

Reply to “Letter to the Editor”

Tenotomy and congenital nystagmus: a null result is not a failure, for “It is not the answer that enlightens, but the question”

In his Letter, Dell’Osso (submitted for publication) argues that we “asked the wrong question and misapplied [...] two analysis techniques” to data from the NEI clinical trial of the tenotomy procedure for CN patients. We strongly disagree, and provide this detailed response to prevent anyone from inferring by the lack of a rebuttal that Dell’Osso’s claims are correct. (NB: Our other co-author, Dr. R.W. Hertle, was given the opportunity to read, edit and comment on this Letter, but declined to sign it because he was co-author on the two analysis papers and the Phase-1 Tenotomy Clinical Trial paper.)

Philosophically, we do not regard our study as a failure. As the quote above from Decouvertes emphasizes, it is not always easy to know which question is the right one to ask. The purpose of the Phase-1 Tenotomy Clinical Trial was to examine the effects of the tenotomy procedure on patients with congenital nystagmus (CN). Whereas the main question is whether tenotomy improves their visual performance, a secondary question is by what mechanism the tenotomy has its effect. To answer the latter question, it is reasonable to look for a change in the *eye movements* of CN patients. Although we reported a null result (Miura, Hertle, FitzGibbon, & Optican, 2003a; Miura, Hertle, FitzGibbon, & Optican, 2003b), we do not think it was unreasonable to look for changes in the eye movements before and after tenotomy as a clue to the mechanism underlying its potential therapeutic effects.

Dell’Osso claims that we made “unsubstantiated speculations about CN data analysis and tenotomy-induced waveform changes resulting in improved potential acuity.” He also claims that we “created the false impressions in the minds of readers that our original hypothesis for mode of action of tenotomy was disproved and that the procedure was not successful.” These criticisms originate in a misunderstanding of the purpose of our work and a misreading of its text. In fact, what we said was:

Horizontal rectus tenotomy with simple re-attachment has been proposed as a therapy for CN. This

therapy might affect vision and/or eye movements. Another paper deals with improvements in visual acuity. This and the companion paper examine changes in eye movements. (Miura et al., 2003a, p. 2345.)

We thought that this statement clearly established that our papers would not address effects of tenotomy on visual acuity, a topic dealt with in the paper by Hertle et al. (2003). As for the claim that we created a false impression about the mode of action of tenotomy, I don’t see how this is possible, because there is no coherent hypothesis about the mode of action. In his letter, Dell’Osso says that his “working hypothesis” is that:

the mechanism by which tenotomy improves CN waveforms is that it alters a proprioceptive feedback loop involved in maintaining resting muscle tension and reduces the small-signal gain of the ocular motor plant; that results in a reduced response to the basically unchanged CN signal. (Dell’Osso, submitted for publication.)

However, it has been known since the classic work of Keller and Robinson (1971) that there is no stretch reflex controlling the extraocular muscles. Furthermore, the ocular motor system is approximately linear over a very large range (at least $\pm 30^\circ$ in humans), so there is no “small-signal gain” that is different from the overall gain. In fact, if the tenotomy procedure did lower the gain of the eye plant, it would reduce the gain of the vestibuloocular reflex, inducing oscillopsia in the patient. The cerebellum would respond to the retinal slip by increasing the neural gain to compensate for the muscle weakness. This adaptive capability makes it unclear how weakness after tenotomy could be a mechanism for improving acuity in CN patients. Finally, the movements in a CN waveform are not small, and thus the question of a “small-signal gain” is moot. Interestingly, Dell’Osso’s working hypothesis also states that the “tenotomy improves CN waveforms.” Unfortunately,

he presents no objective evidence for this. The NAFX measure may improve, but that is not an objective measure, because it requires segments of the record to be selected, allowing operator bias to creep in. Finally, we did not measure the "CN signal" directly, but only the CN waveform; changes in either the CN generator or plant would be observable with our methods. Thus, it can not be said that our study of the waveforms of CN pre- and post-tenotomy is inappropriate or misleading.

Dell'Osso also says that

it is unlikely that the simple muscle surgeries commonly used therapeutically in CN could alter the underlying brain stem mechanisms. Therefore, the negative results of the companion papers' attempts to test their improbable hypothesis were to be expected and should have provided support for our alternative hypothesis. (Dell'Osso, submitted for publication.)

