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Independent patterns of damage within magno-, parvo- and koniocellular pathways in Parkinson's disease

M. F. Silva,[1] P. Faria,[1] F. S. Regateiro,[1] V. Forjaz,[1] C. Januário,[2] A. Freire[2] and M. Castelo-Branco[1]

[1]Department of Biophysics and Center for Ophthalmology, IBILI-Faculty of Medicine and [2]Department of Neurology, Coimbra University Hospital, Coimbra, Portugal

Correspondence to: Miguel Castelo-Branco, Department of Biophysics and Center for Ophthalmology, IBILI-Faculty of Medicine, Coimbra University Hospital, 3000-354 Coimbra, Portugal
E-mail: mcbranco@ibili.uc.pt

Sensory deficits have been documented in Parkinson's disease, in particular within the visual domain. However, ageing factors related to the brain and to neural and non-neural ocular structures could explain some of the previously reported results, in particular the claimed impairment within the koniocellular pathway.This study addressed visual impairment attributable to the magno- (luminance), parvo- (red–green) and koniocellular (blue–yellow) pathways in a population of Parkinson's disease patients. To avoid potentially confounding factors, all subjects underwent a full neurophthalmological assessment which led to exclusion of subjects with increased intraocular pressure, diabetes even in the absence of retinopathy, and ocular abnormalities (from a total of 72 patients' eyes, 12 were excluded). Both parvo- and koniocellular pathways were studied by means of contrast sensitivity (CS) measurements along protan, tritan and deutan axes and also by fitting chromatic discrimination ellipses using eight measured contrast axes. Magnocellular function was assessed, using stimuli that induce a frequency doubling illusion, in 17 locations in the fovea and periphery. Achromatic (luminance modulation) thresholds were significantly higher in Parkinson's disease both in foveal and peripheral locations. A significant impairment was observed along protan and deutan axes, but only marginally along the tritan axis. These results were corroborated by a significant elongation of chromatic discrimination ellipses in our Parkinson's disease group. Correlation analysis showed that achromatic and chromatic CS measures were independent, which implies that multiple visual pathways are affected independently in Parkinson's disease. Magnocellular impairment was significantly correlated with age and disease stage, in contrast to the measured chromatic deficits. We conclude that in Parkinson's disease, independent damage occurs in the early magno- and parvocellular pathways. Furthermore, traditional koniocellular probing strategies in Parkinson's disease may be confounded by ageing factors, which may reconcile the previously reported controversial findings concerning chromatic impairment in Parkinson's disease.

Keywords: contrast sensitivity; koniocellular; magnocellular; Parkinson's disease; parvocellular

Abbreviations: CS = contrast sensitivity; FD = frequency-doubling; IN = inferior nasal field; IT = inferior temporal field; M/Y = magnocellular pathway; SN = superior nasal field; ST = superior temporal field

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Introduction

The nature of previously described visual deficits in Parkinson's disease has been questioned mainly on the ground that the reported deficits do not reflect a sensory deficit, but rather confounding cognitive factors (Crucian and Okun, 2003; Geldmacher, 2003). Moreover, many previous studies have probed contrast sensitivity (CS) using clinical semi-quantitative tests such as the Lanthony D15, Farnsworth–Munsell 100-Hue, Pelli-Robson test charts and Vistech tables (Regan and Maxner, 1987; Buttner *et al.*, 1995; Pieri *et al.*, 2000; Diederich *et al.*, 2002). One should, however, emphasize the important previous work using quantitative psychophysical methods in Parkinson's disease

(Bodis-Wollner *et al.*, 1987; Bodis-Wollner and Regan, 1991; Harris 1998; Regan *et al.*, 1998; Bodis-Wollner, 2003). It is also important to measure CS with such precise psychophysical methods. It is worth emphasizing that most of the clinical tests do not allow for extraction of subject reliability parameters and provide limited quantification power. New psychophysical methodologies are less prone to artefacts than classical clinical methods that assess chromatic and achromatic contrast discrimination. In fact, Regan *et al.* (1994) have previously analysed the potential between computerized approaches and current clinical tests. In general, clinical tests, such as Farnsworth–Munsell 100-Hue or Farnsworth D15 test, are much less sensitive and less reproducible—which we have also confirmed before—in comparison with techniques that allow for very fine contrast adjustments using randomly interleaved staircases (Castelo-Branco *et al.*, 2004; Campos *et al.*, 2005). Roth and Lanthony (1999) provide a good description of the limitations of Farnsworth–Munsell 100-Hue test. Farnsworth himself did consider that 30% changes in test-retest could occur, which was confirmed by Birch *et al.* (1998). Reeves *et al.* (1989) had, in fact, documented that a difference in global score would only be significant if the difference is >50. This led Roth and Lanthony (1999) to conclude that the Farnsworth-100 test is just a semi-quantitative evaluation test. Accordingly, it has been postulated that commonly used clinical colour tests are not suitable for the early detection or monitoring of treatments in Parkinson's disease (Birch *et al.*, 1998). Furthermore, it is also important to use psychophysical tests that do not rely on higher level visuospatial abilities, such as orientation discrimination (Regan and Maxner, 1987; Bulens *et al.*, 1988). In addition, ageing factors related to the brain, and also to the retina and other ocular structures (Wyszecki and Stiles, 1982; Pokorny *et al.*, 1987; for reviews *see* Werner *et al.*, 1990; Packer and Williams, 2003) could explain some of the previously described results, in particular the widely reported deficits in the koniocellular pathway (for a review see Haug *et al.*, 1994, 1995; Harris 1998; Pieri *et al.*, 2000, but *see* Birch *et al.*, 1998; Regan *et al.*, 1998). Common age-related and progressive ocular diseases in older adults such as cataract, age-related maculopathy, glaucoma, and diabetic retinopathy are often associated with sensory deficits (Jackson and Owsley, 2003; Castelo-Branco *et al.*, 2004; for a comprehensive review of the literature *see* Roth and Lanthony, 1999). In spite of such potentially confounding factors, there is strong evidence that spatiotemporal CS deficits do occur in Parkinson's disease (Bodis-Wollner and Yahr, 1978; Marx *et al.*, 1986; Skrandies and Gottlob, 1986; Bodis-Wollner *et al.*, 1987; Regan and Maxner, 1987; Mestre *et al.*, 1990*a*, *b*; Bodis-Wollner and Regan, 1991; Harris *et al.*, 1992; Delalande *et al.*, 1996; Mestre *et al.*, 1996; Tebartz van Elst *et al.*, 1997; for reviews *see* Bodis-Wollner, 1990, 2003; Harris 1998; Langheinrich *et al.*, 2000; Pieri *et al.*, 2000; Diederich *et al.*, 2002).

