Responding to More than a Response: Tenotomy Improves INS Waveforms

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Experience has taught me the damage that can be caused by the publication of anything but the best information in the scientific literature. That is the reason for peer review. Its purpose is to have items for publication pass the careful scrutiny of experts in the field. Sometimes, the peer review process fails; bad information enters the literature, where, even if later retracted, it remains to cause its damage.

The situation that prompted this Report is neither a case of different conclusions drawn by separate groups performing equally good science nor anger over my conclusions being honestly questioned and criticized, resulting in a fit of pique on my part.

When writing a Letter to the Editor regarding a journal publication, one understands that the authors will be given the opportunity to write a Response if they so choose; that is fair. It is expected that their Response will be limited to the criticisms contained in the original Letter; to prevent an unending chain of responses by both parties, that is all that is permitted by the journal. Unfortunately, some authors abuse their opportunity to respond to the scientific concerns of a reader by: 1) not responding directly to the criticisms in the letter; 2) introducing topics that are unrelated to the criticism; 3) withholding critical information that is detrimental to their characterizations; 4) making arguments based on false premises; 5) attacking the author of the Letter, or his work; or 6) combinations of the above. In this way, they hope to obfuscate the key issues underlying the criticisms in the Letter, misdirect the reader, and cast doubt on the source of the criticism. Web publication provides a mechanism for the authors of the Letter to respond to such a Response, particularly when the abuse is egregious.

The subjects of this report are: 1) a pair of papers (companion papers) that attempted to assess the effects of tenotomy on Infantile Nystagmus Syndrome (INS, aka CN for congenital nystagmus) (1,2); 2) a Letter to the Editor (3); and 3) the Response by some of

the authors (4). The circumstances by which one of the companion papers' authors approved the Letter, refused to author the Response, and was also an author of a paper whose results contradicted those of the companion papers are complex and involve questionable behavior on the part of some of the companion papers' authors; that is discussed in more detail elsewhere (5).

With regard to the Response, my use of the term, "authors" refers to its three signatories, Optican, Miura, and FitzGibbon. With regard to the companion papers, for reasons that will become apparent (see below and elsewhere (5)), I also use the term, "responsible authors;" here I am referring specifically to Optican and Miura who were responsible for the data mining and analyses; based on my discussions with Hertle, I do not include him. I have no direct knowledge of the extent of FitzGibbon's involvement in the actual data analyses for the papers (by his inclusion as a signatory to the Response, he appears to be willing to share the responsibility for them). Also, the use of the pronoun "I" in the Response and the irresponsible personal attacks it contains suggest that Optican was the author and, as was done in the companion papers, other "authors" were added later.

In my Letter to the Editor, I restricted my discussion to the problems with the science of the companion papers. The key criticisms of the science were not persuasively addressed in the reply by the responsible authors. I believe their reply misdirects and obscures instead; that is bad science.

Summarizing the Major Criticisms of the Companion Papers

1. The wavelet paper used a method that is neither the accepted standard nor was ever used, or demonstrated to have the necessary sensitivity, to detect the changes in foveation quality that the NAFX does. Therefore, the authors' null finding cannot be used, as they did in their abstract, to conclude that tenotomy had no effect on the waveform.
2. Neither paper used data from controlled fixation by the eye whose data were analyzed; the authors chose not to analyze the 7 of 8 records from each recording session that contained intervals of controlled fixation. Therefore, their analysis included large eye deviations due to switches in the fixating eye and, therefore, could not be used to detect any changes with a significant effect on vision.
3. Neither paper used artifact-free data. Therefore, the data analyzed included artifacts due to blinks, voluntary saccades to other targets, and large involuntary drifting due to inattention; these significantly reduced their signal-to-noise ratio and further increased the likelihood that their methods would prove insensitive to the tenotomy-induced waveform changes and precluded the conclusions in the abstracts.
4. Neither paper used properly calibrated data. Calibration consisted of using mean eye position to get the eye within "10°" of the target and it was presumed (incorrectly, as I showed in my Letter) that the "preferred" eye was always the fixating eye. (This methodological *faux pas* was not evident until the responsible authors' failure to accurately calibrate the data was inadvertently revealed in their Response while attempting to justify their poor choice of which data files to analyze.) Accurate analysis of waveform changes affecting acuity *requires* accurately calibrated data from the eye that is actually fixating, not presumed to be fixating and certainly not 10° or more from the target.

