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Letter to the editor:

**Grating visual acuity in infantile nystagmus in the absence of image motion
(response)**

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22 **Introduction**

23 We would like to thank Dr Dell'Osso for his critique of our work, as well as for highlighting
24 the issue of visual acuity (VA) testing in the presence of infantile nystagmus (IN). It has long
25 been assumed that VA could be improved by reducing the intensity of the nystagmus (i.e.
26 the average velocity of the eye movements), and as cited by Dell'Osso, there are many such
27 claims in the literature (discussed below). Over the last few decades, this intuitively
28 appealing view has become entrenched as the theoretical basis for numerous therapeutic
29 interventions. Indeed, Dell'Osso's critique of our study begins and ends by appealing to this
30 notion, but we would remind him that intuition is no substitute for scientific rigour.

31 **Study design**

32 In our study¹, we have demonstrated that there exists a fundamental underlying limitation
33 in the VA of adults with IN, even in the *absence* of retinal image motion. By presenting
34 grating stimuli using very brief flashes of light that were less than 1 ms in duration, we were
35 able to virtually eliminate any motion blur induced by the eye movements themselves, thus
36 unmasking the underlying VA. Subjects with IN and controls were tested under both
37 constant and brief (tachistoscopic) lighting conditions. The brightness of the flash was
38 adjusted so that control subjects showed no change in VA. However, contrary to the
39 assumption that the eye movements of IN degrade VA, there was also no significant
40 improvement whatsoever in subjects with IN when the effect of their eye movements (i.e.
41 motion blur) was eliminated.

42 Clearly, Dell'Osso has missed the point of our experiment. He erroneously states that we
43 used a flash with a duration of 75 ms, whereas the duration was, in fact, only 0.76 ms. Such

44 a brief presentation ensured that there was virtually *no* retinal smear caused by the
45 nystagmus. His error is further compounded when he suggests that longer (i.e. 100 ms)
46 presentations during foveating periods of the waveform might have worked better – a
47 duration that long would produce substantial retinal smear and completely defeat the
48 purpose of our experiment. Dell’Osso also expresses concern that the waveform
49 characteristics of our participants might have affected the outcome. However, the
50 fundamental premise of the experiment was to *circumvent* the eye movements altogether
51 by eliminating image motion. Our paradigm thus nullified possible effect of waveform
52 variations in order to provide a measure of the subjects’ underlying spatial acuity threshold.
53 For this reason, even if we were inclined to compute NAFX, it would have no meaning in this
54 context. Moreover, the number of presentations available to each participant was
55 unrestricted in order to overcome the possibility (as yet untested, despite Dell’Osso’s
56 claims) that detailed visual information cannot be gathered during non-foveating portions of
57 the waveform. The gratings used in our study were sufficiently large that the fovea was
58 always pointing at the stimulus whenever the flash might have occurred. Dell’Osso also
59 argues that poorer VA for vertical rather than horizontal gratings supports the notion that
60 VA is limited by the horizontal nystagmus, and clearly dismisses the possibility of meridional
61 amblyopia, as originally suggested by Abadi and King-Smith².

62 **Within subject measurements of VA**

63 In our paper, we pointed out that a correlation between VA and various aspects of the
64 nystagmus waveform (e.g. foveation duration, intensity, etc.) appears to be based on inter-
65 subject comparisons. In rebuttal, Dell’Osso cites an impressive list of 12 papers in support of
66 intra-subject improvement in VA³⁻¹⁴, but in our view, his interpretation exaggerates any

67 such support. Close inspection reveals that only one of these papers actually provides
68 statistical evidence of such a change¹³ – as measured using standard letter charts. Of the
69 other studies, six contained three or fewer subjects^{4,6,7,9,11,14}. In fact, four of these studies
70 only used one subject: Dell’Osso himself^{4,7,9,14}. Two of the papers cited were reviews, and
71 thus contained no new data^{8,10}, while the remaining three found statistically significant
72 changes in nystagmus waveform characteristics, but *failed to detect significant changes in*
73 *VA*^{3,5,12}. In three of these studies^{4,7,9}, VA was not even measured, but instead NAFX was used
74 as an outcome measure, from which VA was *predicted*. NAFX is a computed number based
75 on waveform shape and does not include any perceptual component. Thus, these studies
76 only confirm a change in waveform, and any claim that this reflects improvement in VA is
77 completely circular.

78 Despite the lack of clear evidence in the above studies, we are aware of a handful studies
79 that *have* found a statistically significant change in VA in response to waveform
80 modifications. These include the work of Hertle et al.¹⁵, who showed improvements in VA
81 following head posture surgery, and McLean et al.¹⁶, who treated patients with memantine
82 and gabapentin. We did not, and would not, suggest that VA cannot be improved *at all* in
83 every subject with IN. On the basis of our results^{17,18} (and those of others^{19,20}), our
84 conclusion was, and remains, that treatments that seek to slow the eye movements of
85 adults with IN are likely to be *fundamentally limited* with regards to the improvements that
86 can be expected in VA.