In the current study we aimed to analyse visual performance within multiple visual channels, both in the fovea and the periphery, using tests that tackle the function of those pathways in an independent manner. This strategy allowed for the analysis and comparison of relative patterns of damage within magno-, parvo- and koniocellular pathways in Parkinson's disease. To account for the above-mentioned methodological problems, we used age-matched populations and conservative exclusion criteria (e.g. diabetes in pre-retinopathy stage, ocular hypertension in pre-glaucomatous stage, fundus signs of age-related macular degeneration). To study chromatic CS performance, we adopted a new methodological approach, based on the seminal work of Regan *et al.* (1994), with randomly interleaved psychophysical staircases with spatial and luminance noise (see Castelo-Branco *et al.*, 2004; Campos *et al.*, 2005). Stimulus parameters were adjusted along colour modulation axes in order to separate dysfunction within parvo- and koniocellular systems. This strategy allowed independent and non-biased assessment of the relative damage of parvo- and koniocellular pathways.

The parvo- and koniocellular isolating strategy relied on chromatic properties and not on spatiotemporal criteria. The choice was based on neurophysiological and lesion studies in primates, which show that chromatic criteria are by far the best to provide isolation (Lee, 1996). Indeed isolation based on spatial vision often fails, and vernier acuity may be preserved even after wholesale destruction of P-cells, suggesting incomplete isolation (Lynch *et al.*, 1992). This led us to choose chromatic properties as the isolating criteria.

To probe the magnocellular pathway (M/Y) at early retinotopic levels we choose a CS task that uses a sinusoidal grating stimulus at high temporal and low spatial frequency. This spatiotemporal profile of the stimulus is, in general, appropriate to activate the M/Y pathway but may not be sufficient to isolate its function, unless one uses stimulus parameters such that an illusory duplication of number of stripes is perceived (Kelly, 1981). This frequency-doubling (FD) illusion reflects a non-linearity that resembles the response properties of the M/Y system (Shapley and Victor, 1980). Between 5 and 20% of LGN M cells respond with this non-linear Y-type response (Kaplan and Shapley, 1982; Derrington and Lennie, 1984; Purpura *et al.*, 1988, 1990). Neurophysiological evidence has also shown that these stimuli differentially activate magno neurons (Derrington and Lennie, 1984; Merigan and Maunsell, 1993; Lee, 1996). Given the low percentage of responding M/Y neurons, this approach provides functional isolation and improves the likelihood of detecting early level impairment due to reduced compensation by functional redundancy mechanisms.

The value of FD stimuli to assess retinotopic magnocellular damage as early as the retina stage has already been applied in glaucoma, because large retinal ganglion cell fibres (most of which are of magnocellular origin) are preferentially affected in this disease (Quigley *et al.*, 1987, 1988; Maddess and Henry, 1992; Glovinsky *et al.*, 1993; Merigan and Maunsell, 1993; Johnson and Samuels, 1997; Maddess *et al.*, 1999;

Cello *et al.*, 2000; Landers *et al.*, 2000; Trible *et al.*, 2000; Paczka *et al.*, 2001; McKendrick *et al.*, 2003; for a review *see* Shabana *et al.*, 2003). Based on this evidence, we adopted the FD paradigm to study early magnocellular function in Parkinson's disease.

Methods

Patient selection and classification

All Parkinson's disease patients were recruited from the Neurology Department of Coimbra University Hospital. Control subjects were patients' spouses, age-matched hospital or university staff, or relatives, with normal or corrected to normal refraction. Informed consent was obtained from all participants, and the study was conducted in accordance with the tenets of the Declaration of Helsinki, and the guidelines of our local ethics committee were followed. Both groups underwent full ophthalmological examination by two ophthalmologists (P. Faria, L. Duarte). This examination consisted of best-corrected visual acuity (VA; Snellen chart), slit lamp examination of anterior chamber, IOP measurement (Goldman applanation tonometer), angle and fundus examination (Goldman lens), cataract grading by the Lens Opacities Classification System II (LOCS) and the assessment of subjective visual complaints. Neurological examination was performed in our Neurology Department by two of the authors (A. Freire and C. Januário). Dementia was excluded by analysis of Mini Mental State Examination scores (Portuguese-adapted version by Guerreiro *et al.*, 1994 following Folstein *et al.*, 1975). For exclusion of depression, the Hamilton Depression Rating Scale 17 (cut-off 14) was used.

Parkinson's disease patients were classified in stages of the modified Hoehn and Yahr clinical scale [1.9 ± 0.5 (mean ± SD) for both subsets of chromatic and achromatic testing]. The motor Unified Parkinson's Disease Rating Scale (UPDRS) was also applied [UPDRS motor score, 25.0 ± 8.4 (chromatic testing) and 23.9 ± 9.3 (achromatic testing)].

The following exclusion criteria were applied: neurological/psychiatric conditions other than Parkinson's disease (*see* above), diabetes even in the absence of retinopathy, increased intraocular pressure even in the absence of glaucoma, congenital colour vision disorders, VA < 0.6 , high ammetropy (sphere dpt > 4 and cylinder dpt > 2), cataract (LOCS ≥ 2) and other ophthalmological diseases. From a total of 36 Parkinson's disease patients we excluded 6 (3 with diabetes even in absence of retinopathy, 2 with glaucoma and 1 patient with high ocular hypertension). The final subset of Parkinson's disease patients (14 male and 16 female) had a mean illness duration of 4.6 ± 3.0 years. Our patient and control (32; 13 male, 19 female) populations had age distributions that were not significantly different under all testing procedures (chromatic assessment: control subjects: mean age = 57.9 ± 7.6 years; Parkinson's disease: 61.1 ± 10.4 years; achromatic testing: control subjects: 58.5 ± 9.5 years; Parkinson's disease: 60.0 ± 10.8 years). Mean education level was similar across groups, and was not significantly correlated with sensory performance. Ten Parkinson's disease patients were newly diagnosed and were tested free from therapy. The others were receiving conventional levodopa therapy (mean dose of L-dopa: 544 ± 238 mg daily; other agonists: 7 patients with bromocriptine, 7.5 mg; 6 patients with ropinirole, 3.5 ± 0.84 mg). The medicated patients were all tested in the best-on state.

