LETTER TO THE EDITOR


Concomitant impairment of multiple visual pathways in Parkinson’s disease

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We are thankful for the author’s interest in our work, and for his constructive comments. We do also find some of his intriguing speculations on a possible role of dopamine in retinal toxicity quite interesting. However, there are some factual and conceptual misunderstandings that we need to address. Although these are in most cases subtle inaccuracies, they are however critical regarding the main points. Despite these facts we would like to stress that we find that the commentary also contains many valid and interesting points.

We do find concomitant impairment of multiple visual pathways in Parkinson’s disease and made clear in the paper that age-matching eliminates ageing as a between-group confound. It should also be understood, as a major point that was discussed in the paper, that it is also important to carefully exclude within each group disorders typical of aged groups, such as ocular hypertension (even in absence of glaucoma) and diabetes (even in absence of retinopathy). Our main point was that the external validity of any study becomes compromised if this is not taken into account, and we hope that this point has now become clear.

The simple fact that we use an age-matched control population avoids age itself as a confound and is the methodological procedure of choice (Silva et al., 2005). It should also be understood that age-matching is not enough, and should be complemented with strict exclusion criteria, to prevent that subjects with subclinical disorders typical of that age group, such as ocular hypertension or diabetes, are included. These disorders may lead to achromatic and chromatic deficits that are completely unrelated to PD. The possibility that other medical conditions of old populations could influence in particular ‘tritan’ like measures in PD was also previously recognized by Birch et al. (1998), and discussed in our paper. Unfortunately, this paper is omitted from Gaynes’ comment. This omission is somewhat critical because this paper is a more recent update of an older paper (whose senior author and another author shared co-authorship in both) that is cited in the comment (Haug et al., 1995). The more recent paper should have been given weight, because it provides an improved and updated view that is much more consistent with our view (for details and more references, see below).

The author discusses our findings in terms of a ‘single measurement’. This central point is however incorrect. Indeed, the author attempts to discuss ‘independent damage to visual pathways subsequent to PD by a single psychophysical measurement’. This represents a crucial misunderstanding because statistical independence can only be tested with at least two measurements.

Actually the strength of our study is that we have obtained multiple test measures for distinct pathways: for each subject, 17 achromatic test thresholds were obtained in independent locations, 3 chromatic test thresholds were obtained along cone-isolating axes in colour space and eight chromatic colour test thresholds were still obtained along eight additional axes in colour space, to provide measures unbiased to cone spaces. This allowed for testing multiple visual processing pathways, using up to 28 distinct threshold measurements and not 1, as supposed by the author.

It is also noteworthy to point out that all these measures were obtained in a random, interleaved manner, which allowed for simultaneous comparisons. Furthermore, it was possible to extract reliability criteria, such as false positives and false negatives.
These conceptual misunderstandings lead us to further clarify that we use the term ‘independent’ in a rigorous and strictly statistical sense: it simply means that multiple measures (chromatic and achromatic thresholds) are statistically uncorrelated, which is by definition a criterion for independence. This means that performance subserved by one pathway cannot predict performance by another pathway. Statistical independence was analysed using standard correlation methods (Han et al., 2004). As already stated in the paper, if two measures are statistically uncorrelated (using appropriate testing criteria) they must have a different neural source or mechanism, as explained and explored by Han et al. (2004). It is important also to note that partial correlation models show essential if multiple parameters show correlations that are significantly different from 0 (Castelo-Branco et al., 2004; Campos et al., 2005). Independence was measured in terms of cross-sectional performance and not in terms of time course.

There is some incorrect mixing of concepts concerning cone and ganglion cell pathways. Discussing the ‘tritan axis’ in terms of disease mechanisms is probably not correct, since damage occurs at the ganglion cell level, or at least in contrast processing levels (beyond the photoreceptor level). ‘Tritan’ means the axis that isolates blue cones, not blue-yellow ganglion cell axes, as wrongly assumed. It is more appropriate to discuss damage across of relative damage of red-green and blue-yellow pathways.

It is stated that ‘PD patients demonstrate consistent and predominant blue–yellow cone deficiencies’, although blue-yellow cones do not exist. We apologize for this apparently overzealous confusion leads to another subtle but important misunderstanding, which is to assume that tritan (blue cone isolating) measures are the ones that best isolate colour contrast in ganglion cell function, which is not true (see discussion below on discrimination ellipses and colour spaces). Ganglion cells operate under different colour cardinal axes.

