Brain (1997), **120,** 2219–2228

Contrast detection, discrimination and adaptation in patients with Parkinson's disease and multiple system atrophy

L. Tebartz van Elst,[1] M. W. Greenlee,[1] J. M. Foley[2] and C. H. Lücking[1]

[1]*Neurologische Universitätsklinik, Universität Freiburg, Freiburg, Germany and*
[2]*Department of Psychology, University of California Santa Barbara, Santa Barbara, California, USA*

Correspondence to: Dr M. W. Greenlee, Neurologische Universitätsklinik, Breisacherstrasse 64, 79106 Freiburg, Germany

Summary

*Visual spatial contrast thresholds and suprathreshold contrast matches were measured before and after adaptation to high-contrast sinewave gratings in patients with Parkinson's disease (*n = *27), patients with multiple system atrophy (*n = *6) and a group of age-matched control patients without CNS disease (*n = *27). Contrast thresholds were higher in the Parkinson's disease patients than in either the multiple system atrophy patients or control patients. The effect of contrast adaptation on both contrast thresholds and matches was approximately equal in the three groups. This suggests that contrast adaptation is not affected by these CNS disorders and is consistent with the hypothesis that the loss in contrast sensitivity in Parkinson's disease is mediated by retinal effects. The results are discussed in terms of the underlying pathology of the visual deficits in Parkinson's disease and the possible diagnostic implications for differentiating Parkinson's disease and multiple system atrophy.*

Keywords: contrast discrimination; adaptation; Parkinson's disease; multiple system atrophy; neurodegenerative diseases

Abbreviations: pERG = pattern electroretinogram; RT = reaction time; VEP = visually evoked potential

Introduction

Over the last two decades an increasing body of evidence has been collected, which demonstrates visual abnormalities in patients with Parkinson's disease. These patients show longer latencies in visually evoked potentials (VEPs) (Bodis-Wollner and Yahr, 1978; Delwaide, 1980; Gawel, 1981; Marx *et al*., 1986), abnormalities of the pattern electroretinogram (pERG) (Ghilardi *et al*., 1989; Ikeda *et al*., 1994) and reduced contrast sensitivity (Bodis-Wollner *et al*., 1987; Bodis-Wollner, 1990; Mestre *et al*., 1990*a*, *b*; Masson *et al*., 1993). These effects are most pronounced for gratings with a spatial frequency of 2–4 cycles per degree and a temporal frequency of 4–8 Hz (Marx *et al*., 1986; Bodis-Wollner *et al*., 1987). Several studies have shown that dopamine, or the dopamine agonist apomorphine, enhances VEPs and pERGs in healthy volunteers (Domenici *et al*., 1985; Bulens *et al*., 1987; Bulens and Meerwaldt, 1989; Mestre *et al*., 1990*a*), and can also counteract the deficits in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated animal model of Parkinson's disease (Ghilardi *et al*., 1989). Administration of dopamine antagonists like chlorpromazine in healthy volunteers induces modifications of the VEP and pERG similar to those seen in Parkinson's disease (Bartel *et al*., 1990) and leads to a global decrease in contrast sensitivity in patients with schizophrenia Bulens *et al*., 1987).

The functional and anatomical sites of the psychophysically measured visual deficits in Parkinson's disease remain largely unknown. Considerable evidence supports the assumption that these visual deficits are due to a dopaminergic deficiency. The decline in contrast sensitivity in Parkinson's disease can, at least in part, be reversed by the administration of L-dopa (Bulens *et al*., 1987). Monkeys treated with MPTP (a neurotoxin, which predominantly affects dopaminergic neurons) develop a Parkinsonian syndrome and show deficits in contrast sensitivity similar to those found in patients with Parkinson's disease, which again can be ameliorated by the administration of L-dopa (Ghilardi *et al*., 1989). The severity of visual abnormalities increases with progressive stages of the disease, as indicated by the correlation between ERG

amplitudes and the Hoehn and Yahr score (Tagliati *et al*., 1996). The pERG shows characteristic abnormalities in Parkinson's disease (Tagliati *et al*., 1996). Since the pERG mainly reflects ganglion cell activity in primates (Maffei *et al*., 1985), most authors have suggested a retinal dopaminergic origin for the visual deficits in Parkinson's disease (Bodis-Wollner *et al*., 1987; Ghilardi *et al*., 1989; Bodis-Wollner, 1990; Harris *et al*., 1992; Tagliati *et al*., 1996). Accordingly, the increase in VEP latencies could result from pathological transmission at the retinal level. This assumption is supported by experiments in monkeys, where intra-vitreous injection of 6-hydroxydopamine, a neurotoxin affecting catecholaminergic cells, leads to abnormalities in the pERG and VEP similar to those caused by systemic administration of MPTP (Ghilardi *et al*., 1989). Dopamine containing amacrine cells and dopamine receptors have been demonstrated in the retina of vertebrates (Haggendal and Malmfors, 1963; Dowling and Ehinger, 1975; Mariani *et al*., 1984; Massey and Redburn, 1987; Nguyen-Legros *et al*., 1984; Skrandies and Wässle, 1988) including humans (Frederick *et al*., 1982). Harnois and Di Paolo (1990) found decreased dopamine activity in the retina of patients with Parkinson's disease. Bodis-Wollner *et al*. (1987) have argued for a role of the dopaminergic amacrine cells in receptive field organization in human vision, which, in the case of dopaminergic deficiency, could explain the pathological findings in Parkinson's disease.

However, evidence also exists for dopaminergic innervation at the level of the lateral geniculate (Papadopoulos and Parnavelas, 1990) and the visual cortex (Reader and Quesney, 1986; Parkinson, 1989). Regan and Maxner (1987) and Bulens and Meerwaldt (1988) have found orientation-specific losses of contrast sensitivity in patients with Parkinson's disease. Visual search for a target of a given orientation randomly positioned among orthogonally oriented distractors also appears to be impaired (Troscianko and Calvert, 1993; Weinstein *et al*., 1997). Orientation selectivity is a characteristic of visual cortical cells in primates (Hubel and Wiesel, 1962, 1968), which suggests, that the visual cortex might also be affected in Parkinson's disease. Thus not only the retina, but also the visual cortex could be involved in the visual pathology found in Parkinson's disease.

