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Pupil response components: studies in patients with Parinaud's syndrome

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Summary

In addition to light flux changes, it is well established that other stimulus attributes such as colour, spatial structure or movement can also cause a transient constriction of the pupil, even when the onset of the stimulus causes a net decrease in light flux level on the retina. Although experimental findings in human subjects with postgeniculate lesions show that the generation of such responses must involve the processing of stimulus attributes in extrastriate areas of the cortex, little is known about the site of integration of cortical signals into the pupillomotor pathway. We have investigated how visual performance and the various components of the pupil response have been affected in subjects with damage to the dorsal midbrain (Parinaud's syndrome). The results show that the probable destruction of the olivary pretectal nucleus and the nucleus of the optic tract has little or no effect on pupil grating or pupil colour responses. The light reflex response, on the other hand, is virtually abolished, with only a small residual component that is similar to the pupil grating response and may not require an afferent projection to the midbrain. These new findings suggest that the site of integration of cortical signals in relation to pupil colour and grating responses and the generation of sleepiness-induced oscillations of the pupil do not rely on the normal functioning of pretectal nuclei that are involved in the light reflex response.

Keywords: colour; grating; inhibition; Parinaud's syndrome; pupil

Abbreviations: AON = accessory optic nucleus; EW = Edinger-Westphal; NOT = nucleus of the optic tract; ON = olivary pretectal nuclei; PCR = pupil colour response; PGR = pupil grating response; PUI = pupillary unrest index

Introduction

Anatomical background

The size of the pupil is regulated by the tone of two smooth muscles, the sphincter and dilator, each of which can contribute to different extents to both dilation and constriction of the pupil. The sphincter is innervated by the parasympathetic system, involving the Edinger–Westphal (EW) nucleus in the midbrain. This nucleus receives signals from pretectal areas that are mainly responsible for the light reflex. Additional input probably comes from the occipital lobe of the brain, serving a number of functions including the near response. It is suspected that the near-reflex fibres approach the pupillomotor centre through the ventral region, unlike the afferent retinal light-reflex fibres that follow a dorsal route. This accounts for clinical evidence of light-near dissociation in patients with dorsal pretectal lesions (Parinaud's syndrome). In humans, the EW nucleus on either side receives projections from both the ipsilateral and the contralateral olivary pretectal nuclei (ON) (Loewenfeld, 1999). In primates, the ON and the surrounding nucleus of the optic tract (NOT) receive projections from the retina and the cerebral cortex and send projections to a number of pretectal nuclei, including the accessory optic nucleus (AON) and the EW nucleus (Buttner-Ennever *et al*., 1996). The cortical projection to the NOT and the dorsal terminal nucleus in particular includes projections from V1, V4 and the superior temporal sulcus (MT, V5) (Hoffmann *et al*., 1991). Extrastriate visual areas involved in the processing of stimulus structure, colour and movement can therefore, in principle, influence neuronal activity in the EW nucleus either via direct projections, or indirectly via other nuclei in the pretectum that send afferents to the EW nucleus. These anatomical findings are consistent with recent demonstration of pupil responses to stimulus structure, colour or movement in human vision (Barbur *et al*., 1992*b*; Sahraie and Barbur, 1997). In spite of many similarities between the organization and function of various neural substrates in man and monkey,

there must also be significant anatomical and functional differences. Studies of loss of pupil function in patients with damage to the pretectal region may therefore provide useful information on the function of pretectal nuclei in man.

Sympathetic central inhibition of the parasympathetic efferent pupillary pathway

Sympathetic influences upon pupil size in humans can arise simultaneously through the activity of two combined mechanisms (Loewenfeld, 1999). First, the peripheral sympathetic innervation of the dilator muscle, and secondly, the central inhibition of the parasympathetic system. The peripheral sympathetic pathway derives from the area A1/A5 in the brainstem, runs to the hypothalamus and descends through the medulla oblongata and the cervical cord. Neurones leave the cervical cord at the C8 to T2 level to synapse in the superior cervical ganglion. These fibres run through the ciliary ganglion without synapsing and reach the pupillary dilator muscle as long ciliary nerves. The peripheral sympathetic system plays an important role in mediating pupillary dilation to various psychosensory stimuli. Any lesion along this long chain of sympathetic innervation in man results in the well-known clinical features of Horner's syndrome. The pupillary dilator consists of a relatively weak muscle embedded in the iris stroma. The pupil response is therefore dominated by the action of the sphincter muscle, which receives predominantly parasympathetic input. Sympathetic central inhibition of neural activity at the level of the EW nucleus may, however, play a major role in the control of the pupil response. It is known that in the absence of external influences, the firing rate of pupillocontrictor neurones in the EW nucleus is high (Sillito and Zbrozyna, 1970, 1973). This finding has often been used to explain the small pupil size observed during sleep or deep anaesthesia, when the inhibitory inputs to the EW nucleus are presumed to be least effective. Findings from animal research suggest that this central inhibition is itself mediated by two distinct pathways (Szabadi and Bradshaw, 1996). One of these is noradrenergic and projects directly from the nucleus coeruleus to the EW complex (Loewy *et al*., 1973; Breen *et al*., 1983; Koss *et al*., 1984), and the other projects indirectly from A1/A5 nuclei in the brainstem via the hypothalamus (Loewenfeld, 1958; Koss and Wang, 1972; Szabadi and Bradshaw, 1996). A decrease in this central inhibition with age is regarded to be the mechanism behind the well known age-related decrease in pupil size in darkness (Loewenfeld, 1972). Intermittent changes in central sympathetic inhibition of the firing rate of neurones in the EW nucleus may also account for the slow and marked oscillations of pupil size that are observed during sleepiness (Lowenstein *et al*., 1963; Wilhelm *et al*., 1999). This is in marked contrast to the large and stable pupil size that can be observed in darkness for long periods of time in subjects with high sympathetic tone.

