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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 study<sup>1</sup>, 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-Smith<sup>2</sup>.

## 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 VA<sup>3-14</sup>, 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 change<sup>13</sup> – as measured using standard letter charts. Of the  
69 other studies, six contained three or fewer subjects<sup>4,6,7,9,11,14</sup>. In fact, four of these studies  
70 only used one subject: Dell’Osso himself<sup>4,7,9,14</sup>. Two of the papers cited were reviews, and  
71 thus contained no new data<sup>8,10</sup>, while the remaining three found statistically significant  
72 changes in nystagmus waveform characteristics, but *failed to detect significant changes in*  
73 *VA*<sup>3,5,12</sup>. In three of these studies<sup>4,7,9</sup>, 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.<sup>15</sup>, who showed improvements in VA  
81 following head posture surgery, and McLean et al.<sup>16</sup>, 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<sup>17,18</sup> (and those of others<sup>19,20</sup>), 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<sup>17,19</sup> or altered gaze angle<sup>18,20</sup>. 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 conclusion<sup>8</sup>.

### 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 IN<sup>8</sup>.

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<sup>17,19</sup>,  
126 but found no significant change in VA. Similarly, Erichsen et al. and Yang et al. systematically  
127 assessed VA at different gaze angles<sup>18,20</sup>, 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 subjects<sup>22</sup>. 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 children<sup>23</sup>. 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 nystagmus<sup>24</sup>. 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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