

The Jigsaw Effect

Refined perimetric analysis confirms that the brain coordinates bilateral glaucomatous neurodegeneration to optimize the surviving binocular visual field.

BY WILLIAM ERIC SPONSEL, MD

In glaucoma, optic nerve axons connecting the retina and midbrain are lost progressively. As age and other insults to ocular health take their toll on each eye, discrete bundles of these axons are sacrificed so that the remainder can continue to carry visual information to the brain. This programmed sacrifice of certain axons to save the rest, when there are inadequate resources to support them all, is somewhat analogous to pruning some of the limbs of a stressed fruit tree so that the other branches can continue to bear healthy fruit. The apoptotic biochemical pathways at work in glaucomatous ganglion cells are remarkably similar to those that operate within the brain of patients with other age-related neurodegenerative diseases like Parkinson and Alzheimer.^{1,2}

THE BRAIN AND CHRONIC GLAUCOMA

My colleagues and I recently published the results of 100 consecutive surgical patients undergoing Mermoud nonpenetrating deep sclerectomy with mitomycin C.³ This microsurgical filtering procedure conserves the internal trabeculum, typically resulting in a low but safe IOP without medication while minimizing potential problems with the cornea, lens, and macula that might introduce confounding nonglaucomatous defects on subsequent visual field testing. To our knowledge, this was the first published glaucoma filtering study to demonstrate highly reproducible and clinically significant improvement in perimetric function, with a consistent increase of mean deviation on 30-2 Humphrey visual field testing (Carl Zeiss Meditec) 6, 12, and 18 months postoperatively. Among some of the more severely bilaterally afflicted patients, complementary interlocking jigsaw patterns of compensatory visual field conservation became fairly obvious on cursory examination of the paired visual fields (Figure). Once these patients were bilaterally stabilized, overlapping grey areas of partial compromise in each eye disappeared, leaving black zones of permanent vision loss in each eye that frequently coincided with the white areas in the other.

These paired visual fields fit together like the pieces

“The brain’s involvement emphasizes the importance of aggressively treating the worse eye first in patients with severely advanced glaucoma.”

of a jigsaw puzzle, producing a much better bilateral visual field when both eyes are open than could possibly arise by chance. My colleagues and I decided to investigate this phenomenon objectively by performing a comprehensive masked data analysis of the paired visual fields of all perimetrically reliable and clinically stable (medically and/or surgically) patients with comparable degrees of moderate to severe visual field loss in both eyes. We confirmed this bilateral compensatory jigsaw phenomenon to be robust in a very high proportion of patients, with mean binocular light sensitivity values that were 1.6 dB greater than expected across the central 30° with an infinitesimally low associated *P* value.⁴ To our surprise, we did not observe a contribution from inherent anatomic symmetry factors that passively enhance bilateral function. Instead, we discovered the entire phenomenon to be under the meticulous control of the central nervous system.

Our findings reveal that the brain is in charge of the axonal pruning process in chronic glaucoma. This is a big surprise and, frankly, seems counterintuitive, given the long-established focus on individual eyes in the diagnosis and treatment of glaucomatous optic neuropathy. In glaucoma, the progressive loss of vision in each eye appears to be largely haphazard, respecting only the horizontal midline that reflects the internal arrangement of the wiring within the eye, not the brain. Conversely, neural damage within the brain that is caused by strokes or tumors produces visual field loss that extends across