It is also possible that stimulus-specific pupil responses that do not involve changes in light flux level on the retina (Barbur *et al*., 1992*b*; Sahraie and Barbur, 1997) are mediated through central sympathetic inhibition. This hypothesis implies that perturbation of neural activity in extrastriate areas of the cortex, as a result of processing certain stimulus attributes, causes transient weakening of the central sympathetic inhibition of EW neurones. The observed constriction of the pupil when such stimuli are presented to the eye can in principle be caused by an increase in parasympathetic innervation of the sphincter muscle, brought about by a weakening of central sympathetic inhibition (Barbur, 1995). Recent studies have shown that the pupil responds to a number of other stimulus attributes such as colour, spatial structure or coherent movement, even when the stimulus conditions eliminate artefacts that can trigger a pupil light reflex response (Ukai, 1985; Barbur *et al*., 1992*b*). In general, such pupil responses are absent or significantly reduced when the stimulus is restricted to the cortically blind regions of the visual field (Barbur, 1995).

Other findings show that although the pupil colour response (PCR) can be absent in patients with cerebral achromatopsia, the onset of equiluminant achromatic gratings or light flux increments at the same location in the visual field can yield a normal pupil response (Barbur *et al*., 1992*a*; Barbur, 2002). These observations suggest that stimulus-specific pupil responses involve the processing of stimulus attributes in extrastriate areas of the cortex, and that such processing can, in principle, be reflected in the pupil. This can be achieved either through direct weakening of the central sympathetic regulatory input to the EW nucleus, or indirectly via cortical projections to the ON or other nuclei in the pretectum. No clear evidence has emerged so far in support of either one or the other of these possible mechanisms.

Purpose

The purpose of this study was to investigate how damage to the pretectal region of the brain affects the various components of the pupil response. These include the pupil light reflex, pupil colour and grating responses, and the presence of slow pupil oscillations induced by sleepiness. Our aim was to find out more about the mechanisms involved in these responses, and in particular the localization of central sympathetic inhibition of the pupil. It is of great interest to establish whether an intact pretectum is needed for the normal functioning of this central inhibitory pathway.

Methods

Subjects

This investigation focused on two patients with Parinaud's syndrome (J.M. and B.D). Both patients were male (26 and 33 years old), with damage to the pretectum as a result of compressive tumour in the region of the pineal gland (see

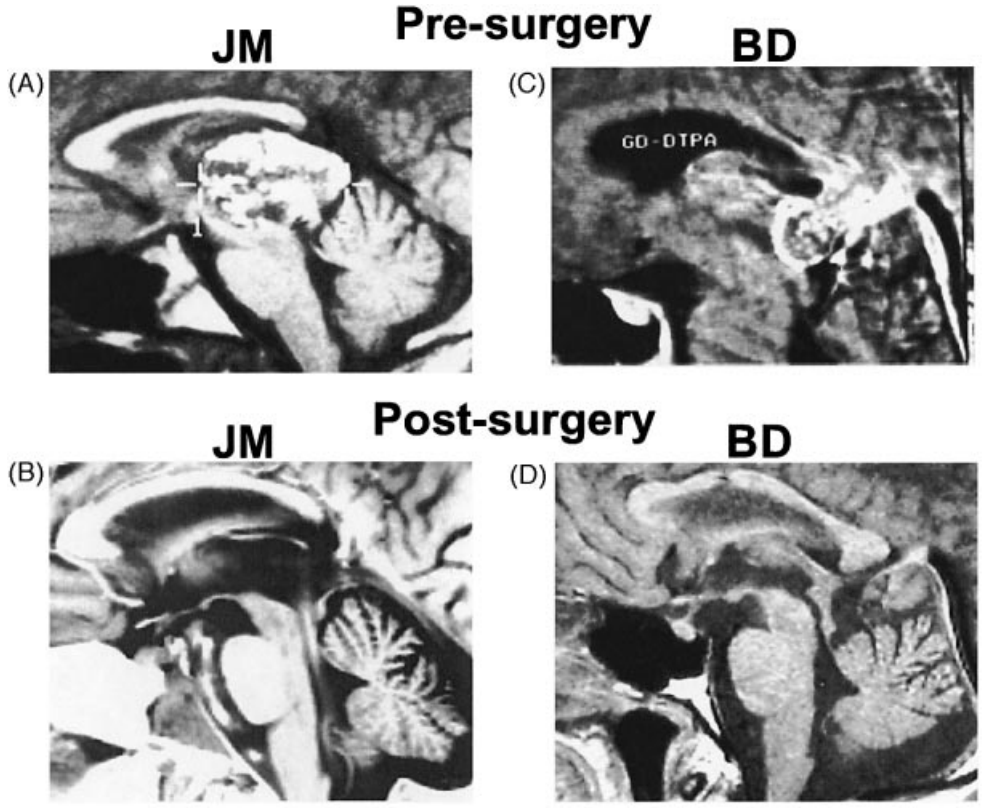


Fig. 1 Mid-sagittal MRI scans for J.M. before surgery and 8 years after surgery (**A** and **B**). **A** shows the extent of the tumour before surgery. The MRI scan shows a clearly demarcated parenchyma defect equivalent in density to cerebral spinal fluid, predominantly on the left side at the level of the tegmentum of the midbrain and extending almost to the fossa interpeduncularis. The region normally associated with the superior colliculi of the pretectum is tilted in the dorsal direction and has large areas missing. (**C** and **D**) Similar mid-sagittal MRI sections for B.D. This patient was diagnosed with cerebral tumour in 1992. Stereotactic biopsy with ventriculo-atrial shunting was carried out to alleviate high intracranial pressure. (**D**) The actual MRI scan (mid-sagittal section) of B.D. with the shunt system in the right ventricle, and a residual non-compressive mass in the right paramedian part of the lamina pretectalis.

patient histories for details). Six normal subjects acted as controls in some of the experiments, and were mostly university students and academic staff [mean age ± standard deviation (SD) 28 ± 8 years]. Formal consent was obtained from each subject who took part in this investigation. All the tests employed (i.e. a number of non-invasive visual psychophysical tests and the measurement of pupil responses) were approved by the City University and the University of Tübingen Research and Ethical Committees. MRI scans and ophthalmological tests were part of the routine follow-up examinations.