The hypothesis we tested is that the extraocular proprioceptive feedback from the muscles influences the CN waveform. Some literature suggests that the feedback signal from the extraocular muscle is not used in controlling eye movements, but may be used in calibrating them; this issue is far from settled yet (Lewis, Zee, Hayman, & Tamargo, 2001). Our results support the conventional hypothesis that proprioceptive afference is not critical to generating normal eye movements, and extends it to include the abnormal eye movements of CN. Thus, at the current stage of oculomotor research, our hypothesis was not unreasonable or improbable, and disproving it does not automatically support any other hypothesis, such as that it is due to changes in "small-signal gains".

Dell'Osso's next charges are quite serious: that we made an "uninformed choice of data paradigm 8 for analysis" and "made severe methodological errors in the application of both types of analysis," thus rendering our results "moot." This ad hominem attack suggests that the four authors, including Dr. FitzGibbon, who made the eye movement recordings from these subjects, and Dr. Hertle, who was the PI on the clinical trial protocol, were clueless about what was going on. That claim is indefensible. The main reasons we chose not to analyze data from other paradigms are that those data were often difficult to calibrate, and the short fixation periods often meant just a few beats of nystagmus were (roughly) near the target. In contrast, the data in paradigm 8 were much simpler to study, because there were long periods of time when the subject was (roughly) near the primary position. We needed long duration records because our analysis techniques were designed to look at changes on both long and short time scales. At least three minute long records were needed to allow time for the effects of the non-stationarity of CN to be observed.

Dell'Osso further argues that we cannot analyze the data from paradigm 8 because the patient was simply asked to fixate a target straight ahead for several minutes. The reason he gives is that:

the driving and modulating force of CN, fixation attempt, could not be controlled for that length of time, nor could voluntary saccades, *changes* in the fixing eye [...], or blinks. (Dell'Osso, submitted for publication.)

He conveniently provides example records in his figure (although all are from pre-operative data) and claims that he can tell when the subject is attending to the target, and which eye is fixating. When anything else is happening, Dell'Osso claims that it is noise, and argues that therefore one cannot analyze the records. That is nonsense. It seems clear to us, even in the figure provided in his letter, that the patient's CN is manifest at all times in the records. Our analyses were chosen specifically because they did not require any subjective judgments about the mental state of the subject. The purpose, remember, was to compare the waveforms before and after tenotomy surgery. Which reminds us of the old adage: "one man's noise is another man's signal." A complete description of the nystagmus correlated with the behavioral state was not required. Indeed, one might argue that our results are not confounded by any assumptions about the patient's mental state and by any bias on the part of the investigator. Dell'Osso is essentially arguing that tenotomy improves the eye movements of CN patients, but only when they are in a certain mental state, and that this occurs so infrequently that it is not detectable without reference to the patient's mental state. This is a difficult argument to disprove, because we have no objective way to monitor the subject's mental state. Nonetheless, we agree that fixational or attentive effort may be an important factor. Thus, in future experiments the question of improvement in patient performance only during brief epochs should be addressed objectively.

Dell'Osso's next point is that CN waveforms are complex, and thus can not be analyzed by our methods without selecting attentive portions of the record. We are not unaware of the complexity of CN waveforms, but make the counter argument that our techniques were correctly chosen to deal objectively with non-stationary, non-linear dynamical systems. Furthermore, our approaches are model-free, so any effects of tenotomy should have been apparent at some time scale or in some part of the state space trajectory, if they were anywhere in the records. Therefore, we stand by our result, that tenotomy has no, or only a quite small, effect on the underlying mechanism of the CN waveform. This should not cause any problems for the future study of tenotomy as a therapy for CN, because Dell'Osso has stated that "tenotomy was neither designed nor predicted to affect the sources of CN."

Dell'Osso concludes by stating that "the papers in question failed to provide either proof or useful insight into whether or not tenotomy affected the underlying mechanisms responsible for CN." We couldn't disagree more strongly. Our papers show that two objective measures of the waveform remained essentially unchanged before and after tenotomy. We think it is reasonable to conclude from this that tenotomy did not affect the underlying CN mechanisms. That certainly does not mean that there cannot be other effects of tenotomy, outside the motor system, that can improve visual performance. Furthermore, it suggests an improved design for future tests of the proposed therapy that distinguish among motor, mental, and sensory effects. Dell'Osso's finding that "tenotomy produces significant, NAFX-measurable CN waveform changes that improve potential acuity" is simply too weak to prove that tenotomy is a useful therapy for patients with CN, because of the subjective nature of the NAFX and the irrelevance of "potential acuity." If improving visual performance in patients is the goal of the therapy, studies should control for non-surgical effects and test acuity with standard psychophysical techniques.

