Definitive Response to Denniss and Artes: The Paired Eyes and Brain in One Person Are One Unit

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We welcome this spirited correspondence¹ on our work,² complete with its thought-provoking title quote borrowed from Carl Sagan and an incisive passage by John Ioannidis. The fact that glaucomatous damage appears to involve the optic nerve head was never questioned by our article. Whether other factors may influence the eventual fate of visual fields in a manner that is manifest “*in late stage bilateral disease*” was the actual the topic of our study.

In our study, we examined Humphrey Visual Field Analyser II (HFA) 30-2 fields from “47 consecutive patients with bilaterally severe glaucoma,” a population with mean mean deviations (MDs) of -12.24 dB oculus dexter (OD) and -13.72 dB oculus sinister (OS). These were clinically stabilized patients with highly damaged fields, all of whom demonstrated good test reliability and acuity. We found that their paired visual fields exhibited a clinically substantial degree of binocular complementarity that had an extremely low probability of occurring by chance. If true, this result would seem to require control by some integrated binocular mechanism. Although the brain presents the most logical site of integration, we left open and appropriately tested the possibility of a purely passive process.

Denniss and Artes¹ now challenge our findings with an intriguing but untested new method for measuring binocular complementarity. For this purpose they also chose to include large numbers of mildly affected fields, the majority of which did not come close to meeting our study inclusion criteria. Indeed, their MD cutoff of -2.5 dB was even more generous than the formula used in the Ocular Hypertensive Treatment Trial^{3,4} in which 86% of presumptive glaucomatous visual field defects improved spontaneously on subsequent testing, a

substantial proportion reverting to normal. Moderate visual field loss typically begins with MD values approximately -6 dB, and severe approximately -12 dB; such fields typically remain firmly pathologic on repeat examination.

As suggested, we have analyzed the Rotterdam visual field database (www.orgids.com), the most readily accessible of those utilized by Denniss and Artes,¹ and compared outcomes with both algorithms. From the Rotterdam spreadsheet we identified a total of 55 patients (21 females and 34 males, mean age 69.6 years, with a mean MD for the two eyes of -15.0) having paired sets of HFA 24-2 fields with MD values ≤ -6 dB in both eyes, and used the most recent available qualifying field pair from each patient for analysis. No reference was made to the visual fields themselves during the selection process. Figure 1 shows an overlay plot of the resulting comparative scattergram distributions applying the two methods of analysis. These highly compatible results from a totally masked dataset appear to provide further validation of our prior observations,² demonstrating highly significant bilateral conservation of binocular function unlikely to be arising by chance.

In a further validation test of the two methods, we analyzed 298 randomly generated sets of *totally complementary* square grid visual field pairs. Every grid pair was laid out with compensatory zones of normal and abnormal function alternating between the right and left visual fields. In order to approximate values seen in a typical adult population, each pair was constrained at random to have central threshold values of 25–35 decibels centrally, with slopes of -4 to -8 dB from the center to 30 degrees eccentricity along all axes. The depth of every

Figure 1. Scattergram of results derived according to the scheme of Sponsel et al.² (filled symbols) and Denniss and Artes¹ (empty symbols) for either of the two patient populations.

scotoma was absolute, with a threshold of zero. The results are shown in Figure 2, wherein values above zero indicate successful identification of these totally complementary visual fields. It is immediately evident that one method readily detected the jigsaw effect across the entire available disease spectrum, while the other could not.

At first glance both methods of analysis appear to be reasonable approaches. Indeed, Denniss and Artes' method successfully identified the jigsaw effect across half the bilateral severity range, between 25% and 75% loss (albeit at a much lower level of confidence, inverting the effect when loss exceeds 90%). How could one method so readily identify and the other so frequently miss the jigsaw effect in both mild and severe bilateral disease? In order to understand this it is best to think clinically. Thanks to recent advances in refined data analysis, an astute clinician today can predict the location of an early scotoma by spotting significant deviations in paired-eye OCT nerve fiber layer (NFL) profiles, even when each eye's double-hump pattern falls entirely within the normal 5–95% green zone. If such an eye's NFL profile were compared with any number of other people's NFL profiles, diseased or normal, there would be no statistical basis whatever to predict the presence of early disease, let alone its specific anatomic location.