Patients' histories

Patient 1

J.M.'s visual problems started with double vision in 1981 followed by unsuccessful strabismus surgery in 1983. Further tests in 1984 revealed raised intracranial pressure with a primary diagnosis of an extended intracranial mass in the region of the pineal gland (3.5 cm in diameter; see pre-operative sagittal MRI section in Fig. 1A). The tumour included the caudal region of the pretectum and the apex of the cella media, and caused the occlusion of the Sylvian cerebral aqueduct. MRI showed a mesencephalic tumour with cystic segments (approximately 2.8 × 4.3 cm) that invaded the transverse cerebral fissure. Surgical intervention in 1984 involved ventriculo-atrial shunting and removal of an epidermoid cyst, as classified histologically. Further surgery and removal of tissue in 1986 resulted in post-operative left lower quadrantanopia (5° to 20°). Two further surgeries were carried out in 1987 and 1989 to deal with local recurrence, with complete removal of the tumour (including the capsule) in 1989. Since then, annual follow-up examinations have not revealed significant changes in symptoms, although the small visual field defect has improved slightly. J.M. is doing well and he has recently completed his studies in economics.

Patient 2

Accidental damage to the head caused traumatic palsy during childhood (1979), with slight residual symptoms (facial nerve paresis). B.D. suffered from a sudden cerebral ischaemia in

Table 1 *Summary of pupil response amplitudes and latencies elicited in two patients with Parinaud's syndrome (J.M. and B.D.) and six normal subjects (mean ± SD), with short and long duration flashes of 10^4 cd/m^2 luminance (CIP)*

Eye tested	Flash duration (s)	J.M./B.D.		Normal subjects (n = 6)	
		Amplitude (mm)	Latency (s)	Amplitude (mm)	Latency (s)
Right	0.2	0.10/0.31	0.520/0.319	1.41 ± 0.34	235 ± 13
Left	0.2	0.05/0.32	0.680/0.362	1.44 ± 0.27	230 ± 15
Right	1.0	0.20/0.42	0.450/0.294	1.48 ± 0.42	231 ± 17
Left	1.0	0.10/0.46	0.640/0.346	1.62 ± 0.25	224 ± 12

1989 with temporary paralysis that affected his right side, but recovered completely. In 1992 his symptoms started with severe headaches. Diagnostics for a cerebral tumour started the same year and he had a stereotactic biopsy with ventriculo-atrial shunting to alleviate high intracranial pressure. Histological examination of the removed tissue revealed a dysgerminoma of the pretectum and a secondary smaller tumour rostral of the left anterior horn of the lateral ventrical. After two chemotherapy cycles he received radiotherapy. Since then he has undergone regular follow-ups, including ophthalmological, neurological examinations and neuroimaging, without evidence of recurrence. The patient retired in 1992 and despite his disability has continued a normal life.

Apparatus

Pupillographic sleepiness test

Spontaneous oscillations of the pupil were recorded in darkness for 11 min by means of infrared video pupillography. Steady pupil size is usually related to high sympathetic tone, whilst fluctuations in the level of sympathetic innervation cause slow pupillary oscillations that are often described as 'sleepiness waves' (Wilhelm *et al*., 1998, 1999). The parameter of interest in this study was the pupillary unrest index (PUI, measured in mm/min) which describes the strength of sleepiness waves in J.M. during a night of sleep deprivation. Full details of the methods developed to measure and quantify sleepiness waves are given elsewhere (Lüdtke *et al*., 1998).

Compact integrated pupillograph

The compact integrated pupillograph (CIP by AMTech, Weinheim, Germany) is mounted on a slit-lamp table. The theoretical spatial resolution of this instrument is 0.01 mm and the temporal resolution is 4 ms. Background luminance was 2 cd/m^2, and a light emitting diode of luminance 10^4 cd/m^2 was used to generate a brief flash of either 0.2 or 1 s duration (see Table 1). While one eye is stimulated with flashes the other eye fixates a target at a distance of 0.5 m. For each stimulus condition, pupil light reflex response parameters were extracted from the average of 10 pupil traces.

Pupil perimetry

Monocular infrared video pupillography was employed to measure the pupil reaction to a 0.2 s flash presented at a number of discrete locations in the visual field. A combined head/chin rest arrangement was used to adjust the position of the subject's eye and to minimize movements of the head. Four response traces were averaged for each stimulus location, and the amplitude and latency of each response were extracted automatically. The subject viewed a uniform background field of luminance 3 cd/m^2. The angular subtense of the background field was 30°. The test stimulus was a disc of 10° diameter and contrast 0.96. Details of this instrument and measurement procedure have been provided elsewhere (Schmid *et al*., 2000).

The P_SCAN apparatus

Preliminary findings from our initial clinical studies were used to design and implement a number of other tests that were carried out using the P_SCAN system (Barbur *et al*., 1987). This apparatus was designed for binocular, simultaneous measurements of pupil size and the two-dimensional movements of the eyes. The measurement of pupil diameter and its centre coordinates employs numerical methods that are statistically equivalent to fitting the best circle to the pupil. This computational redundancy results in a measurement precision of 0.01 mm (Alexandridis *et al*., 1992). The illumination of the iris is achieved by means of a 5 ms pulse of infrared light (λ = 860 nm). This pulse is synchronized with the onset of each video frame so as to generate sharp images of the pupil. The visual stimuli were generated on a 21″ Sony trinitron monitor (Model 500PS, Sony Corporation, UK) driven by an ELSA Gloria XL 10-bit graphics card (ELSA, Germany). Measurement of the spectral radiance output of each phosphor was carried out using a Gamma Scientific telespectroradiometer (Gamma Scientific Model 2030-31, USA). The luminance output of each phosphor was also measured automatically for each possible gun voltage value using a luminance meter LMT Model 1003, Germany.

