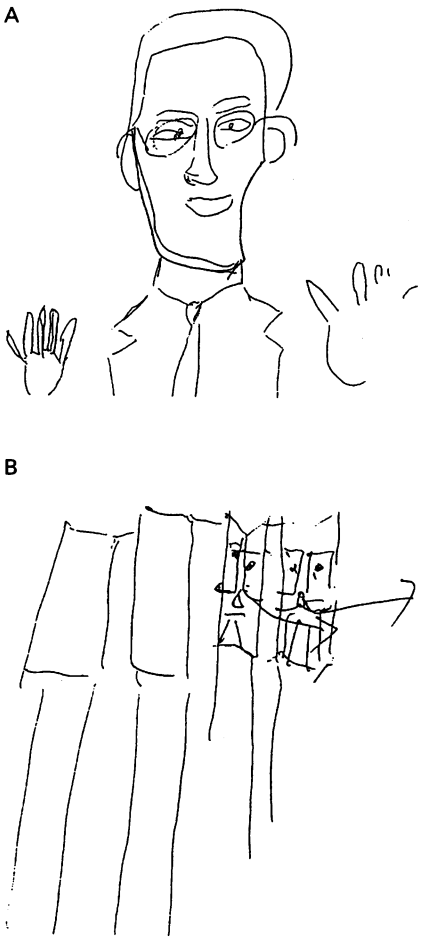

Figure 1 (A) Drawing of the referring doctor's face. His left cheek seemed to have been scraped and some of his left fingers were missing. (B) A drawing of the curtain lace. A fold of the lace seemed to have been transformed into an animal's face and it seemed to flow to the right.

or mass effect in either the occipital or parietal lobes (fig 2). In the pattern shift visual evoked potential (VEP), the latency of the P100 during right visual hemifield stimulation was 112·4 ms, which was moderately delayed compared with 98·0 ms, the latency recorded during stimulation of the left visual hemifield, indicating the involvement of the left visual pathway posterior to the optic chiasm.

Many reports have attributed the lesion of metamorphopsia to the occipitoparietal cortex and its related structures.[2 4 8] However, others have reported that chiasmatic[5] or retrosplenial lesions[6 7] could elicit this symptom. This patient had a common putaminal haemorrhage without involvement of the parietal and occipital lobes, as confirmed by cranial CT. The results of the VEPs disclosed a lesion in the left visual pathway posterior to the optic chiasm. Thus the lesion responsible for his visual symptoms is in the left optic radiation. This is the first report that such a lesion could cause metamorphosia. Based on the above mentioned reports and our own patient, we propose that any lesion along the visual pathway, from the retina to the occipitoparietal cortex, can cause metamorphopsia. Retinal lesions elicit ipsilateral monocular metamorphopsia, chiasmatic lesions give rise to bitemporal metamorphopsia,[5] and occipitoparietal lesions cause contralateral homonymous metamorphopsia.[2 8] This patient with injury in the left optic radiation complained of contralateral homonymous metamorphopsia. The distributional pattern of metamorphopsia seems to correspond to the part of the visual pathway affected.

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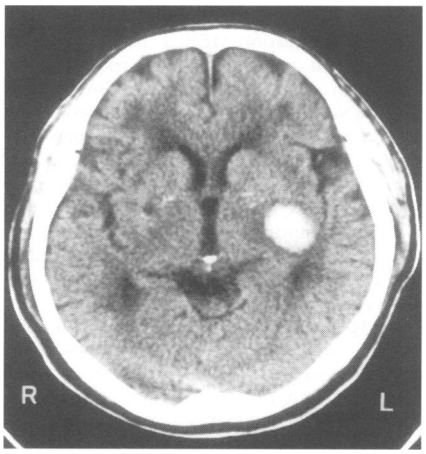

Figure 2 Cranial CT on admission, showing a high density area in the left putamen.

Cardiac autonomic regulation during sleep in panic disorder

Panic disorder is thought to be associated with a dysfunction of the autonomic nervous system. Power spectrum analysis has been used recently to quantify spontaneous variability in heart heart rate in humans. Some authors have detected patterns of cardiovascular responsivity in panic disorder that can be interpreted in favour of sympathetic overactivity[1] or cholinergic underactivity.[2 3] These studies were performed during wakefulness and the result may reflect states of increased anxiety. During sleep there are repetitive modifications of the autonomic nervous system that are constant and not influenced by cognitive factors. In the present study, we used power spectrum analysis of the heart rate variation during sleep in patients with panic disorder to verify a possible intrinsic defect in the autonomic regulation in this disorder.

