released tools for DTI analysis, which make it possible to classify differences at the level of all major white matter tracts. These major structures are defined based on anatomical landmarks and are easily identifiable across individual participants. This type of analysis is known as Automated Fiber Quantification (AFQ). To our best knowledge the current study is the first to apply AFQ to blind populations, though AFQ has already been used successfully to investigate white matter properties in other types of clinical populations [24]. The AFQ technique allowed us to characterize the differences at a macro scale and perform more broad comparisons in these important anatomical structures without requiring spatial co-registration across participants.

The combination of the TBSS and AFQ analyses can provide multilevel insights into the neuroplastic adjustments that take place in a brain deprived of visual input at different stages of visual system development.

Methods

Participants

Diffusion-weighted images were collected from a total of 13 participants (4 female). Four were congenitally blind (CB; 2 female, mean age 52), four had acquired blindness (AB; 1 female, mean age 65), and five were controls with normal or corrected-to-normal visual acuity (SC; 1 female, mean age 49).

DTI Methods

Diffusion imaging data were collected on a Siemens Trio 3T and on a Siemens Prisma 3T using a 2D single-shot Simultaneous MultiSlice (SMS) EPI sequence with 5 b=0 and 64 b=2000 volumes. TR/TE = 3067/70ms, FOV= 220x220x120 mm with 60 contiguous slices and a 110x110 imaging matrix, resulting in a 2x2x2 mm resolution. The acquisition was accelerated by a factor of 2 in the slice direction (SMS) and 2 in the phase encoding direction (GRAPPA). Data was collected from two different scanners with identical protocols. We corrected for this by scaling the whole-brain data from one scanner using the difference in mean fractional anisotropy across the two scanners. This method was verified using two participants who were scanned in both systems.

Analysis: TBSS

Tract-Based Spatial Statistics (TBSS) is a tool from FSL [25, 26]. All data for this analysis was preprocessed through the FSL DTI preprocessing pipeline and corrected for motion and eddy-currents. Each fractional anisotropy (FA) image was then aligned to a 1x1x1 mm standard space; in this case we used the "most typical" participant in the study, a label automatically defined in the TBSS package. The derived nonlinear transforms were applied to each participant, allowing for precise inter-participant alignment. The aligned images were then all combined into a single 4-dimensional data structure, with one structure for each participant group. The resulting images combine to form a white matter skeleton, using the package's default standard threshold of FA = 0.2 to eliminate all other voxels from the rest of the analysis. This step limits the analysis to voxels containing mostly white matter.

Analysis: AFQ

Automated Fiber Quantification (AFQ) is a toolbox first described in Yeatman et al. [24]. We performed preprocessing separately for this step using the Vista Lab mrDiffusion toolbox for Matlab (available at http://vistalab.stanford.edu, Stanford University, Stanford, CA). All data was motion and eddy-current corrected. We then fed each participant's whole-brain profile into the AFQ automated segmentation tool, which also identifies ROIs based on anatomical landmarks. White matter tracts were then segmented into 20 major fiber groups (see Table 1), between pairs of ROIs identified as the ends of each track. We used all package default values for removing outlying fibers (maximum distance within 4 standard deviations (SD), maximum length within 4 SD, number of nodes per fiber = 100). Properties from each of the 20 fiber tracts were then computed based on the means of the fiber bundles. Some tracts were unidentifiable in some participants following removal of the outlying fibers, and these were simply excluded from our analyses. Table 1 shows the number of participants in each group that were included in each analysis by tract.

Table 1. Number of participants from each group with classifiable fibers in each of the 20 major fiber tracts that were identified using AFQ.

Mori Fiber Group	AB	CB	SC
1. Left Thalamic Radiation	4	4	3
2. Right Thalamic Radiation	4	4	3
3. Left Corticospinal	4	4	5
4. Right Corticospinal	4	4	5
5. Left Cingulum Cingulate	4	4	5
6. Right Cingulum Cingulate	4	3	5
7. Left Cingulum Hippocampus	3	0	1
8. Right Cingulum Hippocampus	4	1	1
9. Callosum Forceps Major	4	2	5
10. Callosum Forceps Minor	4	4	4
11. *Left* Inferior Fronto-Occipital	4	4	5
12. Right Inferior Fronto-Occipital	4	4	5
13. Left Inferior Longitudinal	4	4	3
14. Right Inferior Longitudinal	4	3	4
15. Left Superior Longitudinal	4	4	5
16. Right Superior Longitudinal	4	4	5
17. Left Uncinate	4	4	4
18. Right Uncinate	4	4	5
19. Left Arcuate	4	4	5
20. Right Arcuate	4	3	5