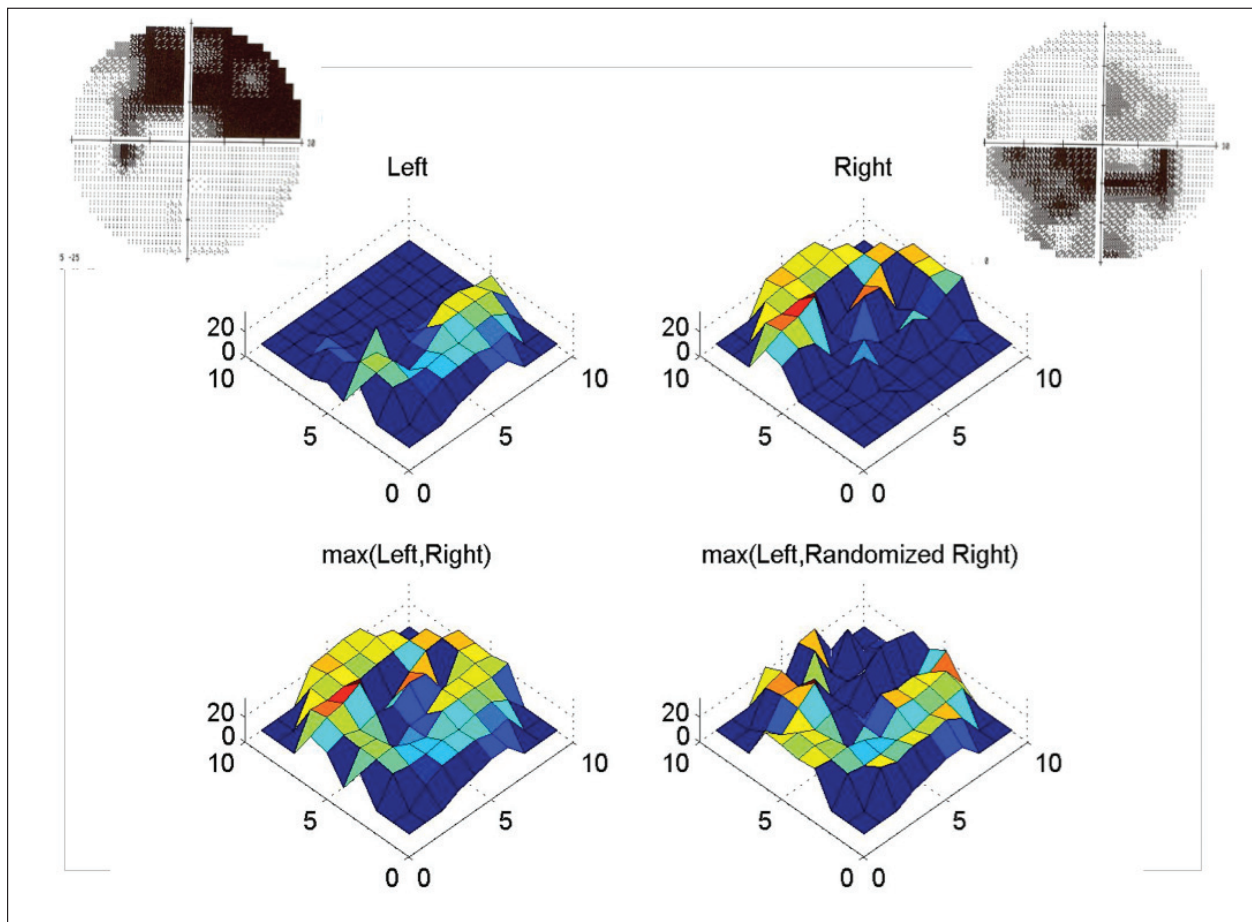


Figure. Example of one of the 47 sets of visual field pairs evaluated by refined data analysis. The left and right eyes' Humphrey 30-2 visual fields are shown, with corresponding heat map three-dimensional isometric projection representations of the same data. The composite binocular visual field on the bottom right emerges after running 10,000 iterations of each of the 74 individual left eye visual field loci with all available co-isopterics partner points on the fellow right eye. The binocular visual field on the lower left is the actual field arising from the direct pairing of each left eye locus with its precise partner point in the right visual field. The lower left visual field result from this composite of the two individual uniocular visual fields was the same as the actual binocular visual field measured with both eyes opened. The lower right composite is the result that would be expected if glaucoma were progressing independently in each eye without the brain's intervention. Adapted and reprinted with permission from Sponsel et al.⁴

large and uniform areas almost identical for each eye, following the major visual wiring patterns in the visual pathway and cerebrum.

Conflicting patterns of damage logically supported the idea that neurodegenerative progression in glaucoma occurs randomly in individual eyes, without the brain's involvement. As uncontrolled glaucoma progresses, areas of permanent visual field loss (where all of the axons have died) mix arbitrarily with other areas where axons are alive but are functioning very poorly (grey zones), supporting the notion that, in a metabolically compromised eye, glaucomatous neurodegeneration is an effectively entropy-driven sequence of axonal sacrifice

that initially eliminates cell bodies in the diffusely wired retinal periphery and then works slowly toward the more densely wired and better-perfused central retinal zones.

Although an attractive model, there is one problem. The central visual region is rarely the last area to be lost in chronic progressive glaucoma; it is usually next to last. The peripheral temporal field that cannot be seen by the fellow eye is nearly always the last area to disappear in severe glaucoma. This area's corresponding ganglion cells are the most nasally distal from the disc, with very diffuse receptive fields, and they are perfused by one of the longest circulatory beds in the retina. The explanation for this physiologically confounding conundrum is now readily appar-

ent: the eyes and brain work together as a unit to conserve the functional binocular visual field as long as possible.