It is fairly obvious that taking the higher value of any paired data sets will always yield a cumulative mean far higher than that of either individual dataset. In healthy paired eyes the differences in value between coisopterics points is relatively small, and the overlap-

Figure 2. Demonstration of the divergence of visual field complementarity detecting capability of the randomization schemes proposed in the original article² (filled symbols) and by Denniss and Artes¹ (empty symbols) showing a progression of 298 randomly generated sets of bilaterally complementary square grid visual field pairs. Every grid pair was laid out with compensatory zones of normal and abnormal function alternating between the right and left visual fields. In order to approximate values seen in a typical adult population, each pair was constrained at random to have central threshold values of 25 to 35 dB centrally, with slopes of -4 to -8 dB from the center to 30° eccentricity along all axes. The vertical axis shows the difference between the patient-specific bilateral field (MS_{true}) and the synthetic bilateral field generated using each algorithm (MS_{rand}). At zero severity both eyes have full fields; once loss levels exceed 50% there will inevitably be zones of overlapping blindness in both eyes. The depth of every scotoma was absolute, with a threshold of zero. Note that the ability to detect complementarity of the visual fields is absolute for the previously published method (i.e., all the results are positive). The newly proposed method grossly underestimates the jigsaw effect in eyes with bilaterally advanced visual field loss, and actually inverts the effect when loss exceeds 90%. The apparent basis for this divergence is demonstrated in Figure 3, below.

ping values from the two eyes tend to be minimally different from one another. In both San Antonio and Rotterdam, the visual fields we analyzed were likely obtained at the same visit, by the same perimetrist, using the same machine, and under the same lighting conditions for both eyes. Both eyes also shared identical nutritional, pharmacologic, psychological, and general health status. The height and slope of the hill of vision varies minimally between paired eyes, but can vary substantially across the population at large. The presence of actual scotomata in the comparative group further adds to this dizzying array of arbitrary variation.

Figure 3. Demonstration of the lack of total field conservation in the randomization schemes proposed by Denniss and Artes.¹ The horizontal axis shows the difference between the sum of all thresholds in both fields from each patient and the sum from the two fields generated using the proposed randomization scheme. Negative numbers on this axis represent bilateral fields for which their randomization scheme adds to the total sum of thresholds in both eyes. The vertical axis shows the difference between the patient-specific bilateral field (MS_{true}) and the synthetic bilateral field generated using their randomization scheme (MS_{rand}). The strong positive correlation here indicates that the proposed randomization scheme achieves binocular fields better than the true fields only in cases where the total field thresholds exceed those found in the true patient fields. The randomization scheme in the original article² avoided this issue by forcing conservation of the overall field threshold values (i.e., all points fall on the vertical line at $x=0$) and nearly all occur in the positive region of the y axis indicating that the true bilateral fields are significantly higher than those that might occur due to chance ($P=2.5 \times 10^{-14}$). In statistical distributions including only positive numbers (i.e., skewed, nonnormal distributions), means are inherently biased by larger numbers.⁵ Thus, any comparison similar to that proposed by Denniss and Artes¹ will yield similar results not because of a lack of complementarity in the visual fields of bilaterally severe glaucoma patients but because of the use of an inappropriate statistical metric by which the fields are compared and quantified.

Our premise is that the sum of both fields should be conserved in the analysis, whereas their method makes no such assumption. Their method does well when it violates this assumption by adding value to the fields and does poorly when it takes value out of the fields via the randomization process. What is the basis for our assumption that glaucoma is a resource-dependent disease rather than due solely to random damage? The null hypothesis they state is correct in that it directly questions this premise and the onus is on us to prove that the null hypothesis does not hold. Using both patient populations combined and both methods, we arrive at the conclusion that pairing fields using their randomization scheme results in eyes that are better than the true binocular fields ($P=0.02$) by 0.59 dB on average. Results are similar for either subpopulation. However, these improvements occur

only in cases where the fields used for comparison have visual fields superior to those of the patient's (Fig. 3).