5. The wavelet paper used data files that were mathematically pre-treated in a manner that further increased their noise content. This had the effect of masking significant changes in the waveforms and reduced their averaged-wavelet-coefficient analysis to the equivalent of a Fourier spectrum. Also, the pre-treatment method can only be used on stationary data; INS is not stationary.
6. The dynamical systems analysis paper was based on the presumption that INS was a single-source oscillation. Decades of research indicate that the multiple types of nystagmus in INS are due to two or three different kinds (read, underlying mechanisms and anatomical sites) of oscillations generated in different ocular motor subsystems. That precludes the conclusion in the abstract.
7. The companion papers were written in a misleading manner, including selective referencing and the omission of critical information.

Summarizing the Responses to the Above Major Criticisms
1. The authors did not address these key criticisms.
2. The authors did not effectively address this key criticism. They falsely claimed that artifacts could not be identified (see below).
3. The authors did not address this key criticism.
4. The authors indicated they could not accurately calibrate the data, but the significance of "analyzing" poorly calibrated data and making critical comparisons between such "analyses" was apparently not appreciated. The authors falsely claimed that calibration was "difficult;" although it might have been difficult for them, it was not for someone with experience in the recording, calibration, and analysis of INS data (see below).
5. The authors did not address these key criticisms.
6. The authors did not address this key criticism.
7. The prevalence of false and misleading statements and the authors' failure to include critical information in the Response was even worse than in the Companion Papers.

Misdirection and Obfuscation in the Response
Page 3095, paragraph 1: Although the description of why Hertle did not sign their Response seems to mirror the statement in my Letter, careful reading shows that it does not. When given the opportunity to read, edit, and comment, Hertle agreed with "the need for and content" of my Letter but not of their Response. There is no indication that he had any effect on the final content of the Response. Dr. Hertle has read this Report and found it fair and factual (see Comment below).

Page 3095, paragraphs 2 - 4: The NEI Clinical Trial was totally mischaracterized in paragraph 2. The *main outcome measure* was the NAFX that specifically measures eye-movement changes resulting from tenotomy; the vision measures were *secondary*. Thus, the approved NEI Clinical Trial was specifically designed to measure "changes in the eye movements before and after tenotomy as a clue to the mechanism underlying its therapeutic effects." In fact, I personally analyzed approximately 880 masked, eye-movement data records over the course of the Trial. The unsupervised data mining of Optican and Miura was neither needed nor approved by all of the members of the Clinical Trial research team. When their early attempts to discredit the Clinical Trial were detected in the middle of the Trial in violation of the NEI DSMC, they were specifically

forbidden to submit their data (5). Their benign description in this paragraph of their "reasonable" efforts served only to hide and justify their clandestine actions. False descriptions of the Clinical Trial are repeated in both paragraphs 3 and 4, for exactly the same reasons. In the Methods of the companion papers the following appears, "The protocol was approved by the NEI Investigational Review Board." Lest anyone be misled by the inclusion of that statement, the NEI IRB approval was for our Clinical Trial; it was *not* an approval of those two studies. Miura and Optican were not a part of the Clinical Trial and conducted the companion studies without the knowledge or approval of all of the scientists conducting the Clinical Trial.

Page 3095, paragraphs 4 and 5: Their introduction and discussion of the proprioception hypothesis for the mechanism underlying the INS waveform changes due to tenotomy was a red herring. Our hypothesis neither invoked nor needed a "stretch reflex." The "small" in "small-signal" is with respect to saccades (6); therefore, INS slow phases are indeed, "small." Büttner-Ennever's recent discoveries of two types of ocular motor neurons ("fast" and "slow") (7,8) and Goldberg's finding that proprioceptive signals reach the monkey primary somatosensory cortex (9) provide both the anatomy and physiology to support our "working hypothesis;" Optican's diversionary arguments were mired in an old, and possibly incomplete, paradigm that did not apply to our hypothesis.

Page 3096, paragraph 1: The NAFX was designed to be applied to data from the fixating eye during fixation of a target; to do otherwise, precludes its tight correlation to visual acuity (10). It has been repeatedly demonstrated by many users, in our lab and elsewhere, to be both objective and the most sensitive measure of precisely those changes in slow-phase waveforms that effect foveation (10-20). All data were analyzed according to a strict paradigm, detailed in our Clinical Trial protocol and approved by the NEI after a site visit to our lab. To state otherwise and invoke false images of data selection and bias was nothing more than a personal attack on the integrity of the method and those that developed it. It was also predicated on the authors' withholding critical information from the reader in an attempt to justify their use of two apparently insensitive methods. Specifically, the authors failed to inform the readers that *all* of the NEI Clinical Trial data analysis using the NAFX was done with *masked* data and *redundant* masked data files to both *prevent bias* and demonstrate the *objectivity* and *repeatability* of the NAFX. In contrast, Optican and Miura used *unmasked* data that *they selected* from our 880 files; therein lays the only opportunity for "operator bias to creep in". The authors' statement that, "changes in either the CN generator (sic) or plant would be observable with our methods" is unsupported by either the companion papers (even if they had applied the methods correctly to viable data) or any others published to date.