In this point we mention a crucial fact that in fact may provide a link between the author’s and our own view. As evidence for a putative specific ‘blue cone’ damage it is somewhat surprisingly stated that ‘Indeed, previous studies have appropriately shown that PD patients demonstrate frank thinning of retinal ganglion cell axons’. This statement demonstrates an impressive interest for new approaches, but also contains several factual and conceptual problems. First, as can be easily appreciated from the title of the single paper that is cited in this context (Inzelberg et al., 2004), it is not true that the diameter of retinal ganglion cell axons is being measured. If this would be true, then the author would be right in assuming that one would have at hand a specific tool to measure impairment in particular ganglion cell types. The authors of the cited study are measuring a full retinal layer and not single axons [in fact, the circumpapillary retinal nerve fibre layer (RNFL)]. This means that what becomes thinner is the layer, due to loss of multiple cell types (the most abundant being the parvocellular). This type of finding actually provides an anatomical substrate for our findings, predicting impairment of multiple pathways, and not just one, as also observed in glaucoma (see also the work of Yucel and colleagues). It should be noted that optical coherence tomography is a technology that cannot currently resolve single ganglion cell axons, as supposed by the author.

Ganglion cell loss in glaucoma has now clearly been shown to affect all ganglion cell populations (see Castelo-Branco et al., 2004 and references therein, as well as the work of Yucel and colleagues), and it does not make much sense to insist on an oversimplified argument that the parvocellular (red–green) pathway should be spared. The same argument applies for PD: if the underlying disease mechanism relates to contrast processing control, and since the red–green pathway is essentially a contrast-processing pathway, it becomes hard to argue that it should be spared. When procedures with unbiased colour sampling strategies are applied, which is one of the main innovations of our study (see below), it becomes obvious that multiple pathways are concomitantly affected. In fact, simple inspection of our chromatic discrimination ellipses (Fig. 1, Silva et al., 2005), which allow for direct simultaneous comparisons of concomitantly obtained measures, show that red–green selective sparing does not occur.

We would also like to note a critical methodological omission in the comment. Measuring chromatic performance along only one or two axes in colour space and finding impairment does not mean that any of these two axes is the most impaired one. The author misses this fact and omits the fact that our discrimination ellipses represent a 4-fold improvement in sampling resolution compared to the study he cites. Furthermore, he critically fails to cite the above mentioned update paper (partly from the same group) of Birch et al. (1998), which critically challenges his own view on the specific benefits of ‘tritan’ measures. This paper has a senior co-author and another co-author from the same group as the cited paper and is more recent, thereby being probably more conclusive. One of the major methodological innovations of our study is that by using chromatic discrimination ellipses we were able to avoid the sampling bias that is inherent to any procedure that only measures along one or two axes in cone spaces. To avoid this problem, our innovative approach in this context was to sample colour space in eight evenly spaced directions, which avoids biased measurements and biased conclusions.

This allowed for determination of chromatic discrimination ellipses (‘confusion areas’, which represent regions in colour space that look identical to the subject). Inspection of the plots in Fig. 1 of Silva et al. (2005) clearly shows that there is not a fixed axis of impairment, and that actually multiple axes can be found, unlike what was supposed by Gaynes. This conclusion was only possible to reach due to our novel unbiased sampling approach.

He also suggests that we did not find any substantial damage in the (misleadingly named) blue cone or tritan...
pathway. However, the measured length, axis ratio and orientation of ellipses’ axes can be used to compare damage along koniocellular (blue–yellow opponent channel) and parvocellular pathways (red–green opponent channel). In contrast to what is supposed, axis ratio measurements indicated damage across both parvo (red–green)—and koniocellular (blue–yellow) chromatic pathways. This finding is further substantiated by analysis of the relative distribution of ellipses’ orientation.

We only meant that subclinical processes within ocular structures, such as the retina and the lens, are more prone to affect tritan measures (Wyszecki and Stiles, 1982; Pokorny et al., 1987; for reviews see Werner et al. 1990; Packer and Williams, 2003) and require strict exclusion criteria. This was misunderstood as a suggestion that tritan impairments are absent. We only suggested that these measures may be less reliable given that even subclinical conditions (Castelo-Branco et al., 2004) may affect them (e.g. diabetes even in absence of retinopathy, ocular hypertension even in absence of glaucoma, subclinical yellowing of the lens). For a similar view, see also Birch et al., 1998.

To avoid potentially confounding factors all subjects (patients and controls) underwent rigorous ophthalmological and neurological screening. In fact to avoid these confounds typically associated with tritan measures, we used very strict exclusion criteria. It is also worth pointing out that our sample is one of the largest in similar types of study. We summarize here information that could already be read in the paper: exclusion criteria included neurological/psychiatric conditions other than Parkinson’s disease, diabetes even in the absence of retinopathy, increased intraocular pressure even in the absence of glaucoma, etc. (for details on other conditions, number of patients excluded and reason for exclusion, see original paper).

In any case, it cannot be overemphasized that it is better to compare red–green and blue–yellow-axes, and not tritan (blue cone axis) versus red–green, as suggested by Gaynes (which in fact would mean to incorrectly compare colour function at cone level with colour function at ganglion cell level).