Results

TBSS

Figure 1 shows comparisons of the fractional anisotropy (FA) of the three groups of participants (congenitally blind (CB), acquired blind (AB), and sighted controls (SC)), using the TBSS method described above. Thresholds for between-group contrasts were set at 95%.

Broadly speaking, we found that at this scale the two blind groups were more similar to each other (bottom row of Figure 1) than to the sighted controls (top and middle rows of Figure 1), in that there were overall fewer significantly different voxels between the two blind groups. When comparing each blind group to the sighted controls, we found that blind participants tended to have significantly higher FA in central structures, while sighted controls had higher FA in white matter nearer to cortex, specifically white matter near the occipital cortex including the optic radiations (top and middle rows of Figure 1). The acquired blind and congenitally blind groups differed mainly in the central structures, with AB showing higher FA in these regions (bottom row of Figure 1).

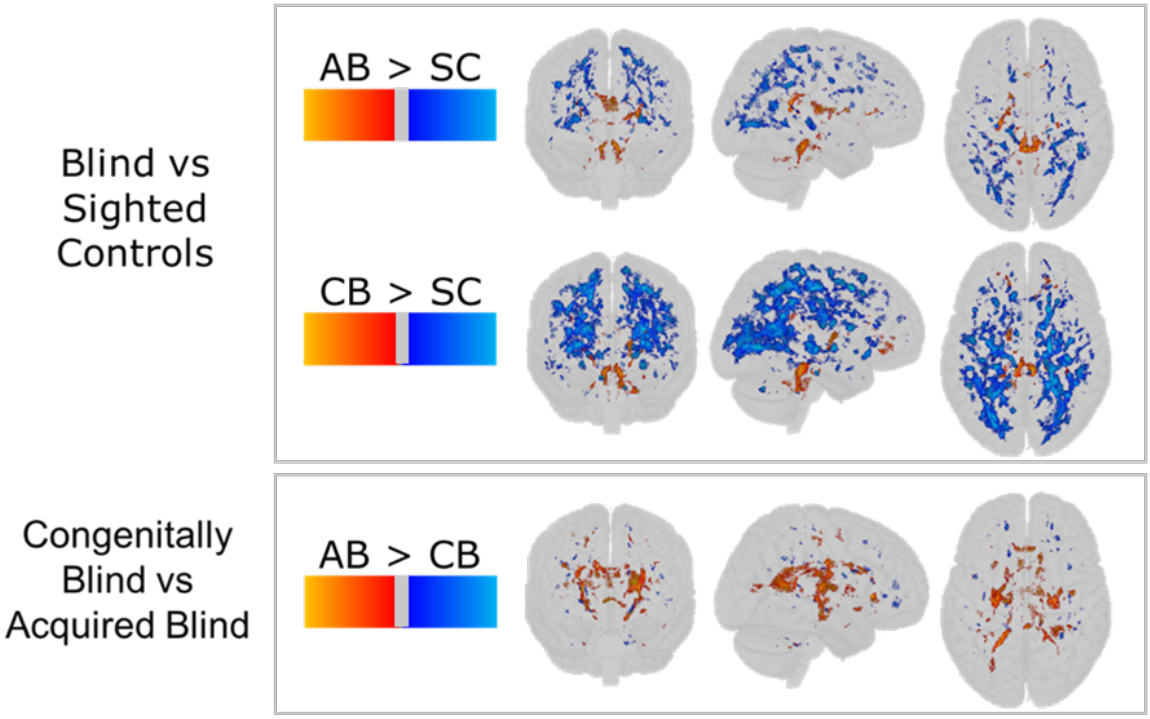

Figure 1. *Fractional anisotropy (FA) was compared for all three participant groups. Results are shown in "glass brains" such that all results are visible simultaneously, as opposed to slice-based brain representations. The top row shows AB vs sighted controls (SC), where red is FA higher in AB than SC and blue is FA higher in SC. The middle row shows CB vs SC, where red is FA higher in CB. The bottom panel shows a comparison of the acquired blind (AB) vs congenitally blind (CB) participants, where red is FA higher in AB than CB, and blue is FA higher in CB. Darker reds and blues indicate voxels with between group comparisons $p < 0.05$, and lighter colors indicate significance closer to $p < 0.001$.*