87 **What is VA?**

88 Crucially, *none* of the studies that purport to have found a change in VA used strict
89 psychophysical procedures to determine the outcome. It is worth noting that all studies of

90 IN that *have* involved such techniques (i.e. forced choice staircase procedure or similar)
91 have failed to detect significant changes to VA in response to modifications of the
92 waveform, whether through stress^{17,19} or altered gaze angle^{18,20}. Nonetheless, some
93 individuals with IN report improvements in their ‘vision’ following treatment, as well as
94 when viewing using their preferred gaze angle (null zone).

95 How might this discrepancy between VA measurement and subjective perceptual
96 experience arise? In order to understand this, it is first worth reiterating the definition of
97 *visual acuity*, i.e. the spatial resolution of a visual system. It has long been suspected that,
98 due to difficulties in the accurate timing and deployment of gaze in IN, letter charts are
99 inadequate as a sole measure of visual function. Dell’Osso himself has published at least one
100 study that reaches this same conclusion⁸.

101 **The limitations of letter charts**

102 Letter charts are generally assumed to provide a pure measure of the spatial resolving
103 power of the visual system, yet there are inherent time constraints. Any good clinician will
104 know to give their patient plenty of time before responding to a chart, and this is especially
105 true in the case of nystagmus. Nonetheless, viewing duration is limited by the ‘need to
106 move on’ to the next test, and the near absence of double-blind clinical trials in the IN
107 literature makes it difficult to ensure that bias does not creep into the testing process when
108 obtaining results (i.e. inadvertently allowing more time). In contrast, these issues are greatly
109 reduced if not eliminated when using forced choice psychophysical testing. Hence, we argue
110 that this level of discipline is necessary in order to claim that a therapeutic intervention is
111 capable of eliciting improvements in spatial or any other visual function. Letter chart testing
112 may ultimately turn out to be part of a sensitive test of *overall* visual function in IN.

113 However, it is likely that changes in VA, as measured with a letter chart, may not represent
114 an actual change in *spatial* acuity but rather intrinsically include a *temporal* aspect of visual
115 performance, such as target acquisition latency, that may well be influenced by changes in
116 nystagmus intensity and/or foveation duration. As Dell’Osso himself has argued, this is why
117 eye movement based assessments of visual function are more appropriate in patients with
118 IN⁸.

119 The participants in our experiment, who were comfortably seated and viewed stimuli using
120 their null zone, did not benefit from the removal of retinal image motion. However, it
121 remains possible that, in other studies, an unusually large *increase* in nystagmus intensity
122 (e.g. due to stress owing to the prospect of undergoing experimental eye surgery) might
123 result in a motion-blur-induced *worsening* of spatial acuity. Nevertheless, such a change in
124 VA has repeatedly escaped detection in controlled psychophysical experiments. Cham et al.
125 and Jones et al. both induced an increase in nystagmus intensity by introducing stress^{17,19},
126 but found no significant change in VA. Similarly, Erichsen et al. and Yang et al. systematically
127 assessed VA at different gaze angles^{18,20}, and they too were unable to elicit statistically
128 significant changes in VA.

129 **The relationship between waveform and VA between subjects**

130 The well documented correlation between VA and waveform parameters, when considering
131 a range of *different* subjects with IN, remains to be explained. Intuitively, increasing the
132 time the fovea spends directed towards the object of regard (i.e. increasing ‘foveation’
133 duration) might be expected improve the visual experience. Indeed, this has been
134 demonstrated in control subjects²². However, in light of our results and those of others, any
135 improvement in the vision of a given individual with IN is unlikely to involve a substantive

136 change in spatial acuity *per se*. We suggested in our paper that the observed inter-subject
137 correlation may result from the waveform parameters, as measured by a metric such as
138 NAFX, being ‘matched’ during development to the available VA in a given subject. This is
139 certainly consistent with a recent longitudinal study of nystagmus in young children²³. An
140 important implication of this view is that, if there truly is such a thing as ‘isolated’ IN (i.e. IN
141 in which there is no comorbid afferent visual system pathology), then reducing nystagmus
142 intensity *during the critical period for visual development* might result in long-term
143 improvements in VA.

144 **Summary**

145 Attempting to measure visual changes using inappropriate tools may be doing a disservice
146 to our patients. The subjective improvements to visual function that patients sometimes
147 report following treatment are not consistent with the disappointing improvements
148 obtained in ‘VA’, which – if they occur at all – are typically less than two lines on a chart.
149 Indeed, the ETDRS chart, a staple in vision research, is known to be relatively insensitive to
150 such small changes, even in the absence of nystagmus²⁴. Directing our efforts towards more
151 appropriate perceptual measures than VA alone may finally provide evidence to back up
152 anecdotal reports for the usefulness of therapies.

153 Dell’Osso has claimed that our conclusions might be used to “deny effective treatment to
154 nystagmus patients”. However, as we have discussed above, although the eye movements
155 may be affected, VA has not been demonstrated to improve after changes to the waveform,
156 which is entirely consistent with our results. Whether this reflects the inadequacy of VA as
157 an outcome measure or the failure of such treatments to actually improve vision remains to
158 be determined. The fact that at least some patients report “improved vision” means that we

159 must strive to determine what other aspects of their vision, such as “time to see”, might be
160 affected by a given treatment. Although waveform-measuring functions such as NAFX
161 attempt to quantify any changes in visual performance, they are unfortunately predicated
162 on aspects of spatial visual function (VA), which have repeatedly been shown to be relatively
163 unmodifiable, when measured appropriately.

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