In healthy volunteers, prolonged viewing of a high-contrast grating reduces contrast sensitivity (Blakemore and Campbell, 1969; Magnussen and Greenlee, 1985; Greenlee *et al*., 1991). This form of visual adaptation also affects the perceived contrast of suprathreshold gratings (Georgeson, 1985). Following half-field adaptation, stimuli presented in the adapted field are perceived to have less contrast than the same stimuli falling in the unadapted field. This reduction in sensitivity and perceived contrast is spatial-frequency and orientation dependent (Blakemore *et al*., 1973; Snowden and Hammett, 1992), suggesting a cortical site of adaptation. Indeed, a number of single-unit studies have shown that the relationship between the firing rates of single neurons and stimulus contrast can be altered by prior adaptation (Albrecht and Hamilton, 1982; Dean, 1983; Ohzawa *et al*., 1985; Sclar *et al*., 1989). Adaptation shifts the contrast response function towards higher levels of contrast. One perceptual consequence of such a shift would be a temporary loss in perceived contrast, assuming that the firing rate of single cortical neurons reflect, among other things, the coding of stimulus contrast. Although GABA (gamma-aminobutyric acid) is an important inhibitory neurotransmitter in visual cortex (McCormick, 1989; Hendry *et al*., 1990), it does not seem to be directly involved in mediating the effects of adaptation (DeBruyn and Bonds, 1986; Allison *et al*., 1993). The above-cited evidence suggests the existence of dopaminergic innervation in the visual cortex. Thus if the same neurotransmitters affected in Parkinson's disease are mediating sensitivity changes in the visual cortex, then it would be possible that the effects of contrast adaptation would also be reduced in Parkinson's disease.

Multiple system atrophy as a pathologic entity was first described by Graham and Oppenheimer in 1969. According to Quinn (1989, 1994) and Wenning *et al*. (1994), two subtypes of multiple system atrophy are defined by a combination of specific symptoms. Since definite diagnosis is possible only at post mortem autopsy, the clinical diagnosis is defined by a cluster of symptoms and divided into possible and probable multiple system atrophy (*see* Wenning *et al*., 1994, their Table 1). Differentiating between multiple system atrophy-subtype with striato-nigral degeneration and idiopathic Parkinson's disease is often difficult, since autonomic failure or signs of pyramidal or cerebellar dysfunction may develop only late in the course of the disease (Wenning *et al*., 1994; Oertel, 1996). Multiple system atrophy pathology is characterized by cell loss and gliosis in at least two of the following structures: striatum; substantia nigra and/or locus ceruleus; pontine nuclei and/or cerebellar pedunculi; vestibular nucleus; Purkinje cell layer of the cerebellum; lower olive; the dorsal motor nucleus of the tenth brain nerve; the intermediolaterale cell column or the nucleus of Onuf in the lower spinal cord (Oppenheimer, 1983; Gray, 1988; Playford and Brooks, 1992). In Parkinson's disease, cell loss and gliosis affect predominantly dopaminergic neurons of the substantia nigra (ventrolateral part) (Gibb and Lees, 1991). Characteristically, there are signs of intracellular eosinophilic inclusion bodies (Lewy bodies). In contrast to Parkinson's disease, where administration of L-dopa is effective in the majority of cases, in multiple system atrophy a good response to L-dopa is seen in only ~30% with a decline of effectivity to as low as 13% in the further course of the disease (Wenning *et al*., 1994).

To our knowledge, there is only one report on the visual performance of patients with multiple system atrophy, where an interocular difference in spatiotemporal contrast sensitivity was found in Parkinson's disease patients but not in those with multiple system atrophy (Delalande *et al*., 1996). VEPs were also normal in the multiple system atrophy group in that study. Patients with the striato-nigral degeneration subtype of multiple system atrophy and idiopathic Parkinson's disease may present clinically in a similar way. We therefore

examined whether these two diseases may lead to differences in contrast sensitivity which, in turn, could promote our understanding of the visual pathology in Parkinson's disease. Vision might be less affected in multiple system atrophy as compared with Parkinson's disease, since the dopamine deficiency in the latter is generally recognized to be more pronounced.

Rationale for this study

Earlier studies with Parkinson's disease patients have concentrated on the measurement of contrast sensitivity at the threshold level. The effect of contrast adaptation has only been measured in one small group of Parkinson's disease patients (Harris *et al*., 1992), where adaptation-induced threshold elevations were found to be smaller in the peripheral vision of Parkinson's disease patients. Following this approach, we examined the influence of adaptation on detection thresholds as well as on contrast matches for three suprathreshold contrast levels. We compare the results from patients with Parkinson's disease or multiple system atrophy with those from a group of age-matched control patients. The purpose of the present study is to examine contrast thresholds more extensively and the effect of contrast adaptation in Parkinson's disease patients in comparison with patients with multiple system atrophy and patients with no CNS disorder.

Material and methods

Stimuli

The visual stimuli were created on a Visual Stimulus Generator graphics board (VSG 2/3; Cambridge Research Systems, Kent, UK) and displayed on a high-resolution colour monitor (Eizo 662; Japan). The voltage determining the luminance of the stimuli was produced with 14-bit digital-to-analogue converters. Correction of the luminance gamma function of the display was calculated using a spectral photometer (Spectra 704; USA) and stored in lookup tables for each phosphor type separately. Circular patches of sine-wave gratings (diameter 4°) with constant orientation (horizontal) and spatial frequency (4 cycles per degree), but differing in contrast, were presented simultaneously for 200 ms, one in each visual field 4° eccentric to the fixation point. Perceived contrast judgments were performed before and after 2 min of half-field adaptation to a high contrast (90%) phase-reversing (4 Hz) grating of the same orientation and spatial frequency. The adaptation stimulus was presented in one run in the left visual field and in another run in the right visual field, and their order was randomized over subjects. Reference contrast levels were 0% (detection threshold), 9.5, 23.4 and 57.4% Michelson contrast.

Procedure

Subjects viewed the stimulus display binocularly from a distance of 114 cm. They were comfortably seated in an examination chair and rested their head and arms on appropriately positioned rests. The patients were instructed to direct their gaze to the centre of the display, where the fixation cross was displayed during each trial. Each measurement consisted of 80 trials (four reference contrast levels, 20 trials per level). Each trial was announced by a computer generated sound presented 200 ± 100 ms prior to stimulus onset, at which time the fixation cross was also presented. This was followed by simultaneous presentation of reference and test stimuli (Fig. 1). The stimulus duration was 200 ms and the onset and offset of contrast was abrupt. The participants responded by indicating which stimulus had the higher contrast. In cases where only one stimulus was visible, they were asked to indicate which side of the fixation cross the stimulus appeared. On some trials where the reference contrast was zero, and the test contrast was low, no stimulus was visible. When this happened patients were instructed to select the reference side. With the algorithm we were using, this had the effect of increasing the contrast on the test side until it became visible. In effect, the task became a yes-no detection task in this condition. Except for this instruction, the method was the same in all conditions.