AFQ

Examples of some of the segmented fiber groups from the automated fiber quantification (AFQ) toolbox are rendered in Figure 2. Figures 3 and 4 show the general results of this analysis. Out of the 20 Mori fiber groups analyzed, 2 were excluded due to their poor segmentation across all participant groups (the left and right cingulum hippocampus fasciculi), leaving 18 major fiber tracts (see Table 1). Out of those 18, there were 3 that showed significant results following correction for multiple comparisons (false discovery rate [27]). Those were the right corticospinal fasciculus comparing between the AB and CB groups (corrected $p < 0.05$), the left superior longitudinal fasciculus between AB and CB, and between AB and SC (corrected $p < 0.01$), and the left uncinate fasciculus between AB and SC (corrected $p < 0.05$). Figure 2 shows an example of the rendered fibers overlaid on an anatomical image from an SC participant, where each tract is encased in a heat map of the mean FA along the length of the tract. The group data for mean FA along the length of each tract is shown in Figure 3. Figure 4 shows the mean FA collapsed across spatial node for each of the identified tracts.

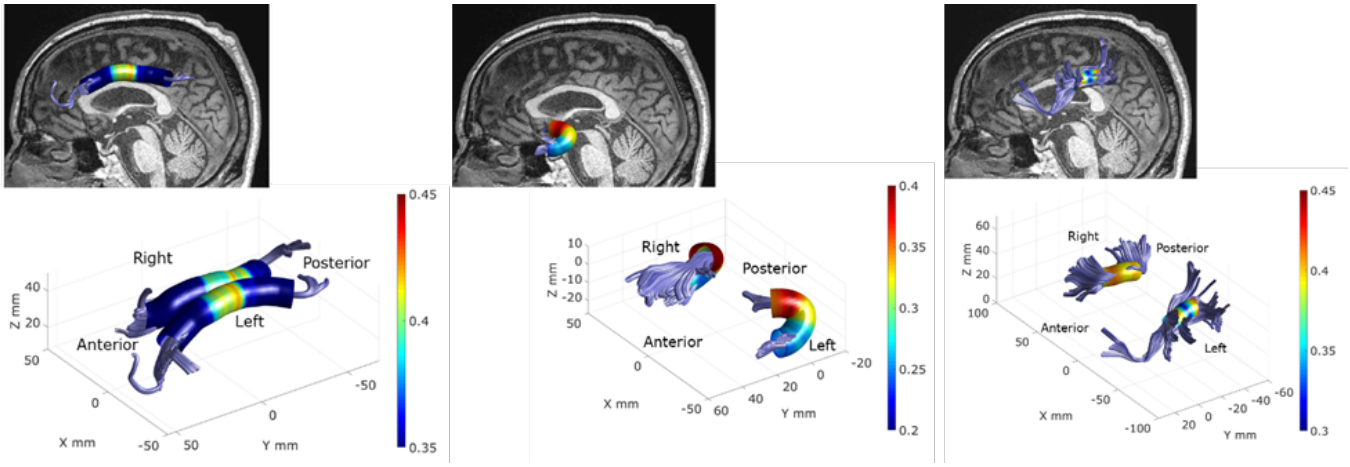

Figure 2. *Rendered fibers for 6 of the Mori fiber groups, encased in a visual representation of their mean fractional anisotropy from a representative SC participant for the Inferior Fronto-Occipital fasciculi (left), the uncinated fasciculi (middle), and the superior longitudinal fasciculi (right).*