These data and the use of standard colorimetric transformations (Wyszecki and Stiles, 1982) made possible the generation of any specified colour/luminance combination

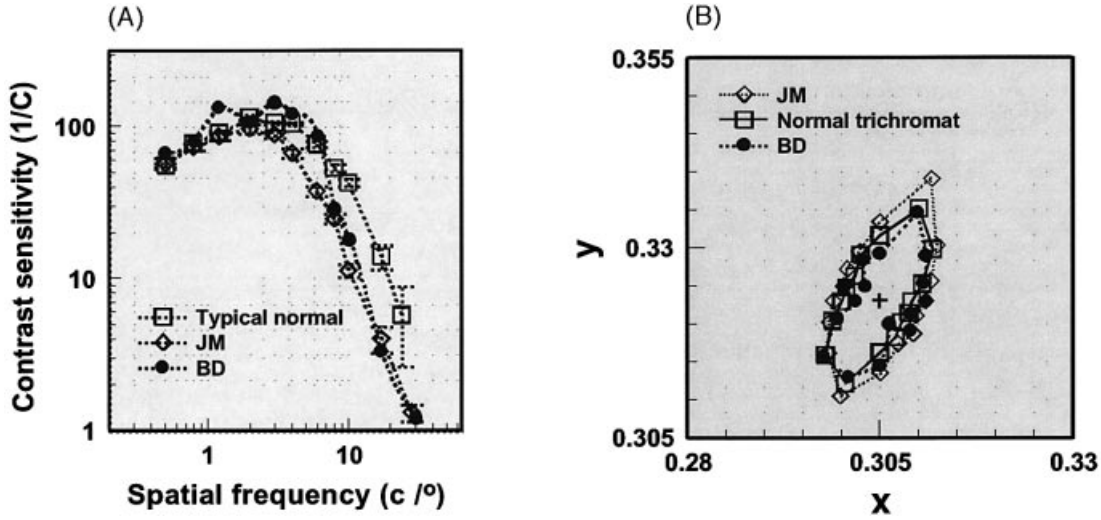


Fig. 2 Contrast sensitivity (**A**) and chromatic threshold measurements (**B**) in J.M. and B.D.

within the limits of the phosphors of the display. The subject viewed the screen from a distance of 75 cm, either binocularly or monocularly, by means of infrared transmitting filters (IR820). Pupil measurements were always binocular. A number of different visual stimuli were employed in every experiment. The stimuli were interleaved randomly and 16–36 pupil response traces were measured for each stimulus condition. A number of experiments designed to isolate different pupil response components were carried out on the two patients with Parinaud's syndrome. Since such pupil responses are known to show large inter-subject variability (Wolf *et al*., 1999), data were also obtained in six normal subjects for identical stimulus conditions.

Visual stimuli

Contrast sensitivity

Chromatic and achromatic contrast sensitivity were measured using standard visual tests implemented on the P_SCAN system (Barbur *et al*., 1987). The 10-bit colour graphics card supports 1280 × 1024 pixels, which provides the resolution needed to measure achromatic contrast sensitivity (CS) from a viewing distance of 3 m. The disc stimulus was Gaussian-weighted and subtended a visual angle of 6°. The chromatic sensitivity test makes use of dynamic luminance contrast noise to isolate chromatic signals (Barbur *et al*., 1994) and required a viewing distance of 75 cm. The subject viewed the screen binocularly for both tests and the stimulus was presented for 0.25 s in the centre of the screen. A staircase procedure with variable step sizes was used to estimate the stimulus contrast the subject needed to detect the gratings bars on 50% of presentations. The uniform background field was of 12 cd/m^2 luminance, and CIE (Commission Internationale de l'Eclairage) chromaticity x = 0.305, y = 0.323.

Pupil light reflex responses

The uniform background field was of 24 cd/m^2 luminance, and CIE chromaticity x = 0.305, y = 0.323, subtended a visual angle of 30° × 24° and provided steady-state, light adaptation of the retina. A high-contrast cross target was always presented in the centre of the visual display and provided the fixation mark. The test stimulus was a disc of 10° diameter and was presented either in the central foveal region or in each of the four quadrants (see schematic stimulus diagram in Fig. 4). The stimulus luminance was 72 cd/m^2 (i.e. $\delta L/L_b$ = 2) and was presented as a square pulse of 0.25 s duration. The stimulus position was interleaved randomly and 24 measurements were averaged for each location.

Pupil colour response

In this experiment the stimulus was a colour-defined disc of 10° diameter and was buried in a large circular field of dynamic luminance contrast (LC) noise (see stimulus diagram in Fig. 5). The dynamic LC noise ensures that the stimulus is effectively isoluminant by masking the detection of any residual luminance contrast signals (Barbur *et al*., 1994). The colour generated had zero scotopic contrast in addition to being photopically isoluminant. This d-isoluminant constraint (Young and Teller, 1991) restricts the number of possible colours that can be generated on the visual display to only two complementary hues. For the background chromaticity employed in this study, the two possible directions of chromatic displacement are one towards the 'green', and the other towards the 'red' region of the spectrum locus. The first appears greenish and the second reddish. Since pupil responses to green stimuli are generally small (Barbur *et al*., 1999), the red stimulus was selected for this study.