Psychophysical techniques to address the function of the parvo- and koniocellular pathways

We have probed the parvo- and koniocellular pathways in Parkinson's disease using a computer controlled psychophysical method developed by Regan *et al.* (1994) and taken from the Cambridge Colour Test [Cambridge Research Systems (CRS), Rochester, UK]. This technique uses a luminance noise strategy that forces the subject to rely exclusively on colour cues to identify the position of a gap in a Landolt-like C-shaped ring (*see* Fig. 1 top inset; gap size: 1.6°, outer diameter: 7.6°, inner diameter: 3.81°, viewing distance: 1.8 m). Implementation and calibration procedures were performed with software and hardware provided by CRS (Minolta colorimeter; calibration software and CRS/VSG 2/5 graphics card, with 15-bit contrast resolution per pixel). Stimuli were displayed on a 21 inch monitor (GDM-F520; Sony, Tokyo, Japan) that was gamma-corrected.

The Parkinson's disease population of this study was probed monocularly for chromatic pathways (n = 30 patients eyes; n = 33 age-matched control eyes). The tested eye was chosen in a pseudo-random manner. All participants viewed with refraction corrected for viewing distance a screen with a pattern of circles of various sizes and luminance with superimposed chromatic contrast defining the C-ring. The viewing conditions were such that of all areas it was the macular area of the retina that the Parkinson's disease patients had to consider to perform chromatic comparisons.

Given the subjects' average age, and to exclude confounding factors such as motor errors, the experimenter (F. S. Regateiro or V. Forjaz) recorded subjects' oral responses using a 4-button response box. To further emphasize accuracy versus speed in the measurement of psychophysical responses, subjects were instructed that they had up to 20 s to report their decision. The subject had to indicate one out of four possible gap positions (bottom, top, left and right) of the Landolt C stimulus. Luminance and size variation of stimulus patches (*see* Fig. 1, top inset) forced the subject to use specific colour cues, since he/she could not use spatial or luminance cues to infer the embedded shape. These patches were randomly assigned six different luminance noise levels (8, 10, 12, 14, 16 and 18 cd/m^{-2}; *see also* Fig. 1 top inset, which illustrates the patches in different shades of grey). A minimum excursion of 0.002 units in CIE 1976 u′ v′ colour space was then superimposed on such noise levels, to define the chromatic shape.

The chromaticity of the Landolt C shape was adjusted according to a staircase procedure (*see* below). Quantitative adjustment in terms of modulation of chromatic contrast allowed for isolation of cone or colour-opponent specific responses in CIE 1976 (u′ v′) colour space (*see* Fig. 3A). Chromatic performance along the classical cone axes (protan, deutan and tritan labels in Fig. 3B) were explored first: psychophysical thresholds were obtained with algorithms implementing three independent random staircases, from the Trivector version of the test, which ensured unbiased measurement of thresholds across the three main chromatic axes.

Chromatic discrimination ellipses ('confusion areas', which represent regions in colour space that look identical to the subject) were fitted along eight symmetrical colour vectors (Fig. 1). Quantification of major and minor ellipse axes and orientation, allowed for comparison of relative damage of red–green and blue–yellow pathways.

The eight colour vectors that were used to measure chromatic discrimination ellipses were modulated in an interleaved manner, with independent random staircases running against a neutral