We studied 10 patients with panic disorder (mean age 29·5 (range 23–35) years) and 10 age matched healthy controls (mean age 27·5 (range 24–34) years). Controls were recruited from the sleep laboratory technicians. Patients satisfied criteria for a diagnosis of panic disorder according to DSM-IV. Protocol exclusion criteria included: (*a*) a history of major medical or neurological illness; (*b*) a history of sleep panic attacks; (*c*) current or past evidence of affective disorders; (*d*) use of psychotropic drugs in the two weeks before the study. All subjects underwent a 48 hour ambulatory polysomnography (Oxford Medilog 9200). The ECG signal was played back from the tape and digitised at 128 Hz with 8 bit resolution using a specific option of the Medilog system. The R-R intervals were detected by means of a derivate-threshold algorithm; the accuracy of the R wave detection on ECG tracing was improved by fitting each QRS complex by a second order polynomial function. The fiduciary point on the ECG was taken as the maximum of the fitting parabola to reduce the error due to the low sampling rate.[4] The heart rate variability signal was processed using an autoregressive algorithm.[5] All the spectral calculations were performed on all the successive 300 second segments of ECG recordings of the second night. The analysed time intervals were chosen from: (*a*) awake state at the beginning of the night; (*b*) stage 2 non-REM sleep; (*c*) stages 3–4 non-REM sleep; (*d*) REM sleep. We focused on two regions of interest in the spectrum: (1) the low frequency (LF) component 0·05 to 0·15 Hz: an increase of the power in this band is commonly associated with sympathetic activation; (2) the high frequency (HF) component 0·2 to 0·4 Hz, mainly expression of parasympathetic control. The following variables were evaluated: the R-R mean and variance, the power of LF and HF components, and the sympathovagal balance (LF/HF ratio). We analysed the normalised spectral component (ratio between the power density of each spectral component and the total spectral density minus the power in the band 0–0·05 Hz) as better measures of the autonomic activity in respect to the absolute numbers; in this way it is possible to remove the effects of the large variability in the total power measures among the several subjects.[5] We applied ANOVA to determine the changes within each group through the different conditions. Differences between the two groups were evaluated by unpaired two tailed Student's *t* test.

Concerning sleep architecture, no difference was found in the percentages of all sleep stages between patients with panic disorder and controls (values are mean (SD)): stage 1 non-REM sleep 4·5 (2) *v* 3·9 (2·7); stage 2 non-REM sleep 49·8 (6·2) *v* 51·7 (7·4); stages 3–4 non-REM sleep 20·6 (8) *v* 18·8 (6·7); REM sleep 25·1 (6·8) *v* 25·5 (3·6). No difference was found in the number of analysed segments in each sleep stage between the two groups.

Mean R-R showed, both in patients with panic disorder and controls, a trend towards an increase in all sleep stages compared with wakefulness before sleep. No difference was found in R-R mean and variance between patients and controls in the various conditions. The LF component (sympathetic activity) decreased during sleep with minimal values during stages 3–4 non-REM sleep, whereas the HF component (parasympathetic activity) displayed a reciprocal

Table 1 Heart rate variability in panic disorder and controls

	Patients (n = 10)	Controls (n = 10)
W:		
LF (nu)	67·9 (11·1)*	53·2 (7·3)
HF (nu)	32·1 (8·1)*	42·7 (4·9)
LF/HF	2·33 (0·88)*	1·28 (0·21)
Stage 2 non-REM sleep:		
LF (nu)	39·9 (13·9)	36·2 (15·5)
HF (nu)	60·1 (15·2)	57·3 (11·2)
LF/HF	0·84 (0·63)	0·76 (0·48)
Stage 3–4 non-REM sleep:		
LF (nu)	26·9 (11·1)	25·9 (8·6)
HF (nu)	73·1 (14·6)	66·2 (11·6)
LF/HF	0·47 (0·41)	0·46 (0·32)
REM sleep:		
LF (nu)	56·3 (12·8)	53·2 (16·6)
HF (nu)	43·7 (8·3)	41·5 (14·2)
LF/HF	1·53 (0·68)	1·83 (1·26)

Values are means (SD). W = wakefulness before sleep; nu = normalised units.
*P < 0·04 *v* controls.

trend both in patients with panic disorder and controls (table). During REM sleep, an increase in sympathetic activity occurred almost to the value of wakefulness, both in patients and controls. These conclusions are corroborated by the LF/HF ratios, which showed a sympathetic preponderance during REM sleep and a parasympathetic preponderance during non-REM sleep stages in both groups. No difference was found between patients and controls in LF, HF, and LF/HF ratio during sleep, whereas an increased LF and a decreased HF were found in patients during wakefulness before sleep.