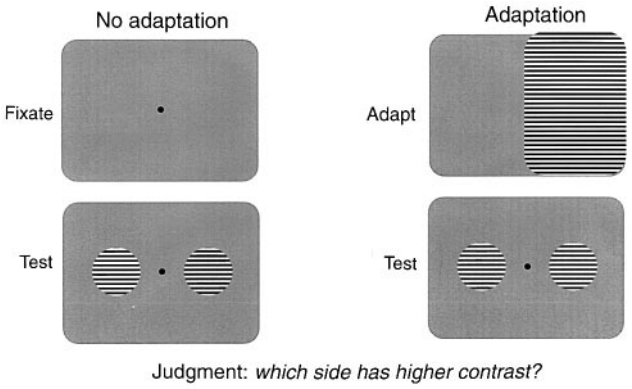

Fig. 1 Schematic illustration of the stimuli used in the experiments. For more details *see* text.

Measurements were made before and after 2 min of adaptation to a high-contrast, phase reversing (4 Hz) adaptation grating (Fig. 1). After adaptation, each trial was followed by a brief (2 s) refresh adaptation period, during which time the half-field adaptation stimulus was presented again. Such a regimen has been shown to maintain the adaptation level in a steady-state (Greenlee *et al*., 1991; Foley and Boynton, 1993). Individual measurements were performed for left and right hemifield adaptation. The order of left and right hemifield adaptation was randomized across subjects; for all subjects measurements without adaptation were made first, to be followed by an adaptation run. All four experimental runs were conducted in a single session. A break of at least 15 min was given between the adaptation measurement and the next run. A sufficient number of practice trials was performed to ensure that the patient understood the task and became acquainted with the response box.

Match and threshold contrast levels were determined using

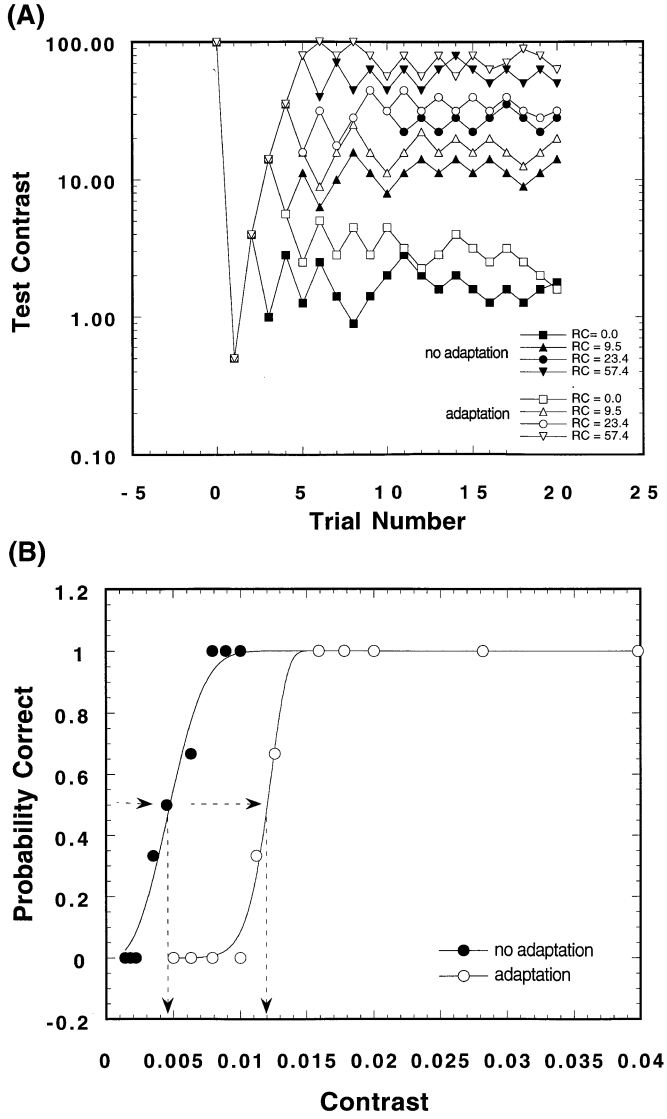

Fig. 2 (**A**) Examples of the variations in test contrast under the control of the Best-PEST algorithm, for experimental runs before (filled symbols) and after (open symbols) adaptation. The different symbols show the results for the detection thresholds and the three suprathreshold match contrasts. (**B**) An example of a psychometric function (percentage correct versus log test contrast). The smooth curves are Weibull functions fitted to the data with the maximum likelihood criteria. RC = reference contrast (% Michelson contrast).

an adaptive search algorithm (Best-PEST) (Lieberman and Pentland, 1982). This algorithm has been shown to optimize the information gained on each trial. The four reference contrast levels were tested in a randomly interleaved fashion, and each of these 'staircases' was controlled by its own PEST routine. All staircases started with the highest possible test contrast level (approaching 100%) and each contained 80 possible contrast steps, each step corresponding to a 1-dB change in contrast. In this way, the possible test contrast levels allowed spanned a 10 000-fold range ($\log_{10}$ of Michelson contrast, –2.0 to +2.0). The individual staircases were guided by the subject's prior responses on that staircase. An example of a typical measurement before and after adaptation is given in Fig. 2A. Note that on the first two trials, all staircases share the same test contrast levels. Only after trial 5 do the staircases begin to 'zoom' into the corresponding subjective contrast match levels. Weibull functions were fitted to the individual data sets to determine the slope of the psychometric functions (differential contrast sensitivity).

Reaction times (RTs) were also determined using a function that accesses the graphics processor, which timed the interval between the stimulus onset and the response (pressing one of two buttons). We could thus achieve temporal resolution of 10 μs (i.e. the duration of the buildup of each line on the display). The subjects were given 2 s to respond. If the subject did not respond within the specified time, the next trial was presented. The lapsed trial was placed back into the trial pool and performed at a later point in the run. In such cases a counter was incremented for that condition, thereby allowing an analysis of the number of lapses.

Subjects

All participants were recruited consecutively from the in-patient clinic of the Neurology Department at the University of Freiburg. They were first informed about the general aims of the investigation. Participation was strictly on a voluntary basis and only occurred after informed consent was given. Approval for the study was obtained from the local ethical board of the University of Freiburg. Any additional CNS disease or eye disease led to exclusion from the study. The ward consultant, who was uninformed as to the specific aims of our study, made the clinical diagnoses. A total of 27 patients with idiopathic Parkinson's disease participated (mean age 63.3 years; SD = 9.8; range 42–75 years), six of these patients were untreated at the time of study. The administration of any drugs, which could affect CNS function, was recorded for further analysis. Possible multiple system atrophy was diagnosed in patients with a Parkinsonian syndrome, who showed little or no response to L-dopa therapy or cerebellar signs. Probable multiple system atrophy was diagnosed in patients with a Parkinsonian syndrome, who showed little or no response to L-dopa and additional autonomic failure, or cerebellar and/or pyramidal signs, or a pathological sphincter electromyogram (Quinn, 1994). In our patient sample, two patients were diagnosed as having possible multiple system atrophy and four patients as having probable multiple system atrophy (mean age 55.3 years; SD = 2.7; range 52–59 years). A third group of inpatients (n = 25), with no clinically determined CNS disorders, served as a control group (mean age 55.7 years; SD = 8.3; range 42–72 years). Care was taken to select control patients so that the Parkinson's disease and control groups were similarly distributed with respect to age, gender and socio-economic status.