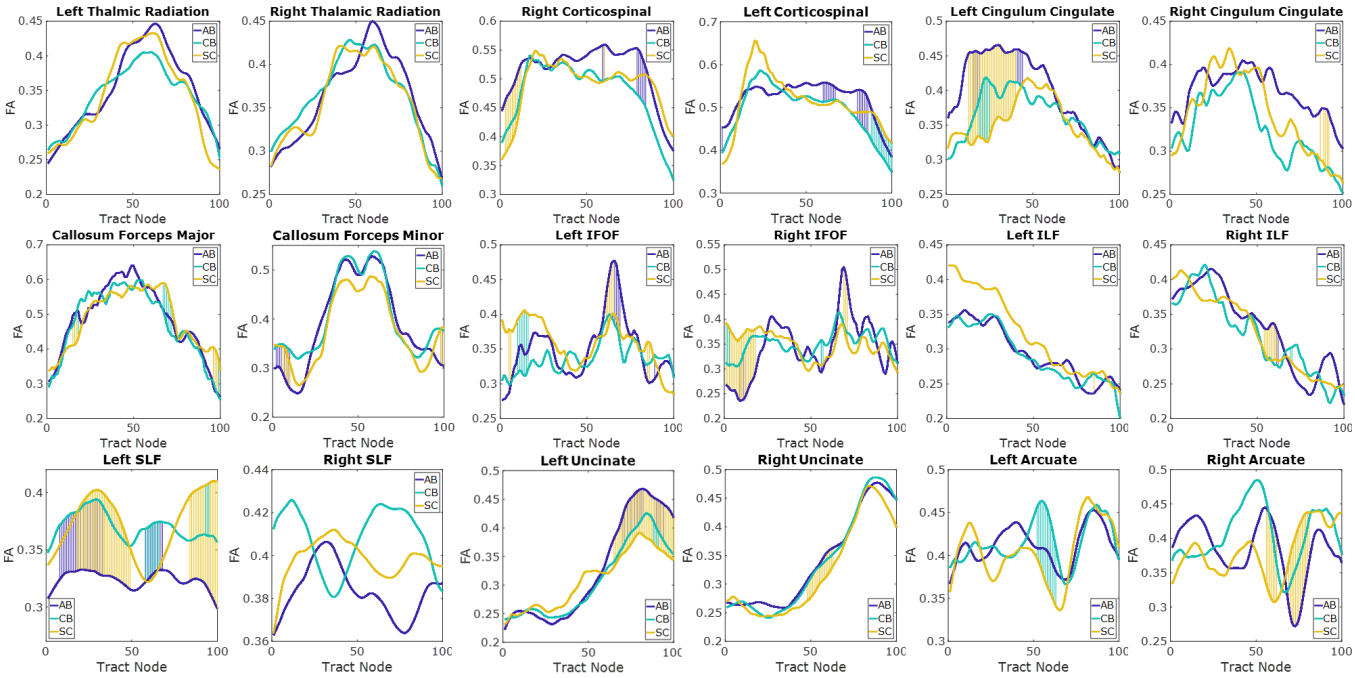

Figure 3. *Mean fractional anisotropy is plotted against spatial tract node for each of the 18 Mori fiber groups identified using the AFQ algorithm. The data for each of the three groups - acquired blind (blue lines), congenitally blind (cyan lines), and sighted controls (yellow lines) - are plotted with solid lines, and the filled in regions between lines represents areas that are significantly different across groups ($p < 0.05$ by individual track nodes), where blue fill designates significant differences between AB vs CB, cyan between CB vs SC, and yellow between AB vs SC.*