Page 3096, paragraphs 2 and 3: Their comments after quoting my Letter may seem reasonable but are irrelevant. Our hypothesis does not claim that proprioception is used for on-line control of individual eye movements. We hypothesized that proprioceptive information is used to set the operating point (read, "small-signal" gain) of the muscles. It is the resetting of that operating point after tenotomy that results in a diminished response (eye oscillation) despite an unchanged brain-stem signal (nystagmus slow phase). Apparently, the authors did not fully understand our hypothesis.

Page 3096, paragraph 4: The authors recognize the seriousness of my criticism that they made an "uninformed choice of data paradigm 8 for analysis," and "made serious methodological errors in the application of both types of analysis." They also recognized the implications of that statement. However, the authors' characterization of these methodological criticisms as "ad hominem" is unjustified and the prelude to their attempt to characterize the companion papers as joint study by the listed authors. I shall not use the word "clueless" to describe Hertle's knowledge of what was being done, how it was being done, or when it was being done; I prefer "preoccupied" (with the recruiting, screening, visual function evaluating (pre- and post-tenotmy), and performing tenotomies on the patients in the NEI Clinical Trial. A case could also be made for "naïve," given his relaxed, trusting, and honest approach to all. Again, I cannot comment on FitzGibbon's personal contributions to the actual analysis of the wavelet paper. However, given the knowledge I have (see (5)), my position is very defensible. I presume the "we" in why they chose the data they did, refers to the responsible authors; given that I trained Hertle and he has extensive experience running his own eye-movement recording labs specifically for INS patients, Hertle certainly knows how to accurately calibrate INS data without "difficulty" and was not involved in choosing the long, uncontrolled data files. In our monocular calibration paradigms, "roughly" (i.e., 10°) is simply unacceptable. Despite what the responsible authors "needed" for their choices of analysis techniques, there simply is no such thing as 10 minutes of uninterrupted fixation of an LED, not by INS patients, not by normal humans, not even by trained, hungry monkeys. The authors acknowledge that CN is non-stationary but their noise-producing, pre-conditioning routines were only valid for stationary signals, one of the methodological errors they failed to address in their Response.

Page 3096, paragraphs 5 and 6: The authors failed to recognize that the representative record I "chose" in my Letter to illustrate their errors was one of those they "chose" to analyze in their paper; whether pre- or post-tenotomy is just another irrelevant factoid to my and Hertle's argument that such records are unsuitable. Are the authors suggesting that post-tenotomy data did not contain those artifacts? If so, that suggests tenotomy also eliminates blinks, periods of inattention, switches in the fixating eye, or voluntary saccades to other targets in the patient's visual field; that certainly would be impressive but would only justify using such records for the post-tenotomy data. The authors continue to miss the point. INS is extremely sensitive to all of the above influences and, therefore, they must be controlled or any analysis will be so confounded as to be useless; but that was exactly my criticism. Our paradigms were carefully written and based on decades of experience first, to allow for accurate monocular calibration of all the data and second, to ensure we were only analyzing periods of fixation by the eye whose data we were analyzing. Under those conditions, an increase in the NAFX translates directly into an increase in visual acuity; no such correlation has ever been suggested for wavelets. With regard to what I "claim" is noise, I can only state that my experience in recognizing all of the above artifacts and distinguishing them from true fixation in an INS patient is highly transferable, as the many post-docs, students, and visiting scientists who studied in our lab can attest; the responsible authors have no comparable experience and to them, it appears magical. They claim their methods required no subjective judgments of the kind

all researchers in ocular motility make to ensure they are analyzing clean data; clearly what was required was the kind of scientific judgment that was not apparent in their papers. The diversion on "mental state" is just that; we routinely differentiate attentive fixational eye movements from different types of artifact, all of which are easily detected from the data by the trained eye. It was refreshing to see that they agreed on the importance of fixation attempt (they *have* learned something from my work); I would only point out again the extensive literature already demonstrating that our objective methodology (the NAFX applied according to our strict paradigm) accurately detects and measures foveation quality from fixation intervals that correlates closely with visual acuity (10-20). What they failed to recognize is that the "future" has been with us for over a decade.