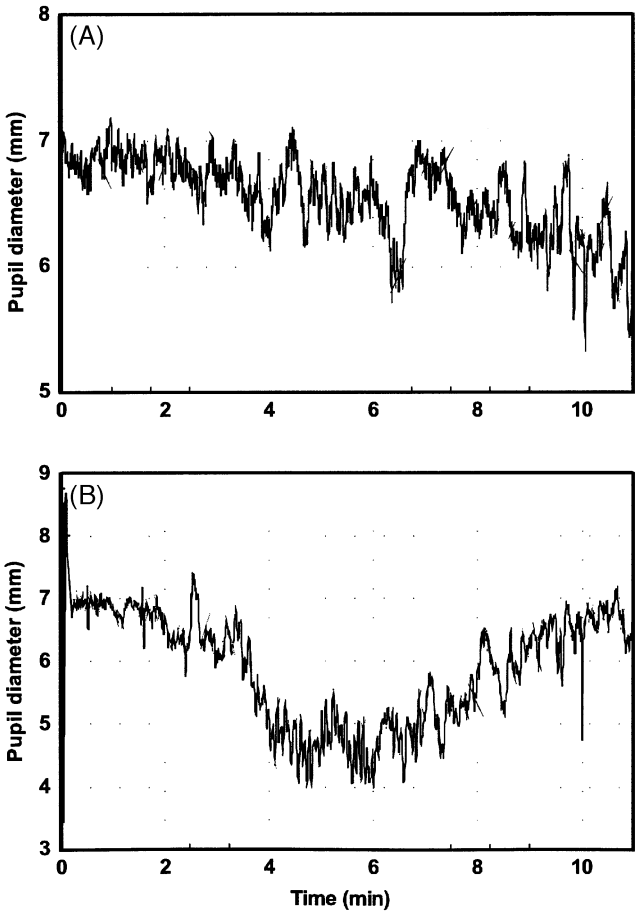


Fig. 3 Typical records showing the diameter of the pupil as a function of time. The graph reveals the existence of slow pupillary oscillations (sleepiness waves) in J.M. (**A**) and B.D. (**B**) following sleep deprivation.

Pupil grating response

The same display and uniform background field were also employed in this experiment, but the stimulus was a sinusoidal grating of 10° diameter and 95% contrast. The space-averaged luminance of the grating was equal to that of the uniform background. Three different spatial frequencies that yield a good response in normal subjects were employed. Fixation was maintained in the centre of the field by means of a small, high-contrast target.

Results

Ophthalmological findings

Patient 1

The anterior eye segments and fundi were normal in both eyes, and the patient had high contrast visual acuity of 6/5 in the right (R) eye and 6/7.5 in the left (L) eye. The pupil constriction to light onset was absent while the pupil near response was preserved. Additionally, there was a slight anisocoria (L > R). Motility examination revealed a vertical gaze palsy, divergent strabismus and convergence retraction nystagmus (when attempting to look upwards).

Patient 2

The anterior eye segments and fundi were normal in both eyes, with high-contrast visual acuity of 6/6 in the right eye and 6/7.5 in the left eye. The pupil constriction to light onset was virtually absent while the pupil near response was preserved. D.B. also exhibited slight anisocoria (L > R), vertical gaze palsy, right eye exophoria, and convergence retraction nystagmus when attempting to look upwards.

High-resolution MRI scans

Patient 1

Figure 1A and B shows mid-sagittal MRI sections for J.M., both before his first surgery and 11 years after the final surgery. Figure 1A shows the extent of the tumour before surgery. Figure 1B shows an MRI scan taken 11 years after surgery. The scan shows a clearly demarcated parenchyma defect of the same density as cerebral spinal fluid located predominantly on the left at the level of the tegmentum of the midbrain, and extending almost to the fossa interpeduncularis. The area of the superior colliculi of the pretectum has large areas missing and is tilted in the dorsal direction.

Patient 2

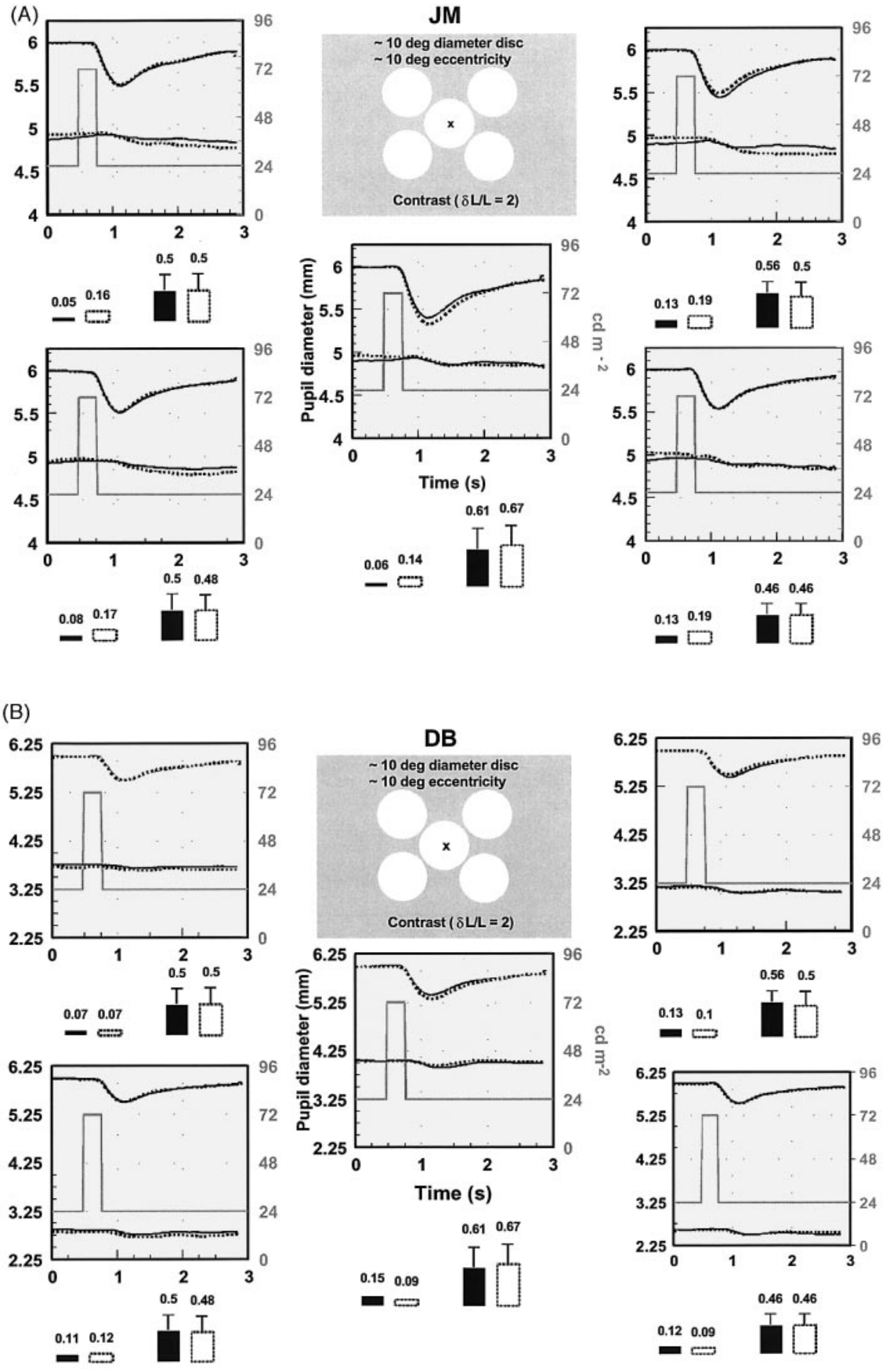
Figure 1C and D shows similar images for patient B.D. Figure 1C shows the tumour before treatment in 1993. Figure 1D shows the actual MRI scan (mid-sagittal section) of B.D. with the shunt system in the right ventricle, and a residual non-compressive mass in the right paramedian part of the lamina pretectalis. There are no signs of tumour expansion.