APPLICATIONS

From an immediate practical perspective, the brain's involvement emphasizes the importance of aggressively treating the worse eye first in patients with severely advanced glaucoma, regardless of its central acuity, as long as that eye still retains its temporal field. Quite apart from the fact that it is inherently prudent to discover tissue characteristics, antimetabolite response, suture hypersensitivity, and inflammatory tendencies in the "lower-stakes" eye first, it is very important to conserve what may remain of the binocular visual field. It has been so strongly protected by the central nervous system that the temporal visual field persisted even after the macular axons had all been sacrificed.

Another practical advantage of our research is one of psychological relief. Many patients claim that their dynamic functional situation with both eyes open is not as dire as it appears from their individual visual fields. This research may actually fuel such assertions. Patients are more likely to take visual fields seriously if they demonstrably correspond to their visual world as they actually perceive it. A proper demonstration of right, left, and binocular fields—followed by alternating hand coverage of each eye in the examination lane—can help patients become more accepting of their actual circumstances and proactive with their therapy. Composite binocular fields that would very closely reflect the true binocular field could be readily generated from the existing data on the right and left eyes from any of the standard commercial automated perimeters.⁵

Perhaps the most exciting consequences of our work are yet to come. Although our study is the first demonstration of this phenomenon in humans, initial recognition that the brain controls neurodegeneration in glaucoma arose from a brilliant series of murine basic science studies by Crish et al at Vanderbilt University.⁶ The potential reversibility of the "grey zone" dysfunction that precedes apoptotic axonal death is also well explained in their neurodegenerative model. Our recognition that the brain resists the concomitant loss from both eyes of equivalent visual input is thus highly consistent with their predictions. It seems likely that other age-related neurodegenerative conditions would similarly favor conservation of at least one of the two bilaterally analogous functional zones in the paired hemispheres of the brain. Advances in the understanding of the cellular biology of this phenomenon in glaucoma might thereby contribute substantially to the development of future therapeutic options for all such disorders.

It was relatively easy for us to discover this tendency in paired eyes capable of generating concordant two-dimensional perimetric overlays despite the absence of as many as 80% of the associated axons. One can imagine the technical difficulties incumbent in finding this propensity, should it exist, in other age-related disorders, intracranially, within three-dimensional convoluted cerebral cortices, where paired anatomic spatial symmetry is imprecise, and a loss of 5% of the total axonal population might have already precipitated the patient's death. Very large numbers of living or deceased subjects would have to undergo neurophysiologic imaging or detailed histopathology, respectively, to begin to approach the confidence intervals we were fortunate enough to have using refined analysis of standard clinical perimetry results. The odds of finding and confirming this form of bilateral central nervous system functional conservation by studying the eye-brain complex were thus stacked heavily in our favor.

CONCLUSION

My fellow researchers and I believe there are many additional ways in which visual scientists can investigate the role of the eye-brain complex in modulating the progression of ocular neuropathy that might contribute greatly to the development of future therapies for conserving bilateral cerebral function in other age-related disorders, including Parkinson and Alzheimer disease. ■

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1. McKinnon SJ. The cell and molecular biology of glaucoma: common neurodegenerative pathways and relevance to glaucoma. *Invest Ophthalmol Vis Sci.* 2012;53:2485-2487.
2. Sivak JM. The aging eye: common degenerative mechanisms between the Alzheimer's brain and retinal disease. *Invest Ophthalmol Vis Sci.* 2013;54:871-880.
3. Sponsel WE, Groth SL. Mitomycin-augmented non-penetrating deep sclerectomy: preoperative gonioscopy and postoperative perimetric, tonometric and medication trends. *Br J Ophthalmol.* 2013;97:357-361.
4. Sponsel WE, Groth SL, Satsangi N, et al. Refined data analysis provides clinical evidence for central nervous system control of chronic glaucomatous neurodegeneration. *Trans Vis Sci Technol.* 2014;3:1-13.
5. Crabb DP, Viswanthan AC, McNaught A, et al. Simulating binocular visual field status in glaucoma. *Br J Ophthalmol.* 1998;82:1236-1241.
6. Crish SD, Sappington RM, Inman DM, et al. Distal axonopathy with structural persistence in glaucomatous neurodegeneration. *Proc Natl Acad Sci.* 2010;107:5196-5201.