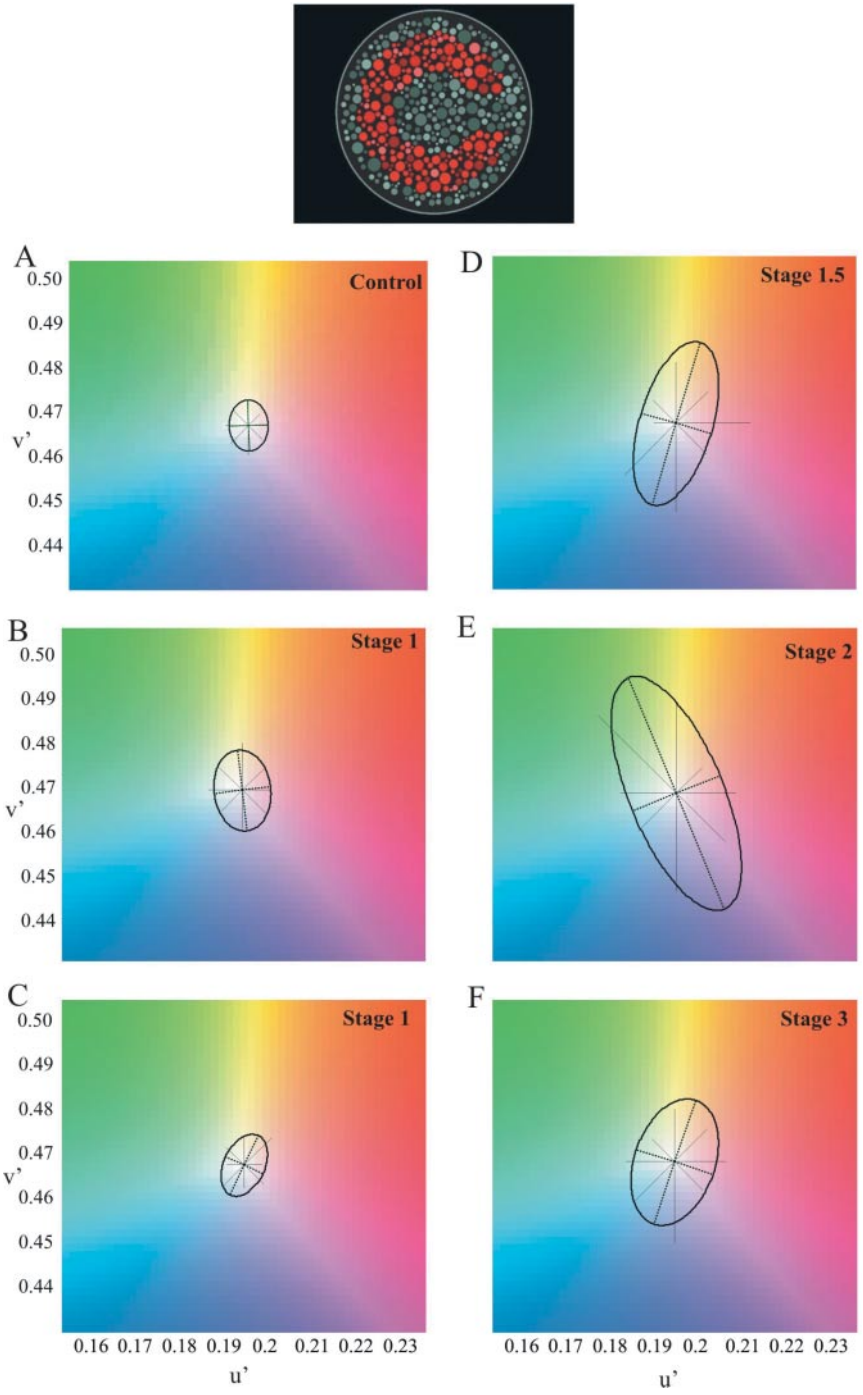

Fig. 1 Top inset: schematic illustration of the luminance noise stimulus and superimposed chromatic target (Landolt C shape, coloured in red). Representative examples of chromatic discrimination ellipses (raw discrimination vectors and fitted ellipses) in Parkinson's disease, over Stages 1–3 of the modified Hoehn and Yahr clinical scale (motor UPDRS: B, 11; C, 13; D, 18; E, 28; F, 40). Solid straight lines: eight measured colour vectors. Curved solid line: fitted ellipse. Colour rendering (which is only approximate in the printed version) is based on the IEC1996 2.1 standard, with the white point set to the white point of the test and the monitor gamut set to the gamut of our Trinitron monitor. Parameters extracted from fitted ellipses were as follows (length, axis ratio and angle, respectively): (**A**) 0.0116, 1.316, 92; (**B**) 0.0184, 1.439, 97; (**C**) 0.0147, 1.594, 65.5; (**D**) 0.0382, 2.334, 73.6; (**E**) 0.0565, 2.673, 112, 3; (**F**) 0.0295, 1.636, 71.5.

background. Neutral background coordinates (CIE 1976 u′, v′ coordinates are shown, respectively): 0.1977, 0.4689; minimum excursion: 0.002 unit's u′ v′; protan confusion (copunctal) point: 0.678, 0.501; deutan confusion (copunctal) point: −1.217, 0.782; and tritan confusion (copunctal) point: 0.257, 0.0. Maximum excursion for trivector test: 0.1100 units (Fig. 3A). This strategy allowed testing all colour axes simultaneously, which made comparisons concerning relative damage of chromatic pathways more reliable. On each axis,

the separation between the background and target chromaticities was initially large, and was decreased after each correct response on that axis and increased after each error. Since the tests were measuring multiple colour axes randomly (independent interleaved staircases), and since there was no fixed order, attentional biases could be prevented. The test terminated after 11 reversals of each of the three individual staircases; and the mean of the last seven reversals was taken as the threshold estimate for a given confusion line. The step size is computed in units of the CIE 1976 uniform chromaticity space and is a function of the number of reversals completed, and of the separation of test and background chromaticities. Small subsets of trials, randomly intermixed with the test trials, were used as control trials to detect malingering and to provide the subject clear cases when he or she is near threshold.

The ellipses fitting method which was developed by Regan *et al.* (1994), produces an ellipse that is centred on the neutral background; and is obtained by minimizing the sum of squares of the log distances between the ellipse and the fitted point, which is a geometric solution for producing discrimination ellipses. The performance varies inversely with the ellipse length. Our four alternative spatial forced-choice strategy allowed the extraction of the following quantitative parameters: confusion vector length, ellipse length, axis ratio and angle. The ellipse length helps in quantifying the magnitude of chromatic CS deficit, the axis ratio estimates the specificity of damage and the angle provides an indication of the most affected type of chromatic pathway.

Psychophysical techniques to address the function of the M/Y pathway

The spatiotemporal profile of the sinusoidal grating FD stimulus was optimized to activate the M/Y pathway. To measure luminance modulation sensitivities, stimuli were generated directly from CRS/VSG 2/5 graphics card (with 15-bit contrast resolution per pixel) using CRS object animation library, (*see* McKendrick *et al.*, 2003; Silva *et al.*, 2004). FD stimuli were displayed on a gamma-corrected 21 inch colour Trinitron GDM-F520 monitor (frame rate 100 Hz). Each stimulus was a $10^\circ \times 10^\circ$ patch of 0.25 c.p.d. (cycles per degree) sinusoidal grating vertically oriented, undergoing 25 Hz counter phase flicker. Mean background luminance was 61.7 cd/m^2. Stimuli were randomly presented, in two zones (*see* top inset of Fig. 4): zone 1, which contains a foveal circular stimulus with 5° radius; zone 2, with 16 peripheral square stimuli between 5° and 20° eccentricity. This perimetry field analysed 17 localizations to mimic as closely as possible the standard strategy of Humphrey FDT (C-20).

Luminance contrast or modulation was expressed according to the Michelson formula:

$$\text{Luminance contrast } (\%) = 100 \times (L_{max} - L_{min})/(L_{max} + L_{min}).$$

An adaptive logarithmic staircase strategy from CRS object animation library was used to obtain luminance contrast thresholds. The value to be used for a given trial was calculated using the previous trials value plus or minus the step size in dB. The initial step size used was 3 dB. Staircases were run for a total of four reversals, with the contrast at the final two reversals being averaged to obtain the threshold estimate.

FD perimetry was done in a monocular way for both eyes in 21 Parkinson's disease patients. The first eye tested was chosen in a random manner. We did not find any significant differences in performance between the two eyes, and we therefore pooled these data. The stimulus disappeared upon a button press and its maximum duration was 400 ms; the interstimulus duration was 250 ms. Subjects were instructed to report the presence of 'flickering striped' targets and the experimenter (M. F. Silva) converted the subjects' oral response into a button response (4-button box). Subjects wore, when necessary, a correction appropriate for the 36 cm viewing distance. Participants' reliability was evaluated by intermittently including false positive and negative 'catch trials'. We excluded all results with false positive and false negative errors $\geq$33%.

A parallel set of control experiments in normal subjects ($n = 100$ eyes; $n = 48$; $n = 81$; $n = 30$ and $n = 15$ for different test configurations spanning at least 17 visual locations) was also performed. This study showed that at the tested spatiotemporal frequencies of our achromatic test, CS thresholds are much better (<6% in most locations) than CS thresholds used at higher frequencies that are less optimal for the magnocellular system (>25% for P-biased stimuli).

Data analysis

Mann–Whitney *U*-tests were used to compare chromatic and achromatic (luminance modulation) performance between the two groups (normal and Parkinson's disease), given the lack of data homoscedascity.

Statistical independence was analysed using standard correlation methods (Han *et al.*, 2004). 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 to note that partial correlation models are 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. Given the data distribution we used Spearman rank correlations (Siegel and Castellan, 1988).

Results

Assessment of parvocellular and koniocellular damage

In order to isolate relative damage of different chromatic pathways we measured contrast thresholds not only along the three main colour axes that isolate cone function, (protan, deutan and tritan) but also along eight evenly oriented vectors that help define discrimination ellipses (*see* Methods). This novel approach in Parkinson's disease allows to fit chromatic 'confusion areas' (ellipses) to individual data, and to estimate in an unbiased way relative damage across chromatic channels. The measured length and orientation of ellipses' axes can be used to compare damage along koniocellular (blue–yellow opponent channel) and parvocellular pathways (red–green opponent channel).