Data analyses

Psychometric functions (probability of correct responses against contrast level) were calculated off-line and Weibull

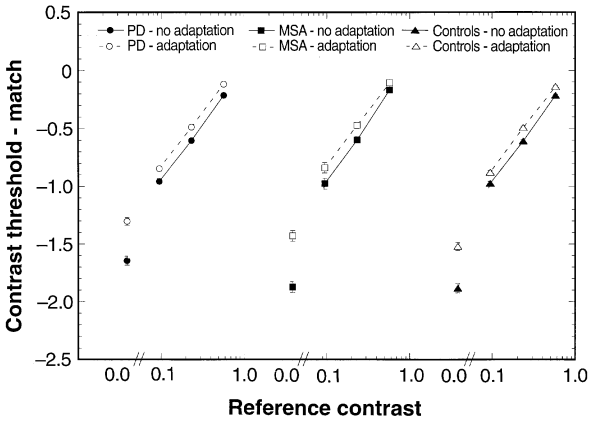

Fig. 3 Log of contrast threshold (single points, left) and contrast matches before (filled symbols) and after (open symbols) adaptation to a high contrast grating positioned either in the left or right visual field. The results are shown for the three patient groups tested. Error bars present ±1 SE of the group mean. PD = Parkinson's disease; MSA = multiple system atrophy.

functions were fitted to these data using the so-called bootstrap algorithm (Foster and Bischof, 1991). Figure 2B gives an example for thresholds measured before and after adaptation. The Weibull functions provided estimates of the threshold or match contrast level, defined as the contrast level where the subject responded 50% of the time when the reference stimulus had a higher contrast level. The slope of the Weibull function gives an estimate of the differential contrast sensitivity, with greater sensitivity reflected by a steeper slope.

Analyses of variance for repeated measures were performed on the logarithms of threshold and the inverse slope data. Log RT and the number of lapses per run were also analysed. The main effects and interactions were determined for the following factors: patient group (Parkinson's disease, multiple system atrophy and control), the adaptation state (before and after adaptation), the side of half-field adaptation (left and right) and the reference contrast level (detection threshold and three suprathreshold contrast levels).

Results

Contrast thresholds and contrast matching before and after adaptation

The results with respect to contrast thresholds and contrast matches before and after adaptation are shown in Fig. 3. The log of the mean threshold value is shown as a function of the reference contrast level for the three patient groups. Although there was a small effect of visual field (thresholds and contrast matches to stimuli in the right visual field ~10% lower), this effect did not interact with any of the other factors in the experimental design. We therefore present the results after averaging over left and right visual fields. Above detection threshold, the matches before adaptation are approximately physical matches. Adaptation increases both the contrast threshold and the test contrast in the adapted field required to match the reference contrast in the unadapted reference field. This increase is greatest for the lower reference contrasts. It is approximately equal for the three patient groups. In support of earlier work, contrast thresholds are significantly elevated in Parkinson's disease patients compared with control patients [main effect of experimental group; $F(2,56) = 6.18$, $P < 0.004$]. This elevation corresponds to a factor of 1.75 ($\log_{10} = 0.245$). The multiple system atrophy patients exhibit thresholds which are not significantly different from those of the control patients (*post hoc* Bonferroni/Dunn comparison, $P > 0.05$). Above detection threshold levels the contrast match values are no longer significantly different. There is a significant interaction term between the main effects of reference contrast level and patient group [$F(6,162) = 7.77$, $P < 0.0001$], where the Parkinson's disease patients show a significant effect at threshold but values above threshold were similar to those of the control patients.

Prior adaptation to a high contrast flickering grating increases the contrast required for detection of the test stimulus in the adapted field. Adaptation also increases the contrast required to compensate for the loss in perceived contrast in the adapted half-field. The effect of adaptation is most pronounced at detection threshold when the mean increase in threshold is by a factor of 2.3 ($\log_{10} = 0.36$), and it declines at higher contrast levels (mean change in contrast match after adaptation by a factor of 1.27; $\log_{10} = 0.10$). This finding is true for all three patient groups, which is reflected by the absence of a significant interaction term between the main effects of adaptation, reference contrast level and patient group [$F(6,162) = 1.1$, not significant].

It could be argued that suprathreshold contrast matches alone are not sensitive to changes occurring in the visual system of Parkinson's disease patients, since presumably both visual fields would be affected more or less equally. Thus, although the perceived contrast of the grating stimuli could be reduced, this reduction would be equivalent for right and left visual fields and thus would not affect the resulting contrast match. Our use of forced-choice methods and the adaptive staircase procedure allows an estimate of the slope of the psychometric function for both threshold and suprathreshold contrast matches. If the differential contrast sensitivity at suprathreshold contrast levels is affected in Parkinson's disease, then this difference should be reflected in a shallower slope of the psychometric function (i.e. a degraded perception of contrast differences).

The results with respect to the slope estimates are given in Fig. 4, which shows a plot of the log of the inverse slope as a function of the log of the reference contrast level for the three patient groups. There is a pronounced effect of reference contrast level on the inverse slope of the psychometric function. The slope declined (1/slope increased) by an order of magnitude over the contrast range investigated [$F(3,165) = 90.0$, $P < 0.0001$]. This decline in differential contrast sensitivity with increasing reference contrast level is well documented (Foley and Legge, 1981; Greenlee and Heitger, 1988). There is some indication that the differential

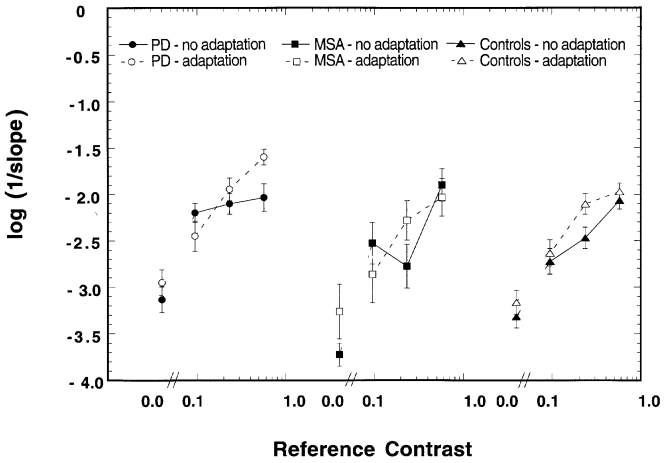

Fig. 4 Log of the inverse slope of the psychometric functions (percentage correct versus test contrast, *see* Fig. 2) is plotted as a function of the reference contrast on a log scale. Error bars present ±1 SE of the group mean.