Chromatic and achromatic sensitivity

The results of these tests are presented in Fig. 2A and B. As expected, the results show that both J.M. and B.D. have normal chromatic and achromatic sensitivity. The major and minor axes and the orientation of the chromatic threshold ellipse (Fig. 2B) are similar to those measured in normal trichromats. The slight reduction of achromatic sensitivity (Fig. 2A) in the high spatial frequency range for both patients is probably caused by rapid eye movements and nystagmus.

Pupillographic sleepiness test

The results of Fig. 3A show that sleep deprivation in J.M. caused typical sleepiness-related oscillations of the pupil in darkness, which were most pronounced in the early hours of the morning. The trace shown (Fig. 3A) was recorded at 6 am



after one night of sleep deprivation. Typical results for B.D. are shown in Fig. 3B.

Unlike normal subjects, B.D. showed vivid pupillary sleepiness waves in the morning. Therefore there was no need to carry out a sleepiness inducing experiment. In normal subjects (both males and females, age range 20–60 years) the PUI is 4.5 ± 1.45 mm/min (mean ± SD) (Wilhelm *et al*., 2001). The PUI of the recordings were above the 80% and 90% percentiles (6.55 for J.M. and 8.91 for B.D.) of the expected normal range values. The results show that both subjects retain the ability to generate pronounced sleepiness waves.

Pupil light reflex

In both subjects, the absence of a light reflex response was apparent from clinical examinations. A number of tests have been carried out to assess the properties of the small residual pupil constriction that would normally go unnoticed in clinical examinations. Initial tests were carried out with the compact integrated pupillograph instrument that is used frequently in clinical studies. When high-contrast stimuli are used with this instrument in normal subjects, the test yields large constrictions of the pupil and short latencies, as shown in Table 1. In contrast to the results obtained in normal subjects, a short flash duration of 0.2 s elicited extremely small responses in J.M. and B.D. that could not be distinguished from noise in single traces. Bright flashes of 10^4 cd/m^2 luminance and of 1 s duration elicited small, but measurable, responses of unusually long latency (see Table 1).

More extensive pupil light reflex (PLR) studies were carried out using the P_SCAN system, by stimulating different regions of the visual field both monocularly and binocularly with a 10° diameter flash under photopic conditions of light adaptation (see Fig. 4 inset for spatial arrangement of test stimuli). The luminance contrast of the test flash was varied systematically and a number of measurements were averaged for each stimulus condition to reveal the presence of small pupil responses. Increasing the luminance contrast of the stimulus had little effect on the measured response amplitudes.

The results for J.M. and B.D. are shown in Fig. 4A and B for the highest luminance contrast employed at each of five different locations in the visual field. Data measured in six normal subjects for the same stimulus conditions are also shown for comparison. Stimulation of the foveal region in normal subjects yields the largest pupil constriction with smaller response amplitudes in each of the four quadrants. In contrast to the normal subject group, the response amplitudes in J.M. and B.D. were very small, with no dependence on stimulus location (see bar graphs in Fig. 4 giving response amplitudes at each location). Pupil response latencies in both J.M. and B.D. were long and difficult to estimate accurately because of the small response amplitude. The mean response trace for the normal group yields a latency of 0.23 s.

Pupil colour response

Pupil responses to chromatic stimuli are normally associated with processing of chromatic signals in extrastriate visual areas, since such responses can be abolished selectively in patients with cerebral achromatopsia (Barbur *et al*., 1992*a*). It was therefore of great interest to establish whether PCRs can still be elicited in the absence of a functioning pretectum that abolishes the PLR response. The results in Fig. 5 show that a d-isoluminant chromatic stimulus can trigger PCRs in both patients. The PCR latency estimated from the traces of Fig. 5 is ~0.38 s for J.M. and 0.32 s for B.D.

A study of six normal subjects for stimulus conditions identical to those employed in this study was carried out to assess the expected level of inter-subject variability. The normal subject data yield a response latency of just under 0.3 s (SD = 0.03 s). The PCR response amplitudes (i.e. J.M.: $\delta d = 0.14$; B.D.: $\delta d = 0.18$) are smaller than the mean amplitude for the normal group (i.e. $\delta d = 0.31$, SD = 0.14, n = 6). The large inter-subject variability within the normal group makes these differences statistically insignificant.