Representative examples of chromatic discrimination ellipses are shown in Fig. 1, both for control and Parkinson's disease patients in different stages of the motor UPDRS and the modified Hoehn and Yahr clinical scale (*see* Methods and Fig. 1 legend). It is worth emphasizing that ellipses have variable length and orientation in the Parkinson's disease examples, suggesting evidence for heterogeneous patterns of damage. This was further confirmed by testing homogeneity of variances in the Parkinson's disease group. The latter showed significantly increased variability (*F*-test, $P < 0.001$ for

all parameter comparisons). Note that one of the patients in Stage 1, shown in Fig. 1, had nearly normal performance, and that all patients above Stage 1.5 showed increased length of both minor and major axes, as compared to a representative normal control.

Chromatic damage was confirmed by statistical analysis of ellipses' main parameters (Fig. 2). We found a significant elongation of ellipses' length (Fig. 2A, Mann–Whitney, $P < 0.0001$). In contrast, axis ratio (a measure of specificity of damage) was not significantly different from the control population (Fig. 2B, Mann–Whitney, n.s.), indicating damage across both parvo- and koniocellular chromatic pathways. This finding is further substantiated by analysis of the relative distribution of ellipses' orientation (pie charts in Fig. 2C). In our Parkinson's disease group there was a wider range of angle distributions, suggesting the absence of a specific axis of damage. It is worth pointing out that a subgroup of Parkinson's disease patients showed protan or deutan-like angles close to 0–30° (the values of 150–180 are actually mirror symmetric).

In order to further investigate whether or not patterns of damage are different along axes that isolate specific cone pathways (*see* Fig. 3A), we independently analysed performance for protan, deutan and tritan colour axes. We found significant impairment of chromatic sensitivity in Parkinson's disease, in particular along the protan and deutan confusion lines (Mann–Whitney: $P = 0.0003$ for the protan axis, and 0.0021 for the deutan axis, $P = 0.0591$ for the tritan axis, which is only close to marginal significance; *see* Fig. 3B).

We found no significant worsening of performance (no fatigue) or learning effects when Parkinson's disease patients moved from the trivector version of the test to the ellipse method. In another set of control experiments, designed to

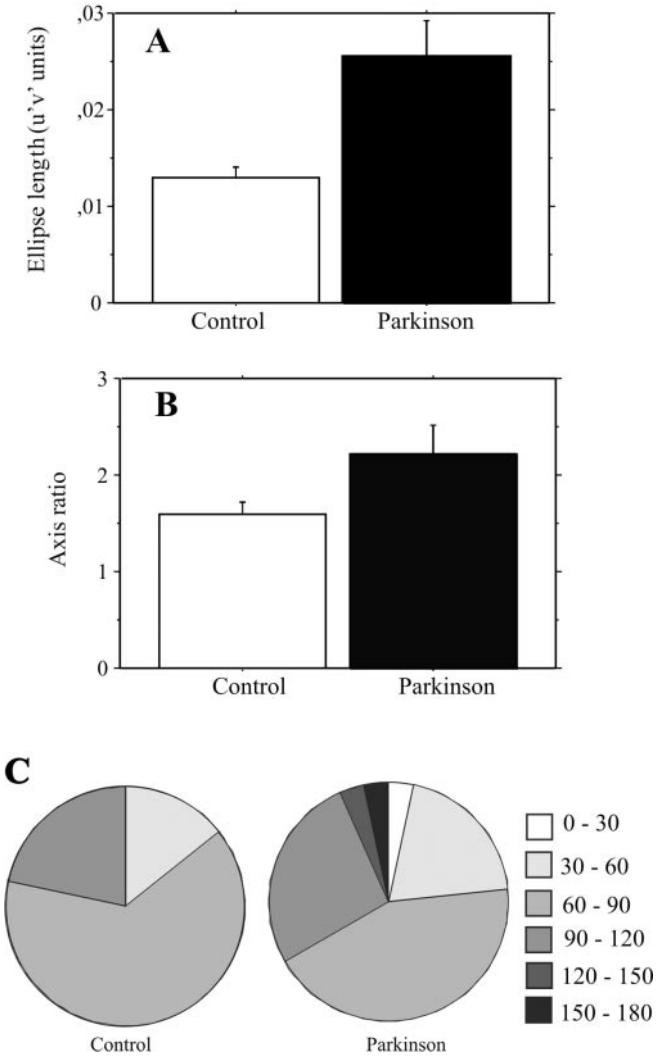

Fig. 2 (**A**) Length of discrimination ellipses is significantly different between control and Parkinson's disease groups ($P < 0.0001$, Mann–Whitney). (**B**) Axis ratios of discrimination ellipses are not significantly different from the control group (n.s., Mann–Whitney). (**C**) Pie chart distributions of discrimination ellipse angles (in degrees) across the two groups.

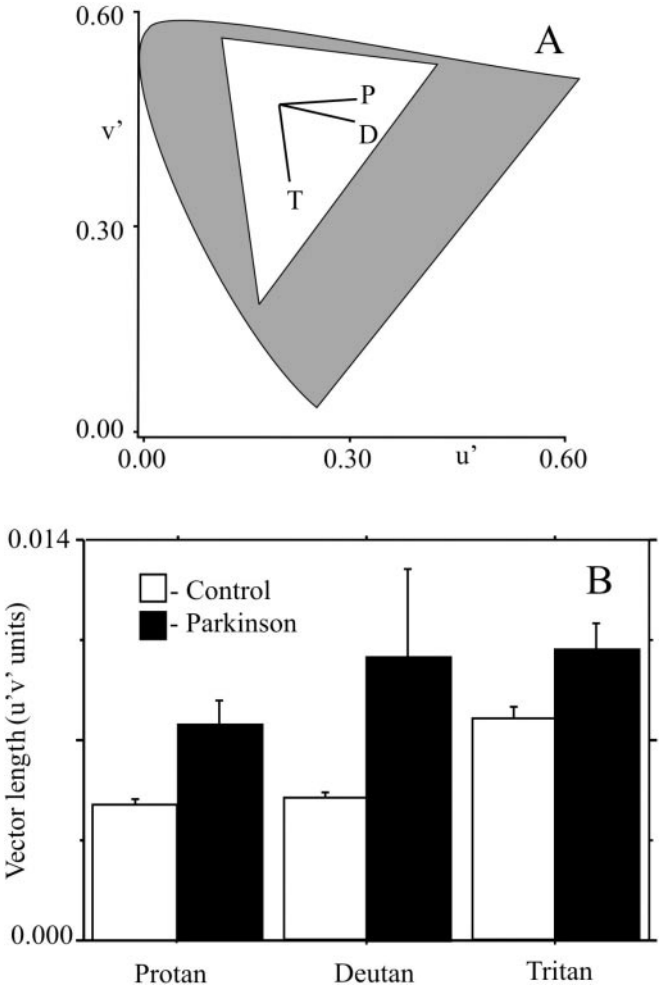

Fig. 3 (**A**) Confusion vectors (in CIE 1976 u′ v′ colour space) along which the data shown in B were collected. P, protan; D, deutan and T, tritan axes. (**B**) Lengths of protan, deutan and tritan vectors are significantly different between control and Parkinson's disease groups (see text for details).

verify whether results were similar under blue cone (preganglionic) adaptation conditions (Shevell, 2003) we tested chromatic performance in seven Parkinson's disease patients. Ellipses were larger than for control subjects, but this increase was proportional to the baseline impairment.