This leaves the scientifically philosophical question: can the true binocular field be better than can be explained by symmetry or chance once both eyes have experienced significant visual field loss? We evaluated that in the original study by performing simultaneous binocular visual field testing, which reaffirmed that at least for the area being tested by HFA 30-2 perimetry this is not the case. Regardless, comparing one field from one patient with numerous fields from other patients is really a distraction from the original hypothesis, which can be stated as follows: given two visual fields, which have naturally arisen in a given patient, what is the likelihood that the combined binocular field can be explained by

symmetry or chance? The answer to this question, based on the combination of our own data set and that of the Rotterdam studies, is that this probability is infinitesimally small ($P = 10^{-17}$). In only 8 of 102 cases were binocular fields found by shuffling the loci of one eye and comparing them with the fellow eye better than the true composite binocular fields for the patients examined here (all 8 were from the Rotterdam study for which we applied a nonpathology-specific masked MD-based cutoff inclusion criterion).

Bilateral data from a mixed patient pool is *expected* to be asymmetric and will inevitably provide locus pairs that have a greater spread than could arise naturally. The predictable binocular outcome is perimetric “white noise.” This is best demonstrated by examining the actual visual fields associated with the points in the lower left of figure 1 of Denniss and Artes’ letter,¹ wherein the purported difference between true and random pairings is far greater than the total mean threshold value available to work with in both visual fields combined. Our simulations using contrived, perfectly interlocking visual fields show that this result is due not to lack of complementarity in the field but because of the mathematics of skewed distributions.⁵

Thus, using diseased eye data sets from various patients tested at various times and settings for comparison, Denniss and Artes¹ failed to account for biological symmetry, while introducing a plethora of well-established sources of additional avoidable variation. We based our analysis on the assumption that each of our glaucoma patients began life with two normal hills of vision in genetically paired eyes spectacularly similar to one another. It is the very dramatic similitude of paired eyes that allows for early detection of disease, even when each eye individually remains well within the normal population range as a single entity. Real credit for identifying the power of perimetric *asymmetry analysis*⁶ goes to David Henson, alongside whom, with Bal Chauhan, one of us was privileged to work. More recently that author also had the chance to join with Mike Sinai of Heidelberg Engineering to introduce now widely popularized forms of asymmetry analysis to tomographic NFL analysis. The statistical power of intra-subject symmetry has been repeatedly exploited in our prior physiologic studies,^{7–11} and by countless others working in various biological fields involving paired-organ systems. In the past, this powerful analytical tool has been systematically avoided in glaucoma research, on the false pretext of avoidance of non-independent variables and clinically insignificant

systemic crossover effects, in a manner that would most certainly aggravate John Ioannidis. Insisting on single eye comparative studies rather than placebo-controlled paired-eye studies cleverly smokescreens the very large contribution of predictable regression-to-the-mean to the purported IOP-reducing effect of topical ocular hypotensive drugs. The scientific methods that we applied in our perimetric refined data analysis were derived objectively, using our own available funds, and with no tangible influence of any commercial or career-serving vested interest.

We appreciate having this opportunity to highlight some of the fundamental principles underlying our approach, and we remain humbled by the extraordinariness of Nature. With that in mind we have already analyzed a new data set from a population of 41 patients with bilaterally comparable degrees of *mild, moderate, and severe* visual field loss, using more sensitive Frequency Doubling Technology Matrix 24-2 perimetry (manuscript in press). These new data reaffirm that substantial and highly significant tendencies toward binocular complementarity exist across the entire chronic glaucomatous disease spectrum, and suggest that additional exciting aspects of biologic symmetry appear to be in play in this process.

We thus enthusiastically agree with Denniss and Artes that the way forward is more data, and to aid that process we propose a friendly collaboration. To quote another cosmologist,¹² somewhat younger and more obscure than Sagan at the time of his utterance, “*The supreme task...is to arrive at those universal elementary laws from which the cosmos can be built up by pure deduction. There is no logical path to these laws; only intuition, resting on sympathetic understanding of experience, can reach them...*”

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