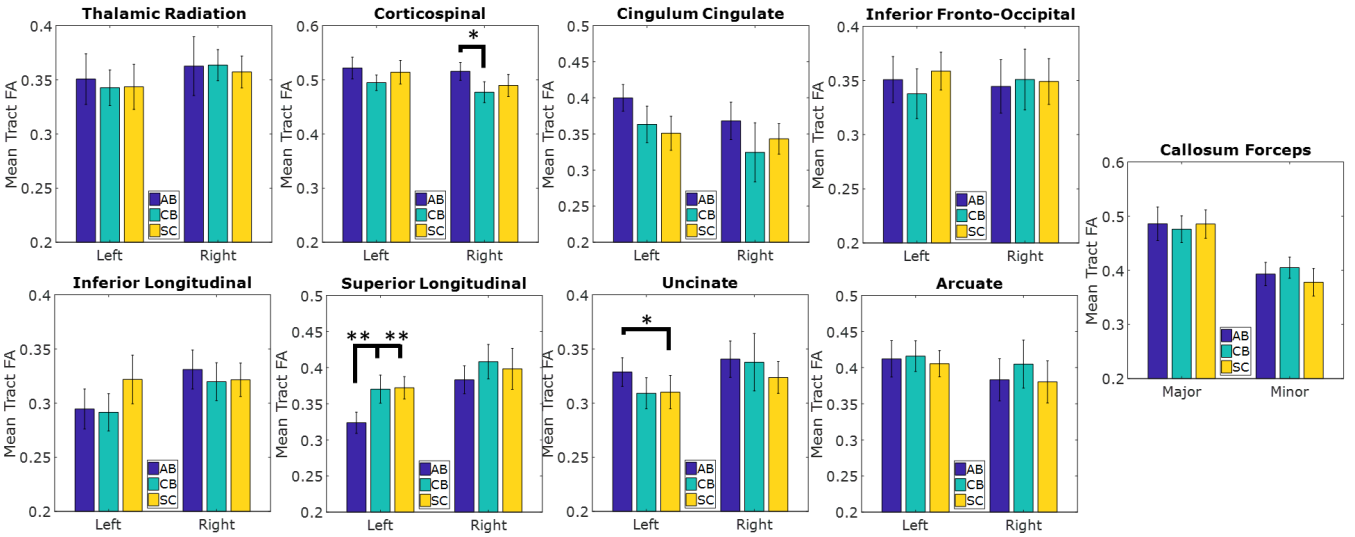

Figure 4. *Mean fractional anisotropy is shown for each of the three groups, averaged across spatial nodes. Error bars are standard error of the means. Single asterisk denotes groups that are significantly different (corrected, $p < 0.05$), and those with double asterisks are significantly different (corrected, $p<0.01$) corrected for multiple comparisons using false detection rate (FDR).*

Discussion

Results from the TBSS analysis revealed a reduction in white matter integrity in both blind groups when compared with sighted controls, specifically in the optic radiations. We also showed a general trend toward higher FA in more central white matter structures for the blind groups, which is in agreement with Wang et al [22]. However, unlike Wang et al., our TBSS revealed that AB did not have lower FA near the optic radiations than CB; in fact, we actually found a trend in the opposite direction. This makes intuitive sense as the optic radiations, which connect the lateral geniculate nucleus to the primary visual cortex, have essentially never been used by congenitally blind participants, resulting in higher levels of atrophy compared to those who became blind in adulthood.

In the AFQ analysis, we found that 3 of the 18 analyzed tracts showed difference between the three groups: the left uncinate fasciculus, the left superior longitudinal fasciculus, and the right corticospinal tract. The left uncinate fasciculus, a tract connecting

the left temporal pole with the orbitofrontal cortex, is generally associated with higher cognitive functions, such as verbal memory, working memory, and name retrieval/recognition [28, 29]. We found elevated FA in this tract for the acquired blind group, compared to the other two. Interestingly, this finding is consistent with results from a different brain imaging method, brain volumetry [30] which showed volumetric differences in "early blind" participants in the region of the left uncinate, a group more comparable to our congenitally blind group (except that they allowed for the inclusion of some early visual experience, whereas our group were all totally blind from birth excluding light perception). We also found that the AB group had significantly lower FA in the left superior longitudinal fasciculus. This is a long-range tract, generally associated with language processing and spatial awareness, which is a cognitive ability of particularly high importance when vision is lost [31]. Finally, we found a significant difference between the AB and CB groups in the right corticospinal tract, which connects the spinal column with superior cortical regions such as somatosensory and motor cortex [32]. This is partially consistent with previous work showing blind participants of both types generally have higher FA in this tract than sighted controls, with a bigger effect in AB than CB [22]. We also found that AB had the highest FA in this tract, however unlike Wang et al., we showed no difference between the CB and SC groups.

This work brings new insights into a larger body of work that have shown connectivity differences between blind and sighted individuals. We showed a general loss of some regions of white matter in blind participants when compared to sighted, which is consistent with Liu et al. 2007 [3]. Importantly, we also showed evidence of compensatory plasticity in regions important to general functions following sensory loss. We also provided evidence that neuroplastic changes continue when visual loss occurs later in life, indicating the existence of a mechanism for unceasing neurophysiological compensation.