No correlations were found between age and chromatic performance (Spearman's rank correlation, $P \leq 0.05$ for all measures). More importantly, no significant correlation was found between the duration of disease and the chromatic measured parameters. Interestingly, also no significant correlation was found between motor UPDRS scale and psychophysical performance, as measured by Spearman's rank correlation coefficients.

The effect of dopaminergic medication was analysed using non-parametric statistics, and no significant correlations were found between L-dopa and trivector measured parameters, as well as with the ellipse measured parameters.

Perimetric assessment of magnocellular function

Concerning perimetric achromatic CS (Fig. 4), measured with a stimulus which isolates the M/Y pathway (FD, *see* Methods), we found significant impairment in Parkinson's disease patients both in the fovea and in the periphery (Foveal Index Measure, Mann–Whitney: $P = 0.029$; Peripheral Index Measure which averages the 16 peripheral locations, $P = 0.012$; *see* Fig. 5A). CS was significantly less homogeneous in Parkinson's disease than for control subjects [*F*-test across quadrants: superior temporal field (ST), inferior nasal field (IN), inferior temporal field (IT), superior nasal field (SN), $P \leq 0.0001$ for all comparisons]. Threshold comparisons remained significant even when the analysis was performed for each visual field quadrant, except for the IN quadrant (Fig. 5B; Mann–Whitney tests: ST, $P = 0.037$; SN, $P = 0.016$; IN, $P = 0.082$ n.s.; IT, $P = 0.0030$). This is a conservative statistical approach, since it does not take into account that multiple locations were measured in each quadrant.

In contrast to our findings for the chromatic tests, psychophysical performance for the achromatic test showed a significant correlation with age in the Parkinson's disease group (Control group, n.s. for all correlations; Parkinson's disease group: Foveal Index Measure, $\rho = 0.47$, $P = 0.0024$; Peripheral Index Measure, $\rho = 0.49$, $P = 0.0017$). These effects in the Parkinson's disease group remained significant even when analysis was split according to visual quadrants (ST: $\rho = 0.40$, $P = 0.0106$; SN: $\rho = 0.44$, $P = 0.0046$; IN: $\rho = 0.35$, $P = 0.0233$; IT: $\rho = 0.41$, $P = 0.0085$; in the Parkinson's disease group). This was corroborated by correlation analyses between disease duration and achromatic parameters: Foveal Index Measure, $\rho = 0.49$, $P = 0.0016$; Peripheral Index Measure, $\rho = 0.599$, $P = 0.0001$; visual quadrants, $\rho = 0.45$, $P = 0.0038$ (ST); $\rho = 0.54$, $P = 0.0006$ (SN); $\rho = 0.66$, $P < 0.0001$ (IN); $\rho = 0.57$, $P = 0.0003$ (IT). We then computed correlations between modified Hoehn and Yahr stage (for UPDRS correlations *see* below) and achromatic psychophysical thresholds. We found that all correlations were significant (Foveal Index Measure: $\rho = 0.41$, $P = 0.0201$; Peripheral Index Measure: $\rho = 0.38$, $P = 0.0304$). Further analysis revealed that nasal visual quadrants were the most significantly affected by stage (ST: $\rho = 0.27$ n.s., $P = 0.126$; IT: $\rho = 0.35$, $P = 0.044$; SN: $\rho = 0.47$, $P = 0.0073$; IN: $\rho = 0.44$, $P = 0.012$). Representative examples are shown in Fig. 4. In contrast to Fig. 1, a clear worsening over stages is observed. Correlation analyses between the motor UPDRS and achromatic performance (luminance modulation) confirmed these results (Foveal Index Measure: $\rho = 0.49$, $P = 0.0019$; Peripheral Index Measure: $\rho = 0.43$, $P = 0.0061$). Thresholds in the SN visual quadrant were the most significantly correlated with the motor UPDRS: $\rho = 0.46$, $P = 0.0032$, ST: $\rho = 0.35$, $P = 0.03$; IT: $\rho = 0.35$, $P = 0.025$; IN: $\rho = 0.39$, $P = 0.014$. The effect of medication in test performance (using non-parametric statistics) showed no significant differences.

It is important to test whether or not our measurements of damage within magno-, parvo- and koniocellular pathways in Parkinson's disease are indeed independent, as is to be expected if parallel pathways were being separately explored. The results of this analysis showed that there was no evidence of an association between measurements of chromatic and achromatic contrast sensitivities. Correlation analysis showed that all of our measurements of chromatic and achromatic CS were independent (Spearman correlations between Foveal/Peripheral Index Measures and protan, deutan and tritan were n.s.; Foveal/Peripheral Index Measures and ellipses' length, also n.s.).

Discussion and conclusions

In the present study, we found clear evidence of independent visual deficits within the parvo, konio and magnocellular pathways in Parkinson's disease. Our measures of assessing sensory performance within the different pathways were statistically independent (*see* Methods), which allows for unbiased comparison of damage within these pathways. Such statistical independence was not surprising, given the considerable amount of evidence that our spatiotemporal method isolates the M/Y pathway (Purpura *et al.*, 1988, 1990). In any case, the value of our FD stimuli in assessing retinotopic magnocellular damage as early as at the retina stage has already been demonstrated in glaucoma (Maddess *et al.*, 1992, 1999; Johnson *et al.*, 1997; Landers *et al.*, 2000; Trible *et al.*, 2000; Paczka *et al.*, 2001; Shabana *et al.*, 2003). There is also direct neurophysiological evidence that these stimuli differentially activate magno neurons (Derrington and Lennie, 1984; Merigan and Maunsell, 1993; Lee, 1996). Likewise, the strategy used in the pure chromatic contrast modulation tests allows isolating two distinct colour pathways (Regan *et al.*, 1994; Pearson *et al.*, 2001; Shevell, 2003). It could be argued that the absence of correlations between chromatic and luminance modulation measures might be due to involvement of different retinal areas. However, correlations remained close to zero even when spatially averaged (global) measures were used.