Page 3096, paragraph 7: I have already listed the many methodological errors in the companion papers specific to each method. The authors' speculation that "any effects of tenotomy should have been apparent at some time scale or in some part of the state-space trajectory" is a supposition that has never been demonstrated, neither by them nor others. The NAFX does detect and accurately measure the very small changes in the duration of the foveation periods of the INS waveforms (or the position or velocity SD's of foveation) that result in increased visual acuity; no one has ever demonstrated that either of their methods are capable of such sensitivity, even when applied to clean fixation data without the methodological errors in the companion papers. One could argue that the INS waveform changes produced by tenotomy (and measured by the NAFX) are "only a quite small effect" especially if one did not understand the significance to improved visual acuity of even a 10-30 msec increase in foveation time or a 20% decrease in either the position or velocity SD of foveation. Perhaps that is why these "small" but mighty changes appear to be undetectable by the global measures used by the authors. Again, the authors try to mirror statements from my Letter but don't quite make it. The "sources" (plural) of INS are not the same as trying to detect a change in a mythical "mechanism" (singular).

Page 3097, paragraph 1: Unfortunately, the only thing the companion papers do show is that two untried (on pre- and post-tenotomy INS waveforms) methods that were never demonstrated to be sensitive enough to detect the post-tenotomy changes measured by the NAFX, did not detect those changes when they were applied to poorly calibrated, uncontrolled, and artifact-ridden data after mathematically incorrect, noise-inducing pre-treatment and wavelet-coefficient averaging. That proved nothing about the effectiveness of tenotomy in improving INS waveforms. Tenotomy does not cause some undefined (magic?) changes in the afferent visual system. It is applied to the peripheral motor system and that is where it has its direct effects. Our dramatic findings on a single canine of improved post-tenotomy NAFX, were considered sufficient evidence by the NEI to conduct the Clinical Trial; that attests to their therapeutic strength. The medical goal of improving vision should not cloud the issue of how to best measure the effects of an EOM surgery; the direct effects of tenotomy are motor and that is why we designed the NEI Clinical Trial to measure the eye-movement changes as the *primary outcome measure*. To do as the authors suggest and measure visual acuity (or other psychophysical measures of visual function) as the primary outcome measure(s) of a muscle surgery is

just bad science; in the Clinical Trial, we measured visual function in several ways as *secondary outcome measures* and, thereby demonstrated again their correlation to the NAFX-measured waveform improvements.

Page 3097, paragraph 2: The authors' gratuitous reference to the paper on the tenotomy procedure applied to a monkey with Fusion Maldevelopment Nystagmus Syndrome (FMNS, aka LMLN for latent/manifest latent nystagmus) without citing the Letter to the Editor pointing out the latter diagnosis, was discussed in my Letter. What is amazing is the authors' statement in their Response that whether the monkeys had FMNS (a diagnosis agreed to by Tychsen) or INS, two mechanistically and clinically different disorders, is a minor point. We demonstrated tenotomy's effects on INS waveforms, not FMNS. The waveform studied in the monkeys was the low-amplitude, high-frequency pendular oscillation that is sometimes seen in addition to either INS or FMNS in humans; its very different characteristics than INS waveforms may make it less sensitive to the effects of tenotomy. My colleagues have repeatedly demonstrated in numerous peer-reviewed publications the objective evidence of tenotomy's INS waveform improvements. We never claimed that those improvements occurred only in brief intervals of attentive fixation effort; in fact they persist for as long as the patient attentively fixates. Inattention can eventually lead to a cessation of the INS waveform and an artificially high NAFX but such a measurement would not be related to visual acuity; that is why the NAFX is only applied to fixation data. The authors' mistaken presumption of a brevity in tenotomy's effects reflects their confusion between tenotomy's permanent improvements with our time-proven experimental paradigms that ensure gathering as much fixation data at as many gaze angles as possible, in as short a time as possible. When dealing with young patients (unlike monkeys) we usually have only one opportunity to get the child's data and, because we are dealing with a low attention span and lack of desire to be there constrained to look at boring LED's, we only present targets for enough time to ensure target foveation for a few seconds at a time (we then repeat the stimuli). Thus, contrary to the false suggestion that we pick the intervals to analyze, we actually use *all* the fixation intervals that the data files contain. It should be noted that this mimics normal visual behavior where one looks at a target, quickly identifies it, and then looks at another; e.g., "target" may refer to different features on someone's face. NAFX analyses on longer intervals (10-30 sec without blinks or other artifact) taken from dedicated adult volunteers yield exactly the same accurate measures of foveation quality as those from shorter intervals.