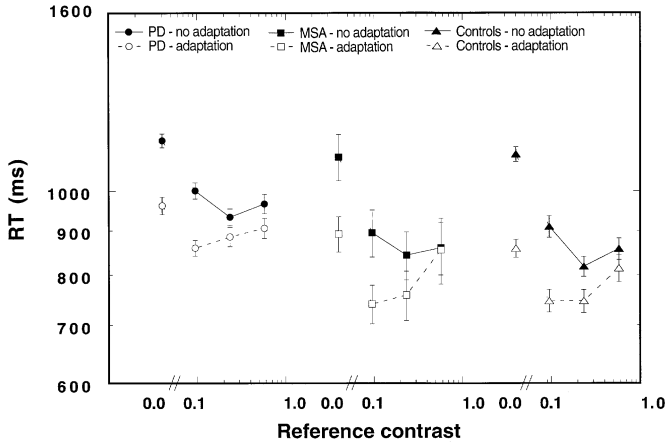

Fig. 5 Reaction times (RT) versus reference contrast are plotted on log–log scales. Error bars present ±1 SE of the group mean.

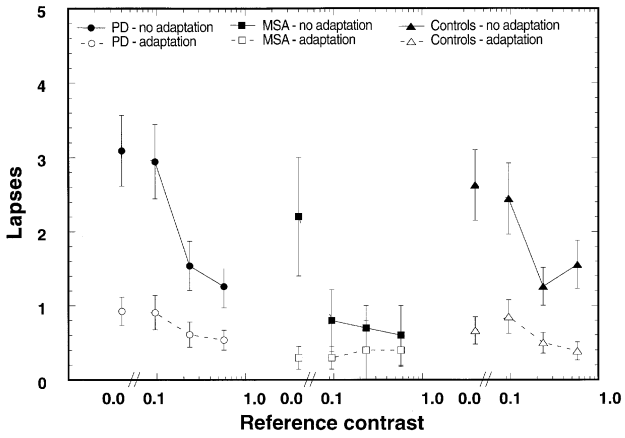

Fig. 6 The mean number of lapses versus the reference contrast level. Error bars present ±1 SE of the group mean.

contrast sensitivity is reduced (lower slope of psychometric function) at suprathreshold levels in patients with Parkinson's disease. The mean slope is reduced in Parkinson's disease patients by a factor of 2.1 ($\log_{10} = 0.32$), and this effect is significant [$F(2,56) = 3.98$, $P < 0.03$].

Adaptation has only a marginal effect on the slope of the psychometric function [$F(1,56) = 3.13$, $P < 0.08$]. Generally, the psychometric functions are shallower in slope after adaptation (by a factor of 1.44), which would correspond to an overall loss in differential contrast sensitivity at these suprathreshold contrast levels. This effect of adaptation is in line with earlier work, which shows that contrast discrimination thresholds are elevated by prior adaptation for contrast levels <0.5 (Greenlee and Heitger, 1988; Ross and Speed, 1991; Foley and Boynton, 1993).

Reaction times

All participants were instructed to respond accurately and as quickly as possible. We could thus determine the RTs on each trial and look at how RT was affected by the different stimulus conditions. The results for the three patient groups are shown in Fig. 5, where the log RT is plotted as a function of the reference contrast. Prior to adaptation, log RT decreases with increasing stimulus contrast, in line with earlier results (Breitmeyer, 1975; Harwerth and Levi, 1978; Ejima and Ohtani, 1989; Greenlee and Breitmeyer, 1989). The main effect of reference contrast was highly significant [$F(3,162) = 86.6$, $P < 0.0001$]. All patients seem to benefit by additional stimulus contrast. Interestingly, adaptation leads to a reduction in log RT and this effect is highly significant [$F(1,56) = 150.1$, $P < 0.0001$]. Patients with Parkinson's disease exhibit significantly prolonged RTs compared with the control patients. Patients with multiple system atrophy do not significantly differ from control patients with respect to RTs. The main effect of patient group was highly significant [$F(2,56) = 5.6$, $P > 0.006$]. The patients with Parkinson's disease had a geometric mean RT of 1188 ms, while that for patients with multiple system atrophy was 1090 ms, and for the control patients, it was 1088 ms.

Task completion, lapses

Several of the patients suffered from bradykinesia or akinesia. This resulted in some patients being unable to respond within the time allotted to each trial. The number of trials on which the participants did not respond was recorded. Figure 6 shows how the number of lapses is affected by the reference contrast level and adaptation. Most patients lapsed only on a few trials and this number depended on the reference contrast level. Due to the adaptive staircase procedure, the reference contrast condition of zero contrast (detection threshold) often led to trials where the test stimulus had a subthreshold contrast level. As a result of the uncertainty of the task in these circumstances, the patients were more likely to fail to respond during the trial period. As can be seen in Fig. 6, this tendency was true for all patient groups. The presence of the adaptation stimulus during the inter-trial interval appears to

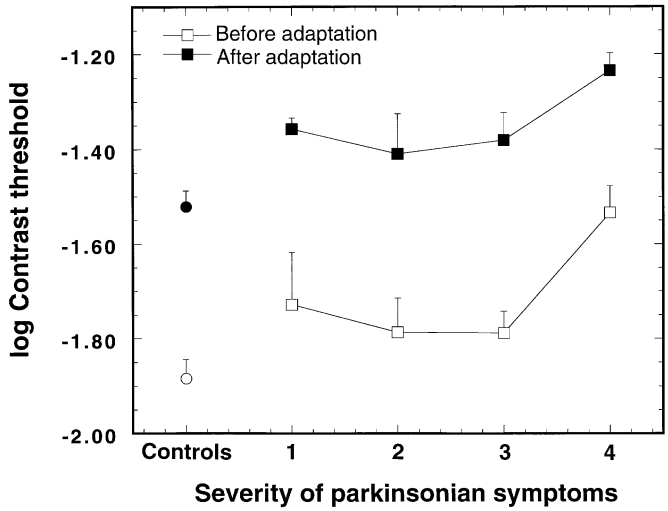

Fig. 7 Log of contrast thresholds is plotted before and after adaptation for patients with Parkinson's disease as a function of the severity of the disease (according to the Hoehn and Yahr rating scale).

have acted like a 'prime' or 'pacemaker' for all patients; this is evident from the observed reduction in the number of lapses and a corresponding decrease in RT (Fig. 5). The benefit of paced responses in patients with Parkinson's disease has been reported earlier (Crawford *et al*., 1989). Overall, the results in Fig. 6 suggest that, on average, all three patient groups could perform the task and demonstrated a similar frequency of lapses.