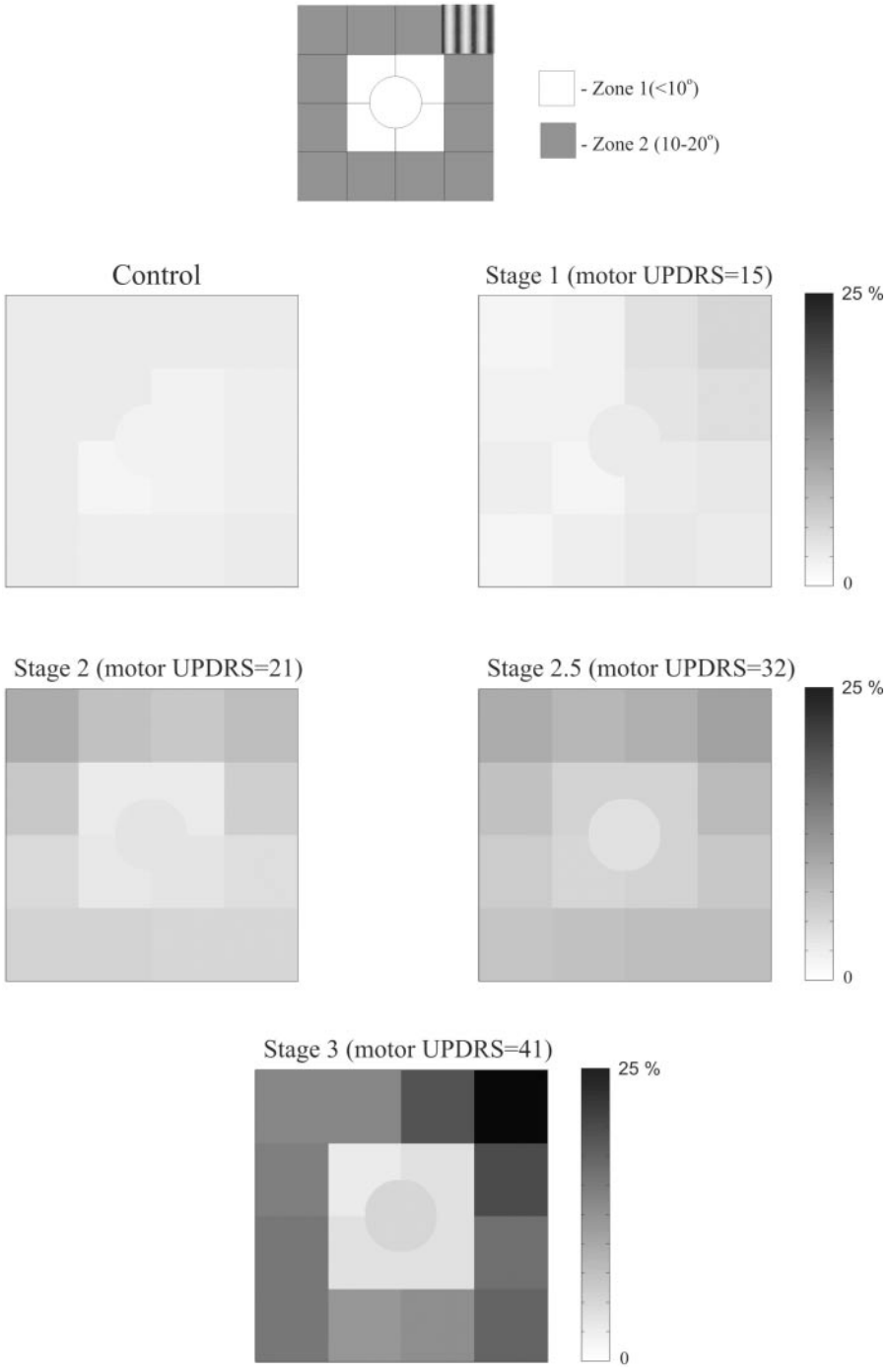

Fig. 4 Top inset: basic scheme of tested locations of the sinusoidal grating stimulus which induces a magnocellular-isolating frequency-doubling (FD) illusion (for details see Methods). Lower panels: representative examples of achromatic CS plots (left eye), where darker grey regions correspond to higher (worse) contrast thresholds (%). Grey level scale bar depicts % contrast thresholds. Note the clear-cut deterioration across stages.

We have observed involvement of chromatic pathways in Parkinson's disease even in some recently diagnosed patients. Surprisingly, predominant effects were found in measures of the function of the parvocellular pathway. Koniocellular involvement found in earlier reports may have been overestimated due to ageing effects. This may help explain the results of Birch (Birch *et al.*, 1998), who concluded that clinical tests for tritan colour deficiency are unlikely to be helpful in identifying Parkinson's disease (but *see* Haug *et al.*, 1995). These observations are also compatible with the notion that ageing 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). Thus, it is important

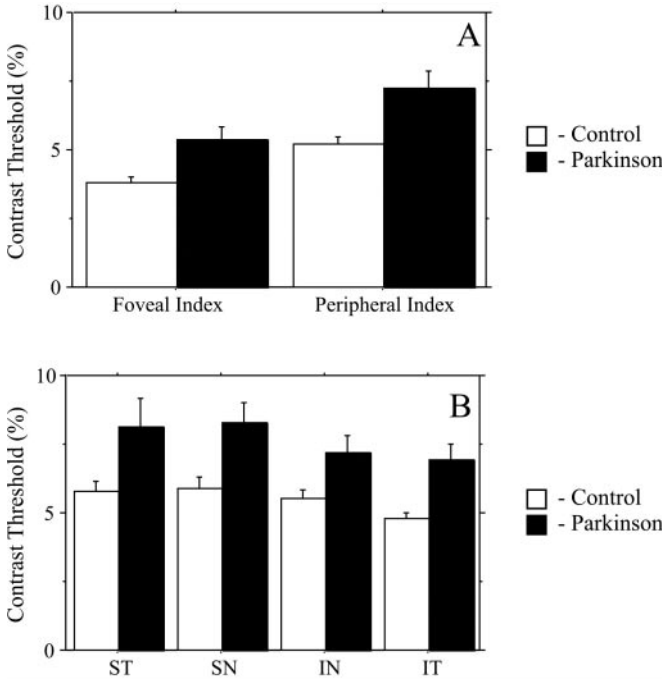

Fig. 5 (**A**) Both Foveal Index and Peripheral Index Measures (which average the 16 peripheral locations) are significantly different between control and Parkinson's disease groups. (**B**) Achromatic CS detection thresholds compared across visual field quadrants for each group of subjects. ST, superior temporal; SN, superior nasal; IN, inferior nasal; IT, inferior temporal quadrant. Error bars correspond to 1 SE.

to ensure that neither significant lens opacification is present nor age-related senile changes are observed in fundus examination, even when groups are age-matched. Our careful ophthalmological examinations allowed exclusion of these and other confounding factors such as increased intraocular pressure; even control subjects underwent the same type of careful assessment, with exactly the same exclusion criteria. All tests were measuring multiple colour axes randomly (multiple interleaved staircases), and since there was no fixed order there is no possibility that an attentional bias could have occurred during the tests.