The single electroretinography paper that is cited corroborates our own findings that achromatic, red–green and blue–yellow pathways are impaired. The given study (Sartucci et al., 2003) in fact states, that ‘in PD patients, the PERG amplitude was significantly reduced (by 40 to 50% on average) for both chromatic and luminance stimuli’. This was observed in spite of the fact that very different stimulus conditions were used (suprathreshold 90% contrast, reversed at 1 Hz).

A general cautionary note is important here: one should not assume that classical electroretinography provides evidence for specific chromatic damage because full-field stimulation with standard flashes or pattern stimuli will activate all colour pathways, unless isoluminance is ensured. This is only possible in some parts of the display, due to spatiotemporal variation in colour vision (Wyszecki and Stiles, 1982). This is mainly because colour matching functions are only available for 2 and 10 degree fields. Thereby measures taken with ERG will only be reliable in focal parts of the display. This will render comparisons concerning differential impairment only valid for local equiluminant regions.

It should also be noted that correlation analysis does not at all imply the use of group categories, as wrongly implied by the author. For correlation with psychophysical measures every subject UPDRS raw score is used weighted in the same way and no subgroups are generated, since each score is entered as input to the correlation analysis. In any case, the conclusions are rather straightforward. The author agreed himself that the ‘deterioration of achromatic frequency doubled contrast sensitivity . . . occurs in parallel with performance on the Unified Parkinson’s Disease Rating Scale (UPDRS) classification’. Recent publications are well in agreement with our study and generalize these findings and correlations to these and other visual functions (Mossimann et al., 2004; Uc et al., 2005) and make clear that even if there is a short term beneficial therapy effect, it will be probably cancelled out by intrinsic disease progression. Disease progression is used in the sense of disease stage and should not be mistaken with ageing (whose between-group effects can of course be studied in longitudinal studies).

Speculations concerning drug induced toxicity and retinal degeneration are interesting, although direct experimental evidence is not offered (not a single original research paper). In fact the cited (in another context) paper of Sartucci et al. (2003) shows that visual impairment may occur in PD in the absence of therapy, which is in agreement with our results in the subsample of patients without therapy.

Only one of the cited reviews on general potential neurotoxicity discusses a link to retinal degeneration (Djamgoz et al., 1997). There is however, a subtle confound here: in retinal degenerations, such as retinitis pigmentosa there is loss of dopaminergic control as a consequence of disease processes and not as a cause. And even then this is not really an instance of neurotoxicity, although we agree that this is a rather interesting proposal.

It should also be noted that ERG data are not valid as evidence of agonist induced toxicity since they may merely correspond to pharmacological modulation of physiological responses within the retina. Closure of gap junctions could lead to changes in effective receptive field size, thereby leading to suboptimal pattern size and reduced ERG responses. Retinal dopamine-related impairment is widely accepted to alter retinal visual processing primarily by changing the receptive field properties of ganglion cells (Jackson and Owsley, 2003) and no direct demonstration of toxicity is available. FERG findings in PD suggest that changes are the result of indirect modulation by dopaminergic neurons in the retina (Jackson and Owsley, 2003).

We do however point out that one should be careful about difficulties in detecting a beneficial therapeutic effect as evidence for their non-existence. In fact, a decisive test for
such an effect can only be done by applying a repeated measure design, which only takes into account within-subject variability and prevents between-subject confounding sources of variability. This is indeed what was done in some instances (e.g. the work of Buttner and colleagues, 1994, 1995, 2000). Such designs are easier to apply in short term studies (see the work of Jaffe et al., 1987, who have studied the effect of levodopa intravenous infusion) but it remains a challenge to apply them for long term studies. In any case, the necessity of repeated measure-like designs to uncover the beneficial effects of therapy is well documented by studies, such as from Peppe et al. (1998). There is widespread evidence for beneficial effects of dopamine agonists in many repeated measures approaches (before and after therapy; see also the animal work of Ghilardi et al., 1989, for a review of older data see also Tebartz van Elst et al. 1997).

The fact that the decline in contrast sensitivity in PD can, at least in part, be reversed by the administration of L-dopa is well known for a long time (Bulens et al., 1987; Tebartz van Elst et al., 1997) but it is rather obvious that a reversal in decline does not imply better thresholds, and this is a critical point that goes often unrecognized. In fact, most of these points relate to Bodis-Wollner’s (1990, 2003) tenet that ‘studies showing correlation between reduced levels of neurotransmitters and behavioural deficits, should be complemented with data on kinetics of the same substances in health and disease states.’

Finally, we would like to stress that we could define very objective and unbiased measures of visual function, following the tenet of Geldmacher (2003) that precise definitions are needed to characterize ‘visuospatial dysfunction’.

In conclusion, we believe that our approach, focusing on improved methodological assessment and rigorous patient and data sampling criteria, and using multiple independent measures, represents a promising strategy to better understand patterns of visual impairment, and in particular, to document concomitant damage of multiple visual pathways in PD. We would like to thank the commentator for interesting and positive discussion, and for giving us the opportunity to further clarify these important issues.

References


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