Correlation with clinical course

The performance of the patients varied to a considerable extent with respect to their clinical course and the severity of Parkinsonian symptoms. One estimate of the patient's status is a rating scale suggested by Hoehn and Yahr (1967). This scale takes into account the extent of disability caused by the disease. The extent to which contrast detection thresholds before and after adaptation were affected by the severity of Parkinson's disease is shown in Fig. 7. The reduction in contrast sensitivity increases with severity especially during clinical stage IV. However, even at stage I, where there is little or no or disability, there is already a significant reduction in contrast sensitivity in Parkinson's disease patients compared with control patients. The effects of adaptation remain robust even for the later stages of Parkinson's disease.

Discussion

The results confirm earlier reports that contrast perception is impaired in Parkinson's disease. Although to a lesser extent, sensitivity to suprathreshold contrast differences is also reduced in these patients. Parkinson's disease patients exhibited adaptation effects which were similar in magnitude to those shown by the control patients, suggesting that the neural processes underlying pattern adaptation are unaffected by Parkinson's disease. Patients with multiple system atrophy did not show a significant threshold elevation and showed adaptation effects similar to those in the control group, suggesting that the pathology underlying the visual deficits in Parkinson's disease is not effective in multiple system atrophy.

Contrast thresholds and contrast matching

In agreement with earlier studies, we found a significant elevation in the contrast detection thresholds in patients with Parkinson's disease. Compared with control patients, patients with Parkinson's disease exhibited contrast thresholds which were significantly elevated (Fig. 3). Contrary to this finding, suprathreshold contrast matching values were not significantly affected by Parkinson's disease. The differences in the slope of the psychometric functions at the four reference contrast levels suggest that suprathreshold contrast discrimination is also somewhat affected in Parkinson's disease. However, the magnitude of the effects above detection threshold are relatively small and are thus only marginally significant.

Contrast adaptation in Parkinson's disease

Our original hypothesis that the effects of contrast adaptation could be reduced in Parkinson's disease, was not supported by the present results. Although patients with Parkinson's disease had significantly higher detection thresholds, these thresholds were affected by prior adaptation in the same way as those observed in the control group. Following adaptation detection, thresholds were increased by a factor of 2.1 ($\log_{10} = 0.33$) in patients with Parkinson's disease, by a factor of 2.75 ($\log_{10} = 0.44$) in patients with multiple system atrophy, and by a factor of 2.3 ($\log_{10} = 0.363$) in the control group. Although the effects of adaptation are smaller for suprathreshold contrast matches (varying from a factor of 1.14 to one of 1.37), the magnitudes of these effects are similar across the three groups studied. In a group of six patients with Parkinson's disease, Harris *et al*. (1992) reported that contrast adaptation could be elicited in central vision. Contrast matches between centrally and peripherally located grating patches indicated that the contrast gain in the peripheral vision might be affected by Parkinson's disease. In support of the former finding, the present results suggest that, within a 6° radius of the fovea, contrast adaptation is normal in patients with Parkinson's disease.

Reaction times

Patients with Parkinson's disease exhibit longer RTs in tasks demanding a simple response (Montgomery and Nuessen, 1990), as well as in more complicated choice RT or dual tasks demanding allocation of attention and efficient perceptual processing (Bloxham *et al*., 1987; Pullman *et al*., 1988; Brown and Marsden, 1991). The present results indicate that patients with Parkinson's disease have significantly prolonged

RTs compared with control patients. The overall RTs are most prolonged for the detection task, in which the patient must decide on which side the low contrast stimulus was presented. Although this, at first glance, would appear to be an easy task, there is more temporal uncertainty in it, since the exact time of stimulus onset is less obvious. Furthermore, in trials where the stimuli remained below threshold, the patient had to indicate the reference stimulus location, which can be interpreted as a further cognitive load. Indeed, both the patients with Parkinson's disease and the control patients required more time to respond to this task (Fig. 5).

Differences between Parkinson's disease and multiple system atrophy groups

While Parkinson's disease patients exhibited a significant reduction in contrast sensitivity, patients with multiple system atrophy showed contrast sensitivity values similar to those of the control patients. This result suggests that the visual system is not affected in the same way in these two patient groups. Taken together with the clinical observation that only a small proportion of patients with multiple system atrophy respond to L-dopa therapy, the present results suggest that the reduced contrast sensitivity in Parkinson's disease is related to a dopaminergic pathology. The observation that the visual system is less affected in multiple system atrophy suggests that its pathogenesis differs from that of Parkinson's disease.

Underlying pathology of loss in contrast sensitivity

The question remains as to which site in the visual pathway is affected by Parkinson's disease. The pathogenic mechanisms in Parkinson's disease that induce cell dysfunction and loss in subcortical nuclei (e.g. substantia nigra and the locus coeruleus) might also be involved in the pathology of retinal amacrine cells. Our observation, that cortical adaptation is not significantly affected in Parkinson's disease, indicates that cortical pathology probably plays only a minor role with respect to reduced contrast sensitivity. However, further studies are needed to substantiate this claim. Furthermore, post-mortem studies of abnormal retinal morphology in Parkinson's disease would help to clarify, whether there is amacrine cell loss or whether there are Lewy bodies in the amacrine cells of the retina in Parkinson's disease. Also a simultaneous evaluation of the contrast sensitivity and the pERG could help in the understanding of the relationship between a progressive loss of contrast sensitivity and pathological findings in the pERG (Langheinrich *et al*., 1997). Differential effects of pathology on the pathways leading to magno- and parvo-cellular layers in the lateral geniculate nucleus could also play a role in near-threshold versus suprathreshold contrast discrimination. Finally comparative studies of patients with different Parkinsonian-like disorders such as Parkinson's disease and multiple system atrophy may clarify whether visual testing can contribute to the differential diagnosis of the Parkinsonian syndrome.

Acknowledgements

The authors would like to thank the patients for their participation. This research was supported by Hermann and Lilly Schilling Stiftung (to M.W.G.), the German Academic Exchange Service (D.A.A.D.) and the Hoffmann-LaRoche Foundation (to J.M.F.).