Pupil grating response

Pupil grating responses were measured in both patients for three different spatial frequencies that elicit significant response amplitudes in normal subjects. Both PCRs and pupil grating responses (PGRs) show considerable inter-subject variation in amplitude and latency (Wolf *et al*., 1999).

The results for J.M. and B.D., and the mean data for the normal subject group are shown in Fig. 6 for each spatial frequency employed. The averaged data for the normal subject group for the 3.5 c/° grating yields a mean PCR

Fig. 4 Pupil light reflex responses measured foveally and with the stimulus presented in each of the four quadrants. (**A**) Data for J.M. with equivalent results for B.D. shown in (**B**). The spatial arrangement of the graphs is intended to reflect the position of each stimulus in the visual field with the central graph representing the foveal region. The five stimulus locations are also shown schematically in each part. The display was viewed binocularly and the pupil response was measured simultaneously in each eye. The right eye response is shown as a continuous black line and the left eye as a dotted line. The stimulus trace (shown in dark grey) shows both the duration and the luminance of the test flash. Mean data for six normal subjects measured under identical stimulus conditions are also shown in each graph (upper traces) for comparison. The bar graphs show the right and left eye response amplitudes for each patient and the mean response amplitudes for the normal subject group.

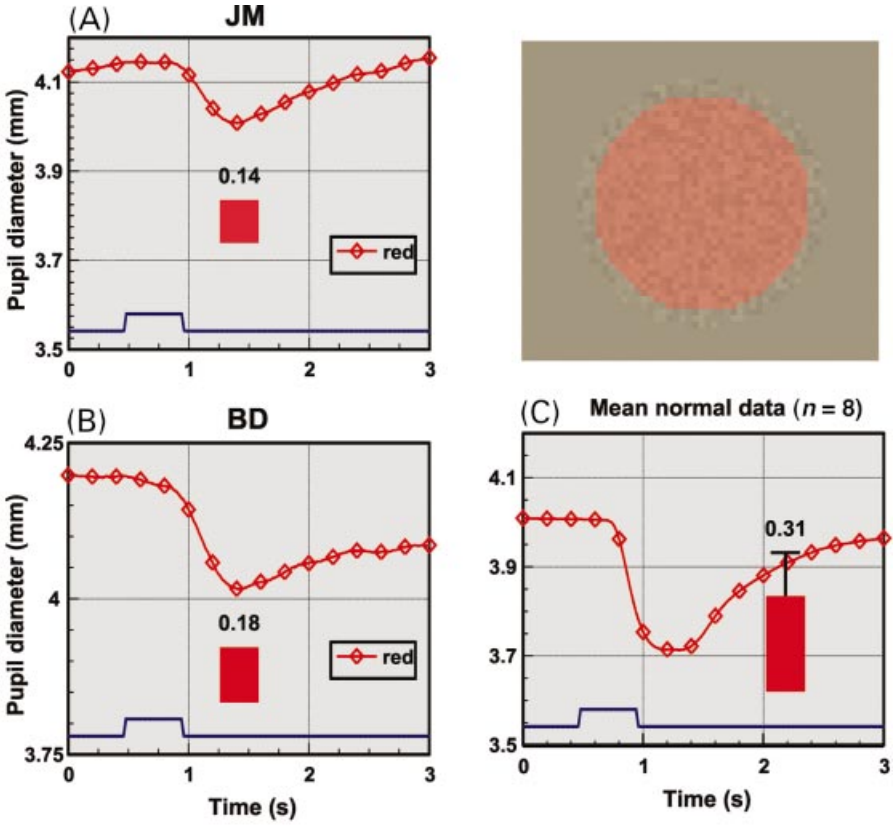


Fig. 5 Pupil colour responses measured under stimulus conditions that isolate the use of chromatic signals. In addition to the two patients, six normal subjects were also investigated using identical stimulus conditions. (**A**) J.M.'s PCR response trace (average of 16 measurements). (**B**) Similar data for B.D. (**C**) The normal subject data showing considerable inter-subject variability (δd = 0.31, SD = 0.14, n = 6).

amplitude of ~0.41 ± 0.13 mm and latencies of 0.3 ± 0.03 s (see Fig. 6). The corresponding response amplitudes and latencies for the two patients were: (J.M.) δd ~0.25 mm, latency ~0.38 s; and (B.D.) δd ~0.28 mm, latency ~0.38 s. Pupil responses to gratings and chromatic stimuli are usually of smaller amplitude and have increased latency by comparison with light reflex responses (Barbur, 1995). Although PGR response amplitudes in both J.M. and B.D. were smaller than the mean amplitudes measured in the normal subject group, the measured differences are not statistically significant because of the large inter-subject variability.

Discussion

Parinaud's syndrome describes a number of related clinical observations brought about by lesions of the dorsal midbrain. J.M. and B.D. exhibit a normal near reflex response, largely absent pupil response to light increments, vertical gaze palsy and associated vergence problems. Both these clinical observations and the MRI evidence available for our patients suggest that the retinal afferent input to the pretectal nuclei has been damaged. In addition to the preserved near response, this investigation shows that other pupil functions that rely on central inhibition are also spared. These findings suggest that the pupil continues to respond to visual stimuli other than light flux increments, even in the absence of a direct subcortical input to the EW nucleus.