Conclusions

To investigate the effect of the onset of blindness on structural connectivity at the whole-brain, voxel-wise level and at the level of all major white-matter tracts, we applied two complementary DTI analysis methods, TBSS and AFQ. To our knowledge, this is the first study to apply AFQ to blind populations, as well as the first to combine AFQ with TBSS in these clinical populations. The TBSS results were generally consistent with previous work, however, our study found that the participants who have had functioning vision for much of their lives (the AB group), tended to have higher FA in the optic radiations than the participants in the CB group, who have never had visual function. Furthermore, the AFQ method allowed us to compare for the first time 18 major fiber tracts across populations of people blind from birth, people who acquired blindness later in life, and people with normally functioning visual systems. The AFQ tract profiles suggest that, surprisingly, congenitally blind participants were generally more similar to sighted controls than to acquired blind participants in tracts that differed between groups. This inversion, which is specifically in tracts associated with spatial awareness and working memory, could be indicative of a higher level of plasticity in the pathways of the readjusting brains of people who become blind later in life. Generally, the major-tract-based analyses provide important new insights into plasticity of white matter of the human brain.

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Author's Biography

Katherine E.M. Tregillus *received her Ph.D. from the University of Nevada, Reno in 2017. She then went onto a postdoctoral position at the Smith-Kettlewell Eye Research Institute under the mentorship of Lora T. Likova, in whose lab the work on this paper was done. She is currently a postdoctoral researcher at the University of Minnesota, Twin Cities, studying visual adaptation and neuroplasticity.*

Lora Likova, Ph.D., *has a multidisciplinary background that encompasses studies in cognitive neuroscience and computer science, with patents in the field of magnetic physics and many years of experience in brain imaging, brain plasticity, human vision, and neurorehabilitation research. She is the Director of "Brain Plasticity, Learning & Neurorehabilitation Lab" at Smith-Kettlewell Eye Research Institute. Dr. Likova is a long-standing member of the Organizing Committee of HVEI.*

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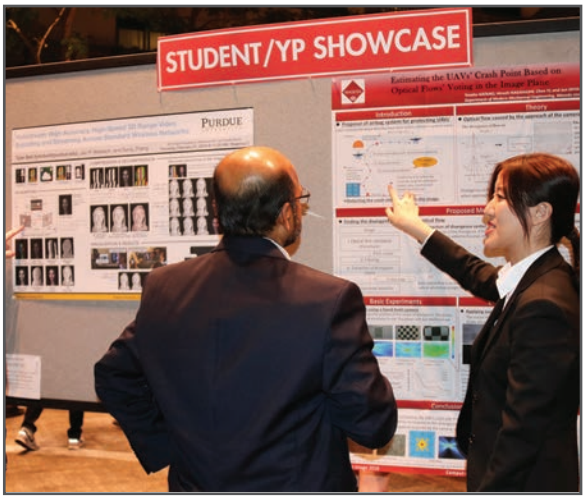

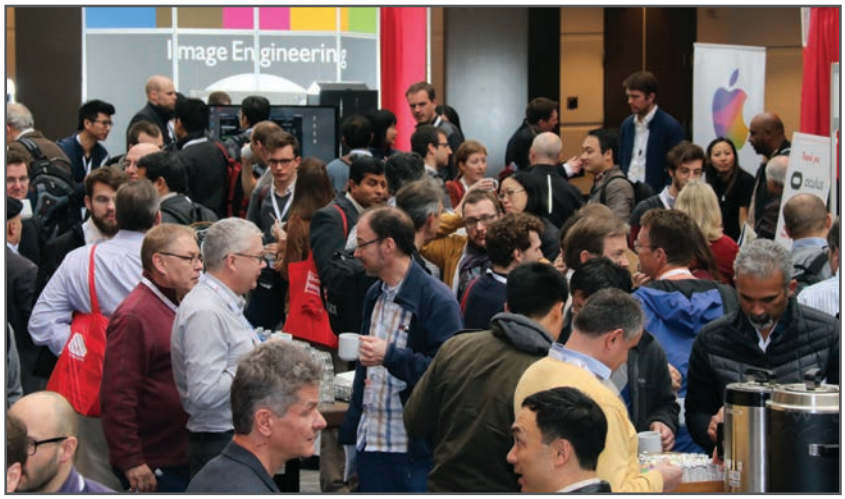

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