References

Albrecht DG, Hamilton DB. Striate cortex of monkey and cat: contrast response function. J Neurophysiol 1982; 48: 217–37.

Allison JD, Casagrande VA, Debruyn EJ, Bonds AB. Contrast adaptation in striate cortical neurons of the nocturnal primate bush baby (Galago crassicaudatus). Vis Neurosci 1993; 10: 1129–39.

Bartel P, Blom M, Robinson E, Van der Meyden C, Sommers DK, Becker P. Effects of chlorpromazine on pattern and flash ERGs and VEPs compared to oxazepam and to placebo in normal subjects. Electroencephalogr Clin Neurophysiol 1990; 77: 330–9.

Blakemore C, Campbell FW. On the existence of neurones in the human visual system selectively sensitive to the orientation and size of retinal images. J Physiol (London) 1969; 203: 237–60.

Blakemore C, Muncey JP, Ridley RM. Stimulus specificity in the human visual system. Vision Res 1973; 13: 1915–31.

Bloxham C, Dick DJ, Moore M. Reaction times and attention in Parkinson's disease. J Neurol Neurosurg Psychiatry 1987; 50: 1178–83.

Bodis-Wollner I. Visual deficits related to dopamine deficiency in experimental animals and Parkinson's disease patients. [Review]. Trends Neurosci 1990; 13: 296–302.

Bodis-Wollner I, Yahr MD. Measurements of visual evoked potentials in Parkinson's disease. Brain 1978; 101: 661–71.

Bodis-Wollner I, Marx MS, Mitra S, Bobak P, Mylin L, Yahr M. Visual dysfunction in Parkinson's disease. Loss in spatiotemporal contrast sensitivity. Brain 1987; 110: 1675–98.

Breitmeyer BG. Simple reaction time as a measure of the temporal response properties of transient and sustained channels. Vision Res 1975; 15: 1411–2.

Brown RG, Marsden CD. Dual task performance and processing resources in normal subjects and patients with Parkinson's disease. Brain 1991; 114: 215–31.

Bulens C, Meerwaldt JD, Van der Wildt GJ. Effect of stimulus orientation on contrast sensitivity in Parkinson's disease. Neurology 1988; 38: 76–81.

Bulens C, Meerwaldt JD, Van der Wildt GJ, Van Deursen JB. Effect of levodopa treatment on contrast sensitivity in Parkinson's disease. Ann Neurol 1987; 22: 365–9.

Bulens C, Meerwaldt JD, Van der Wildt GJ, Keemink CJ. Visual contrast sensitivity in drug-induced parkinsonism. J Neurol Neurosurg Psychiatry 1989; 52: 341–5.

Crawford T, Goodrich S, Henderson L, Kennard C. Predictive responses in Parkinson's disease: manual keypresses and saccadic eye movements to regular stimulus events. J Neurol Neurosurg Psychiatry 1989; 52: 1033–42.

Dean AF. Adaptation-induced alteration of the relation between response amplitude and contrast in cat striate cortical neurones. Vision Res 1983; 23: 249–56.

DeBruyn EJ, Bonds AB. Contrast adaptation in cat visual cortex is not mediated by GABA. Brain Res 1986; 383: 339–42.

Delalande L, Destee A, Hache JC, Forzy G, Bughin M, Benhadjali J. Visual evoked potentials and spatiotemporal contrast sensitivity changes in idiopathic Parkinson's disease and multiple system atrophy. Adv Neurol 1996; 69: 319–25.

Delwaide PJ, Mesraoua B, De Pasqua, V. Les potentiels evoques visuels dans la maladie de Parkinson. Rev Electroencephalogr Neurophysiol Clin 1980; 10: 338–42.

Domenici L, Trimarchi C, Piccolino M, Fiorentini A, Maffei L. Dopaminergic drugs improve human visual contrast sensitivity. Hum Neurobiol 1985; 4: 195–7.

Dowling JE, Ehinger B. Synaptic organization of the amine-containing interplexiform cells of the goldfish and Cebus monkey retinas. Science 1975; 188: 270–3.

Ejima Y, Ohtani Y. Analysis of simple reaction time to a sinusoidal grating by means of a linear filter model of the detection process. Percept Psychophys 1989; 46: 119–26.

Foley JM, Boynton GM. Forward pattern masking and adaptation: effects of duration, interstimulus interval, contrast, and spatial and temporal frequency. Vision Res 1993; 33: 959–80.

Foley JM, Legge GE. Contrast detection and near-threshold discrimination in human vision. Vision Res 1981; 21: 1041–53.

Foster DH, Bischof WF. Thresholds from psychometric functions: superiority of bootstrap to incremental and probit variance estimators. Psychol Bull 1991; 109: 152–9.

Frederick JM, Rayborn ME, Laties AM, Lam DMK, Hollyfield JG. Dopaminergic neurons in the human retina. J Comp Neurol 1982; 210: 65–79.

Gawel MJ, Das P, Vincent S, Rose FC. Visual and auditory evoked responses in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1981; 44: 227–32.

Georgeson MA. The effect of spatial adaptation on perceived contrast. Spat Vis 1985; 1: 103–12.

Ghilardi MF, Marx MS, Bodis-Wollner I, Camras CB, Glover AA. The effect of intraocular 6-hydroxydopamine on retinal processing of primates. Ann Neurol 1989; 25: 357–64.

Gibb WR, Lees AJ. Anatomy, pigmentation, ventral and dorsal subpopulations of the substantia nigra, and differential cell death in Parkinson's disease. J Neurol Neurosurg Psychiatry 1991; 54: 388–96.

Graham JG, Oppenheimer DR. Orthostatic hypertension and nicotine sensitivity in a case of multiple system atrophy. J Neurol Neurosurg Psychiatry 1969; 32: 28–34.

Gray F. Neuropathologie des syndromes parkinsoniens. Rev Neurol (Paris) 1988; 144: 229–48.

Greenlee MW, Breitmeyer BG. A choice reaction time analysis of spatial frequency discrimination. Vision Res 1989; 29: 1575–86.

Greenlee MW, Heitger F. The functional role of contrast adaptation. Vision Res 1988; 28: 791–7.

Greenlee MW, Georgeson MA, Magnussen S, Harris JP. The time course of adaptation to spatial contrast. Vision Res 1991; 31: 223–36.

Haggendal J, Malmfors T. Evidence of dopamine-containing neurons in the retina of rabbits. Acta Physiol Scand 1963; 59: 295–6.

Harnois C, Di Paolo T. Decreased dopamine in the retinas of patients with Parkinson's disease. Invest Ophthalmol Vis Sci 1990; 31: 2473–5.

Harris JP, Calvert JE, Phillipson OT. Processing of spatial contrast in peripheral vision in Parkinson's disease. Brain 1992; 115: 1447–57.