In our papers, we were interested in the general issue of the common properties of the underlying mechanism that generates CN. We never claimed in these two papers that the visual performance of individual patients was not changed by tenotomy surgery. We merely suggested that there was no common effect on the nystagmus across the patients that would elucidate the underlying mechanism for CN. This finding was similar to the one obtained by Wong and Tychsen (2002), who performed the tenotomy procedure on monkeys and found either no change or a speeding up of the nystagmus slow phase. Thus, we cited their paper. Whether their monkeys had congenital or latent or manifest latent nystagmus is a minor point (Dell'Osso & Hertle, 2002). The major point is that they did not see consistent changes in the nystagmus in their monkeys. Thus, we have seen no objective evidence that tenotomy causes a consistent change, let alone improvement, in nystagmus waveform (CN, latent, or manifest/latent) in monkeys or humans. If Dell'Osso disagrees, he needs to demonstrate with some objective measure exactly what it is about the nystagmus waveforms that is improved after surgery, and why that improvement occurs only in brief intervals during attentive fixation effort.

Our null result may seem so surprising because it is well known that strabismus surgery (e.g., Anderson-Kestenbaum procedure) can ameliorate nystagmus in some strabismus patients with CN (cf. Dell'Osso & Flynn, 1979). However, interpreting the effects of surgery in patients with both CN and strabismus is difficult because of the confounding of the two disorders. It also seems surprising because it is commonly assumed that tenotomy surgery caused a big change in the nystagmus

of Belgian sheep dogs. Unfortunately, the evidence for the success of tenotomy in dogs is not very compelling. Dell'Osso reported on a family of achiasmatic Belgian sheep dogs with congenital and see-saw nystagmus (Dell'Osso & Williams, 1995; Dell'Osso, Williams, Jacobs, & Erchul, 1998), and later studied the effects of tenotomy on just one of those dogs, M5 (Dell'Osso, Hertle, Williams, & Jacobs, 1999). In the dog tenotomy paper, only one pre-operative record, lasting just six seconds, is shown for M5. The paper's eight other figures show only post-operative data. Thus, to appreciate how big the change in nystagmus was for M5, it is necessary to compare records from the earlier reports on the dogs, several years before the tenotomy. Fortunately, data from M5 appears in Figs. 1–3 of the 1998 paper. (M5 also appears in figure 4b of the 1995 paper, but the data was uncalibrated.)

Comparisons of those earlier recordings with the post-operative data in the 1999 paper does not clearly show a long-term effect of the tenotomy on the dog's nystagmus waveform. The problem is that the waveforms are highly variable in the pre-operative data, and the post-operative data falls within that range. There is no way to know whether the changes in the post-operative data were caused by the surgery, some non-surgical effect, or simply because the data shown were a subset of the full range of waveforms. Thus, without a more thorough investigation of the variability of the nystagmus both before and after surgery it is not clear what can be concluded about the effects of the tenotomy. A similar problem was found in the human CN patients in this clinical trial, because there was a lot of variability across patients and within patients across visits, but there were not enough visits to characterize this variability (Miura, FitzGibbon, Hertle, & Optican, 2001).

Although our investigation found a null result, it was not meaningless because the mechanism and etiology of CN remains a compelling mystery. As shown in Dr. Hertle's other study of these same patients (Hertle et al., 2003), the visual performance was improved after tenotomy surgery in some patients. However, we don't know why it improved. Was there a psychological effect of paying more attention to the patients, or more experience in testing, or better use of the visual information available, or less afferent "noise" coming from the tenotomized muscles, or less nystagmus during attentive fixation? Taken together, Hertle's paper and Miura's two papers suggest that the mechanism generating CN has not changed, but some other mechanism related to viewing skill, driven by the patient's attention or intention, might be improved after the procedure. What we can not conclude is that such a change was due to the effects of the tenotomy, as opposed to some other, psychological, mechanism.

In conclusion, we follow the old adage that "extraordinary claims require extraordinary proofs". If one

is proposing an invasive eye surgery, with all its attendant risks, as a therapy for a non-progressing, non-disabling disorder, one should have to show a significant benefit to the patient. Even after this phase-I clinical trial of the tenotomy procedure, the risk/reward balance is still unclear for CN patients who are otherwise normal. This is especially important because it is possible to study the effects of tenotomy in patients who would otherwise undergo surgery anyway, as in patients with both CN and strabismus (Dell'Osso & Flynn, 1979). In the future, such studies must include controls for non-surgical effects on the patient's performance.

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