Page 3097, paragraphs 3-4: This attack on a pioneering and revolutionary body of work involving this author with other respected scientists (including Hertle) in the study of the ocular motility of the first mammals with achiasma (12,21-30) is but an extension of the authors' biased attempts to discredit the source of the methodological criticisms of their companion papers contained in my Letter. It is replete with the same kind of false statements, mischaracterizations, and refusal to admit the obvious. All who were involved in the studies, who ever saw the dog pre- and post-tenotomy, and the scientific community who read our papers recognized the significance of the work. Tenotomy totally damped (horizontal INS) or eliminated (vertical SSN) the nystagmus and radically improved the dog's visual behavior; the impressive NAFX improvements merely put an

objective number to the obvious success of tenotomy. I will not dignify their diversionary attack on the integrity of that body of work with a point-by-point discussion of their misstatements as I have done with the rest of their Response. If they disagreed with the findings of any one of those papers, they should have written a Letter to the Editor, as I did. Unlike the authors of the Response, my Response to such a Letter would have been confined to their specific criticism. Regarding their comments on the data shown in a paper, all papers can only show a representative subset of the data; their vacuous statement is not valid criticism. INS waveforms show idiosyncratic variability pre- and post-therapy; the important measure is in both the range of and average value of key measures. In both, the NAFX shows post-tenotomy improvements. In our experience, our paradigms show no significant variability in the NAFX across patient visits; the number of return visits in the Clinical Trial conformed to the NEI protocol and were sufficient to confirm what we already knew from our years of experience.

Page 3097, paragraph 5: Perhaps these authors don't know why visual function improves post-tenotomy but our published data prove that it is the foveation improvements in the INS waveforms that result in improved visual function, including in patients with significant afferent visual deficits (10-15,17-20). As to the etiology of INS, there is an excellent behavioral ocular motor system model whose hypothetical causal mechanism for most INS waveforms has been supported by its subsequent emergent predictive responses (31-33). The rest of this paragraph is simply random speculation caused by their failure or unwillingness to objectively evaluate the NAFX results.

Page 3097, paragraph 6 (onto Page 3098): The demonstrated improvements in visual function brought about by tenotomy are not "claims," they are measurable facts already proven to objective minds. These authors are not in a position to determine how INS affects an individual (something about which I have direct knowledge) or what therapeutic measures should be taken to greatly improve visual function; that is a clinical opinion. The responsible authors do not have, to my knowledge, the training or experience to offer this opinion. I know they lack my training and experience in the study of INS waveforms. The responsible authors are casting aspersions on results drawn from data that were properly obtained, correctly calibrated, and analyzed (while masked) with objectively proven methods; they did none of these things.

Conclusions

The Response failed to adequately respond to the important scientific criticisms in the Letter. Instead, it was written in a manner both to confuse and mislead the readers and used as a platform for a personal attack (dressed up to look like "science") on the author of the Letter. The responsible authors revealed both a single-minded bias and a remarkable ignorance of the past 45 years of INS research, beginning with, but not limited to, the ability to accurately calibrate nystagmus patients' eye movements. Bad science can appear in good journals both in the form of papers and "Responses" to legitimate criticism, in this case, both. The false conclusions in their abstracts remain unsupported by their own analyses. Tenotomy produces significant improvements in INS waveforms that can be measured by the NAFX and that result in improved visual function.

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Comment:

"You have a done an excellent job being fair and factual, I have no problem with the text." Richard Hertle, 7/9/07.

Addendum (added 9/23/08):

Able et al. published a paper that demonstrated the inability of wavelet analysis (even when done correctly) to differentiate pre- and post-therapy INS waveforms; wavelet analysis could not even differentiate classical INS waveforms with very poor foveation quality from those with very good foveation quality. The NAFX easily measures and differentiates all nystagmus waveforms with differing foveation qualities. Thus, this paper demonstrated conclusively that: 1) wavelet analysis of INS waveforms is too insensitive to detect the visual-function improvements in foveation-period characteristics, produced by the tenotomy and reattachment procedure and 2) the NAFX does measure those waveform changes.

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