Harwerth RS, Levi DM. Reaction time as a measure of suprathreshold grating detection. Vision Res 1978; 18: 1579–86.

Hendry SHC, Fuchs J, de Blas AL, Jones EG. Distribution and plasticity of immunocytochemically localized GABAa receptors in adult monkey visual cortex. J Neurosci 1990; 10: 2438–50.

Hoehn MM, Yahr MD. Parkinsonism. Onset, progression and mortality. Neurology 1967; 17: 427–42.

Hubel DH, Wiesel TN. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J Physiol (Lond) 1962; 160: 106–54.

Hubel DH, Wiesel TN. Receptive fields and functional architecture of monkey striate cortex. J Physiol (Lond) 1968; 195: 215–43.

Ikeda H, Head GM, Ellis CJ. Electrophysiological signs of retinal dopamine deficiency in recently diagnosed Parkinson's disease. Vision Res 1994; 34: 2629–38.

Langheinrich T, Tebartz van Elst L, Lagreze W, Bach M, Lücking CH, Greenlee MW. Contrast response functions in Parkinson's disease (PD) measured by PERG, VEP and psychophysics [abstract]. Invest Ophthalmol Visual Sci: ARVO Suppl 1997; 38: S633.

Lieberman H, Pentland AP. Microcomputer-based estimation of psychophysical thresholds: the best PEST. Behav Res Meth Instru Computers 1982; 14: 21–5.

Maffei L, Fiorentini A, Bisti S, Holländer H. Pattern ERG in the monkey after section of the optic nerve. Exp Brain Res 1985; 59: 423–5.

Magnussen S, Greenlee MW. Marathon adaptation to spatial contrast: saturation in sight. Vision Res 1985; 25: 1409–11.

Mariani AP, Kolb H, Nelson R. Dopamine-containing amacrine cells of Rhesus monkey retina parallel rods in spatial distribution. Brain Res 1984; 322: 1–7.

Marx M, Bodis-Wollner I, Bobak P, Harnois C, Mylin L, Yahr M. Temporal frequency-dependent VEP changes in Parkinson's disease. Vision Res 1986; 26: 185–93.

Massey SC, Redburn DA. Transmitter circuits in the vertebrate retina. [Review]. Prog Neurobiol 1987; 28: 55–96.

Masson G, Mestre D, Blin O. Dopaminergic modulation of visual sensitivity in man. [Review]. Fundam Clin Pharmacol 1993; 7: 449–63.

McCormick DA. GABA as an inhibitory neurotransmitter in human cerebral cortex. J Neurophysiol 1989; 62: 1018–27.

Mestre D, Blin O, Serratrice G, Pailhous J. Human spatio-temporal contrast sensitivity: dopaminergic induced variations. Eur J Pharmacol 1990a; 183: 1022–3.

Mestre D, Blin O, Serratrice G, Pailhous J. Spatiotemporal contrast sensitivity differs in normal aging and Parkinson's disease. Neurology 1990b; 40: 1710–4.

Montgomery EB Jr, Nuessen J. The movement speed/accuracy operator in Parkinson's disease. Neurology 1990; 40: 269–72.

Nguyen-Legros J, Botteri C, Le Hoang P, Vigny A, Gay M. Morphology of primate's dopaminergic amacrine cells as revealed by TH-like immunoreactivity on retinal flat-mounts. Brain Res 1984; 295: 145–53.

Oertel W. Multisystematrophie. In: Bastian C, Ceballos-Baumann AO, editors. Bewegungsstörungen in der Neurologie. Stuttgart: Georg Thieme Verlag, 1996: 69–77.

Ohzawa I, Sclar G, Freeman RD. Contrast gain control in the cat's visual system. J Neurophysiol 1985; 54: 651–67.

Oppenheimer D. Neuropathology of progressive autonomic failure. In: Bannister R, editor. Autonomic failure: a textbook of clinical disorders of the autonomic nervous system. Oxford: Oxford University Press, 1983: 267–83.

Papadopoulos GC, Parnavelas JG. Distribution and synaptic organization of dopaminergic axons in the lateral geniculate nucleus of the rat. J Comp Neurol 1990; 294: 356–61.

Parkinson D. Evidence for a dopaminergic innervation of cat primary visual cortex. Neuroscience 1989; 30: 171–9.

Playford ED, Brooks DJ. In vivo and in vitro studies of the dopaminergic system in movement disorders. [Review]. Cerebrovasc Brain Metab Rev 1992; 4: 144–71.

Pullman SL, Watts RL, Juncos JL, Chase TN, Sanes JN. Dopaminergic effects on simple and choice reaction time performance in Parkinson's disease. Neurology 1988; 38: 249–54.

Quinn N. Multiple system atrophy – the nature of the beast. [Review]. J Neurol Neurosurg Psychiatry 1989; 52 Suppl: 78–89.

Quinn N. Multiple system atrophy. In: Marsden CD, Fahn S, editors. Movement disorders 3. Oxford: Butterworth-Heinemann, 1994: 262–81.

Reader TA, Quesney LF. Dopamine in the visual cortex of the cat. Experientia 1986; 42: 1242–4.

Regan D, Maxner C. Orientation-selective visual loss in patients with Parkinson's disease. Brain 1987; 110: 415–32.

Ross J, Speed HD. Contrast adaptation and contrast masking in human vision. Proc R Soc Lond B Biol Sci 1991; 246: 61–9.

Sclar G, Lennie P, DePriest DD. Contrast adaptation in the striate cortex of macaque. Vision Res 1989; 29: 747–55.

Skrandies W, Wässle H. Dopamine and serotonin in cat retina: electroretinography and histology. Exp Brain Res 1988; 71: 231–40.

Snowden RJ, Hammett ST. Subtractive and divisive adaptation in the human visual system. Nature 1992; 355: 248–50.

Tagliati M, Bodis-Wollner I, Yahr MD. The pattern electroretinogram in Parkinson's disease reveals lack of retinal spatial tuning. Electroencephalogr Clin Neurophysiol 1996; 100: 1–11.

Troscianko T, Calvert J. Impaired parallel visual search mechansims in Parkinson's disease: implications for the role of dopamine in visual attention. Clin Visual Sci 1993; 8: 281–7.

Weinstein A, Troscianko T, Calvert J. Impaired visual search mechansims in Parkinson's disease (PD): a psychophysical and event-related potentials study. J Psychophysiol 1997; 11: 33–47.

Wenning GK, Ben Shlomo Y, Magalhaes M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy. Brain 1994; 117: 835–45.

Received March 3, 1997. Revised June 16, 1997.
Accepted July 21, 1997