Pupil colour and grating responses have been studied extensively in normal subjects and in patients with damaged central visual pathways (Barbur *et al*., 1992*b*; Barbur, 1995). Such responses cannot be accounted for in terms of residual light flux increments or accommodation changes (Keenleyside, 1989), and can often relate specifically to the location of the lesion. For example, the pupil fails to respond to chromatic stimuli in patients with cerebral achromatopsia, but the same patients show normal pupil light reflex and grating responses. Pupil colour, grating and motion responses are either reduced significantly or absent in patients with damage to the geniculostriate projection or the primary visual cortex in man. Interestingly, when patients exhibit 'blindsight', pupil grating, colour and motion responses can also be demonstrated, although spatially large stimuli are needed and the measured pupil response amplitudes are much reduced in comparison with normal subjects (Weiskrantz *et al.*, 1998, 1999). A possible mechanism to explain such findings can still rely on the processing of stimulus attributes in extrastriate visual areas. It is well established that signals of retinal origin can reach extrastriate areas V4 and MT (V5) via subcortical projections to the SC and the pulvinar (Cowey and

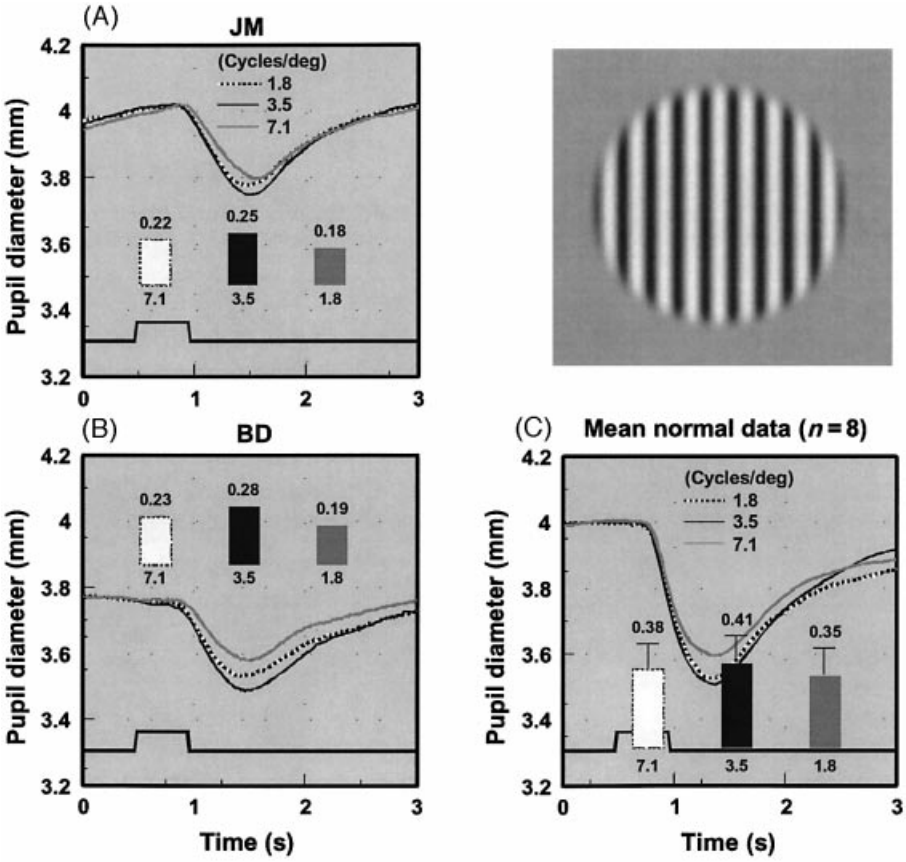


Fig. 6 Pupil responses to sinusoidal gratings of space-averaged luminance equal to that of the uniform background field. The grating stimulus subtended a visual angle of 10° and was viewed binocularly from a distance of 75 cm. Six normal subjects were also investigated using identical stimulus conditions. The normal subject data (**C**) show considerable inter-subject variability (e.g. for a spatial frequency of 3.5 c/°; $\delta d = 0.41$, SD = 0.13, $n = 6$). (**A**) J.M.'s responses to different spatial frequencies and (**B**) equivalent data for B.D.

Stoerig, 1991). Based on findings in patients with damaged primary visual cortex and/or extrastriate visual areas, we have proposed that such stimulus-specific pupil responses arise as a result of transient weakening of the steady-state sympathetic inhibition of the EW nucleus. This can happen when a stimulus presented to the eye causes sudden changes in neural activity in extrastriate visual areas. The presence of pupil sleepiness waves in J.M. and B.D. under sleep deprivation conditions supports the view that in spite of extensive damage to pretectal nuclei, the sympathetic inhibition of the parasympathetic pupillary system is functioning normally. The sleepiness-related pupillary oscillations observed in both patients are regarded as the effect of intermittent fluctuations in central sympathetic inhibition at the level of the EW nucleus (Lowenstein *et al*., 1963; Loewenfeld, 1999; Wilhelm *et al*., 1999).

It is of interest to examine whether the patients' small, residual pupil light reflex response can also arise as a result of cortical processing of the visual input through central inhibition. In general, all pupil responses elicited in J.M. and B.D. were characterized by long latencies and small amplitudes. The small, residual response to light flux increments passed unobserved in clinical examinations, but could be demonstrated convincingly when averaging a number of pupil traces in response to bright, long-duration stimuli (see Fig. 4). Although we cannot be certain, this small residual response to light flux increments may not necessarily involve any subcortical light-reflex pathway. Given its small amplitude and long latency, the involvement of a cortical pathway in this response cannot be ruled out.

Another explanation for this residual response could involve changes in sympathetic input to the dilator muscle of the iris, caused by a large increment in light flux level on the retina. The possible weakening of the sympathetic input to the dilator muscle triggered by an increase in light level could normally help the action of the sphincter to cause a more effective constriction of the pupil. The afferent pathways involved in the control of sympathetic innervation of the dilator muscle in response to a change in ambient illumination may rely, at least in part, on a direct cortical input. The longer latencies that characterize these residual pupil light

reflex responses support this view. Although plausible, we do not know of any conclusive experimental evidence in man to support this hypothesis. The sympathetic, afferent pupil pathway in man is not very well understood, which makes it difficult to distinguish between these two possible mechanisms.

The present findings support our original hypothesis that pupil responses to colour, grating or coherent movement arise through cortical modulation of central inhibition at the level of the EW nucleus.

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