Our nocturnal findings do not suggest autonomic dysfunction in panic disorder. However, our data do not exclude a role of the autonomic nervous system in the pathophysiology of panic disorder. In fact, our study shows that patients with panic disorder have sympathetic overactivity (and cholinergic underactivity) during wakefulness before sleep. Thus an intrinsic defect in autonomic regulation may be excluded in panic disorder, but these patients have a higher sympathetic tone than controls during the awake state, probably dependent on cognitive activity. This diurnal increase in cardiac sympathetic activity could play a part in fatal cardiac arrhythmias in panic disorder, as recently suggested.[6]

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Large deletion (7·2 kb) of mitochondrial DNA with novel boundaries in a case of progressive external ophthalmoplegia

Chronic progressive external ophthalmoplegia (CPEO)[1 2] is a well characterised form of mitochondrial myopathy; it occurs with single or multiple deletions of mitochondrial DNA (mtDNA), or with the 3243 point mutation.[1] Single deletions occur sporadically and are usually not transmitted to offspring, whereas point mutations are transmitted maternally and multiple deletions are inherited in an autosomal way. Single deletions are often flanked by direct repeats of three to 18 base pairs (bp).[1] The "common deletion"[1-3] found in one half of patients with CPEO is 4·9 kb long and occurs between direct tandem repeats at positions 8470–8482 and 13 447–13 459.[3] A partial duplication of mtDNA can be associated with the deletion and was reported to be specific for Kearns-Sayre syndrome.[4] We describe a young woman with a sporadic CPEO and a large deletion (7·2 kb) of mitochondrial DNA with novel boundaries, flanked by a 14 bp imperfect tandem repeat at positions 8407–8420 and 15 658–15 671.

A 28 year old woman was referred to us for investigation of CPEO. At the age of 12 she developed a progressive ptosis of the left eyelid. A contralateral ptosis appeared two years later, with a fluctuating vertical diplopia. Since then, progressive ophthalmoplegia was noticed. Subjectively there was no limb weakness; she did not have nyctalopia, or cardiac arrhythmia. Her family history was negative for neuromuscular disorders, diabetes, and hearing impairment. Relatives were not examined.

Neurological examination confirmed bilateral ptosis, and severe limitation of eye movements in all directions during voluntary and reflex movements. Visual acuity was 6/15 in the right eye and 6/10 in the left; fundus was normal. Hearing was not impaired. There was a mild facial paresis affecting predominantly the orbicular palpebral muscles, and moderate paresis of the trapezius and sternocleidomastoid muscles. Muscle strength was slightly reduced proximally and distally in the four limbs. Tendon jerks and detailed sensory testing were normal.

Electromyography showed a full recruitment on submaximal effort with polyphasic potentials in the examined muscles (right arm and right leg) suggesting a myopathy, whereas nerve conduction studies were within the normal range. An ECG was normal. Lumbar puncture was not performed. Brain CT was normal. There was a moderate rise of creatine kinase and lactate dehydrogenase concentrations. Diabetes mellitus was not present.

Quadriceps muscle biopsy showed an increased variability in the size of fibres; few fibres showed subsarcolemmal accumulation of mitochondria, without a typical ragged red pattern on trichrome-Gomori staining. Few fibres were cytochrome oxidase negative. Electron microscopy showed paracrystalline mitochondrial inclusions. Enzymatic activity of the respiratory chain complexes (I to IV) was within the normal range. When compared with citrate synthase, complex III activity was slightly reduced (6% of citrate synthase activity, normal range, 10–53%, n = 25).

Total DNA was extracted from muscle and blood by standard techniques. Southern blot analysis of total muscle DNA digested with PvuII and hybridised with a polymerase chain reaction (PCR) generated tRNALeu (UUR) probe (3130–3558) disclosed an additional band of approximately 9 kb in length (figure, A), suggesting the presence of a large deletion of mitochondrial DNA. The mean (SD) proportion of mutant versus total amount of mtDNA evaluated by scanning densitometry was 51 (4)% (n = 3). The deletion was present in 51% of mitochondrial DNA molecules in deltoid muscle but it was absent from leucocyte mitochondrial DNA. The presence of an associated duplication was ruled out by digestion of total DNA with BamHI, which cuts within the deletion. Hybridisation with the tRNALeu(UUR) probe (figure, A) showed two slower migrating bands, whereas a probe (11 713–11 832) lying within the deletion only hybridised to the 16·5 kb band (figure, B). (Double digestion with SnaBI and BglII gave similar results, data not shown.) Therefore, the two upper bands do not contain the full length wild type sequence, and cannot be duplications, but most likely are a circular deletion monomer (CDM) and circular deletion dimer (CDD).[2] Amplification by PCR with primers flanking the "common" deletion[3] yielded a 5 kb fragment in leucocyte DNA amplified from wild type DNA. Muscle DNA amplification yielded an additional 1 kb fragment (not shown). This fragment was cloned in a pT7 blue vector (Novagen™); The DNA sequence was determined in an automated sequencer (ALF™) to map precisely the deletion. The length of the deletion was 7·2 kb and it was flanked by a 14 bp imperfect tandem repeat at positions 8407–8420 and 15 658–15 671. (Figure, C).

Surprisingly, sequence analysis also showed that primer H2[3] did not prime where expected (13 506–13 255) but hybridised instead at position 16 248–16 255 where there is a perfect homology over eight nucleotides at the 3′ end.

The phenotype of the patient suggested a mitochondrial myopathy. Analysis of DNA showed a large deletion of mitochondrial DNA with novel boundaries. Similar deletions are described with similar phenotypes and not with healthy controls, strongly sug-