We suggest that assessment of parvocellular pathways may be more promising than the traditional koniocellular assessment strategy, even when chromatic discrimination ellipses show a tritan tilt. One should, however, note that some Parkinson's disease patients may have entirely normal thresholds. Some studies have indeed pointed out that only a subset of Parkinson's disease patients (as low as 22.7%) may show chromatic deficits (Birch *et al.*, 1998; Regan *et al.*, 1998).

Magnocellular thresholds, as measured using a tailored achromatic CS task, were significantly higher in Parkinson's disease both in foveal and peripheral locations. The spatiotemporal profile of the stimulus used in the task was optimized to independently isolate the M/Y pathway. The high CS at high temporal frequencies, observed under our *M*-test conditions (*see also* Mestre, 1990*b*), is a hallmark of magnocellular isolation (Lee, 1996).

In contrast with chromatic tasks, performance under luminance modulation conditions showed a significant deterioration with stage. Future studies should investigate the role of intragroup ageing effects (since normal controls did not show any effect of age on magnocellular performance).

In any case, our findings imply a significant involvement of early (probably in the retina) magnocellular maps in Parkinson's disease (for details on their topography *see* Curcio *et al.*, 1990; Silveira and Perry, 1991; Yamada *et al.*, 2001).

The significant change in foveal CS that we have found is consistent with evidence suggesting that dopaminergic innervation around the fovea is reduced in Parkinson's disease patients (Nguyen-Legros, 1988). An electrophysiological study from Ikeda *et al.* (1994), in newly diagnosed Parkinson's disease patients (in Stage 1), suggests that the retina is a likely source of impairment (as revealed by early changes in EOG). Follow-up of these patients revealed subsequent (in Stage 2) global ERG abnormalities. We do also believe that the found deficits are likely to be at least partially located in the retina. In the subset of 21 patients in which both eyes were tested using the magno isolating stimuli, we observed a pattern of asymmetry very similar to the one typically observed in glaucoma (*see* references above) which represents evidence for involvement at the level of the retina, as previously suggested by Harnois and di Paolo (1990). Retinal impairment could, in turn, lead to specific metabolic occipital glucose hypometabolism (Bohnen *et al.*, 1999). The main source of the retinal deficit is probably at the ganglion cell level which is consistent with the PERG (pattern electroretinogram) literature (Tagliati *et al.*, 1996) in Parkinson's disease, and the fact that PERG responses predominantly reflect the activity of retinal ganglion cells (Fiorentini *et al.*, 1981; Harrison *et al.*, 1987; Bach, 2001). This is also consistent with recent evidence showing retinal nerve fibre layer thinning in Parkinson disease (Inzelberg *et al.*, 2004). The work of Bodis-Wollner and Tzelepi (1998) is in this sense seminal, because it discusses the PERG spatial contrast response function in terms of the envelope output of retinal ganglion cells or the average or 'equivalent' retinal ganglion cell. It also postulates the existence of a 'push-pull' mechanism related to two dopamine-sensitive pathways with different weights for two classes of ganglion cells. One uses D1 receptors and is primarily affecting the 'surround' organization of ganglion cells with large centres, while the other uses D2 post-synaptic receptors and contributes to 'centre' response amplification of ganglion cells with smaller centres. A preganglionic mechanism is unlikely to contribute to the chromatic data as well because experiments performed under blue cone adaptation conditions showed that although ellipses are larger than for control subjects, this increase is proportional to the baseline impairment.

Since we could show that our quantitative measures of chromatic and achromatic CS are independent, and differently related to stage, future studies should address the role of medication in sensory impairment in early disease stages

(Buttner *et al.*, 1994, 2000; for a review *see* Bodis-Wollner, 1990, 2002; Mestre *et al.*, 1990*a*, *b*, 1996). Most of our patients were in early stages, and some were even newly diagnosed without any medication (similarly to the study of Ikeda *et al.*, 1994). We have seen no significant difference between the treated versus the untreated 'de novo' patients, although average scores were better for the treated group. These results are consistent with the idea that the dopaminergic treatment may partially compensate (Buttner *et al.*, 1994) the progression of visual impairment.

Some studies of colour discrimination and CS in Parkinson's disease have analysed the influence of disease progression on performance (Price *et al.*, 1992; Buttner *et al.*, 1994). Diederich *et al.* (2002) have tested Parkinson's disease patients with relatively normal visual acuity (Snellen fraction >0.6 in the best eye) and have used classical procedures, which do not allow for the extraction of patient reliability indexes (e.g. percent false positive and negative measures). These tests (Lanthony D15 test, Farnsworth–Munsell 100-Hue test, monocular and binocular Pelli–Robson test and the Vistech tables) have been widely used before to study CS deficits in Parkinson's disease (Harris, 1998; Pieri *et al.*, 2000; Diederich *et al.*, 2002; for a review *see* Bodis-Wollner, 2003). Some have further suggested independent impairment of both colour and contrast discrimination (Pieri *et al.*, 2000). However, these methods are only semi-quantitative, owing to low score reproducibility (Roth and Lanthony, 1999). Recent quantitative studies of chromatic function were able to determine reliability indexes for every patient, and proved to have excellent reproducibility in detection of early visual damage (Regan *et al.*, 1994; Castelo-Branco *et al.*, 2004; Campos *et al.*, 2005; for other previous quantitative achromatic CS studies *see* Bodis-Wollner *et al.*, 1987; Mestre *et al.*, 1990*a*, *b*). We suggest that future studies should use random psychophysical staircases due to their improved sensitivity and robustness against cognitive confounding factors.

Taken together, our findings suggest a differential and independent involvement of parvo- (red–green), konio- (blue–yellow) and magnocellular visual pathways in Parkinson's disease. This indicates that distinct mechanisms, possibly related to different patterns of dopaminergic modulation (Bodis-Wollner and Tzelepi, 1998; Buttner *et al.*, 2000), contribute to sensory impairment in Parkinson's disease. Future studies should address the effect of medication in these different types of deficit, in distinct disease stages.

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