ELECTROPHYSIOLOGICAL INVESTIGATION OF THE VISUAL PATHWAY IN HUMAN ALBINOS

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Thesis submitted for the Degree of

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SUMMARY

The general features of human albinism are reviewed. Further studies discussed show evidence for an increase in the number of contralaterally projecting optic nerve fibres in albino animals compared to their normally pigmented counterparts. A hypothesis is proposed that this misrouting should be reflected in scalp recorded visually evoked potentials in the form of contralateral hemispheric lateralisation on monocular stimulation in albino subjects but not in pigmented individuals.

A total of twenty-six human albinos were examined using psychophysical and electrophysiological techniques. Reduced visual acuity and a high incidence of strabismus and nystagmus were evident.

The visually evoked cortical potential (VECP) was recorded using different stimuli. Pattern reversal is shown to be unsuitable for evoking responses in albinos. The flash VECP, however, exhibits the predicted contralateral monocular lateralisation using reference recording. The major positive (P2) component shows a reduction in latency over the hemisphere contralateral to the eye stimulated in the albino group at a statistically significant level ($p < 0.001$); such a result was not found within a group of age and sex matched controls. Using a pattern appearance-disappearance stimulus contralateral monocular lateralisation is present in albinos but only in bipolar occipital recordings.

The flash visually evoked subcortical potential (VESP) does not consistently show contralateral monocular lateralisation within the albino group and recordings did not clearly differentiate between albino and control subjects. The reason for this failure is discussed in terms of the anatomical arrangement of the human visual pathway. The results, however, do provide further evidence for the independence of the VESP and VECP.

The flash VECP and VESP were recorded in three albino babies. The VECP reflected the albino misrouting but the VESP did not show consistent contralateral lateralisation on monocular stimulation.

Albinism; lateral geniculate nucleus; visual cortex; visually evoked cortical potential; visually evoked subcortical potential

CONTENTS

FIGURE CONTENTS

FIGURE NUMBERS

TABLE CONTENTS

CHAPTER 1

HUMAN ALBINISM

"There is one complexion so singular....that I never saw nor heard of any like them in any part of the world....They are white....much like that of a white horse....From their seeing so clear as they do in a moon-shiny night, we us'd to call them moon-ey'd. For they see not very well in the sun....their eyes being but weak, and running with water if the sun shine towards them....when moon-shiny night's come, they are all life and activity....Neither is the child of a man and woman of these white, white like the parents, but copper-color'd as their parents were.... They were but short-liv'd"

Lionel Wafer 1699

1.1 Introduction : the melanin pigmentary system

Albinism is a hereditary disorder characterised by a congenital reduction or absence of the pigment melanin.

In man only four body tissues contain substantial amounts of melanin; the skin, hair, uveal tract and retinal pigment epithelium (RPE) (Carr and Siegel 1979). Melanin synthesis takes place within specialised cell types called melanocytes. A brief account of the biochemical processes involved is given here, more details can be found in Witkop (1971); Witkop, White and King (1974) and Garcia, Szabo and Fitzpatrick (1979). Melanin is synthesised in the melanocytes, within membrane bound particles called melanosomes, from the amino-acid tyrosine. The classical theory is that this process takes place in the presence of molecular oxygen through the catalytic action of tyrosinase. This copper containing enzyme catalyses the hydroxylation of tyrosine to dopa and the oxidation of dopa to dopaquinone which then undergoes non-enzymatic oxidation and polymerisation to form melanin. However, it has recently been suggested that the reactions may be catalysed by either peroxidase on its own or in conjunction with tyrosinase.

In animals and birds it appears that under certain conditions, melanocytes are capable of producing, at different times, two forms of melanin: black-brown eumelanin or red-yellow pheomelanin. The latter pigment is responsible for the red and yellow colouration of animal fur, feathers and

human red hair. Its synthesis is restricted to hair follicle and feather germ melanocytes; there is no evidence for its synthesis elsewhere. Consequently, unless stated otherwise, any future reference to 'melanin' refers to black-brown eumelanin.

The melanocytes in the skin, hair and eyes have a common feature in that all are capable of synthesising tyrosinase and producing melanosomes. However, in many respects, RPE melanocytes differ from those at other sites.

1) Embryologically, RPE melanocytes are derived from the outer layer of the optic cup while others originate from the neural crest (Garcia et al. 1979). Both are, however, closely associated with the nervous system.

2) Structurally, RPE melanosomes are larger than those found in the epidermis (Taylor 1978).

3) Melanocytes in the epidermis transfer their melanosomes into keratinocytes; those in the RPE melanocytes are permanent residents (Garcia et al. 1979).

4) Melanosome development occurs in the RPE before it is seen elsewhere. Tyrosinase activity is detectable early but it quickly reaches a peak and is thought to be absent before gestation ends (Miyamoto and Fitzpatrick 1957). This implies that whatever melanin is present in the RPE at birth is all that an organism will possess.

However, work on the adult bovine RPE has led Garcia et al. (1979) to believe that there may be a regular slow turnover of melanosomes in the mature RPE. Epidermal melanocytes definitely retain their ability to synthesise new melanin throughout life. Melanosomes, which are transferred into keratinocytes, proceed up the epidermis as they keratinise and are eventually sloughed off, thus producing a constant demand on melanocytes for new melanosomes (Garcia et al. 1979).

The precise functions of melanin are not totally clear, but Garcia et al. (1979) conclude that it may:

a) Act as a neutral density filter. b) Attenuate impinging radiation by scattering. c) Absorb radiant energy in the ultraviolet and visible spectrum, dissipating the absorbed energy as heat.

In the eye, therefore, the melanin in the RPE will prevent excess light entering through the sclera, absorb light energy and reduce light scatter. All these factors may help to improve image resolution.

1.2 Types of human albinism

Albinism can be caused by a block at any stage in the process of melanin synthesis. Acquired albinism is rare but can accompany severe protein malnutrition such as in Kwashiorkor, however, ocular depigmentation is usually

absent (Witkop 1971). Children with Menkes syndrome and phenylketonuria may become depigmented but are normally pigmented at birth (Witkop, Quevedo and Fitzpatrick 1978). Albinism may also occur in conjunction with other rare systemic conditions: Hermansky-Pudlak syndrome; Chediak-Higashi syndrome and Cross syndrome (see Witkop 1971, Witkop et al. 1974 and 1978). However, in man, the most common forms of albinism are hereditary in nature. Two main types can be distinguished:

1) Oculocutaneous albinism - the reduction or absence of pigment affects the whole melanocyte system. Hence, the skin, hair and eyes are all involved.

2) Ocular albinism - the reduction or absence of pigment is restricted to the melanocytes in the eye.

1.2.1 Oculocutaneous albinism

This classic form of albinism was described in the monograph of Pearson, Nettleship and Usher (1911-13). The condition is inherited as an autosomal recessive trait (Witkop 1971) and therefore occurs sporadically among both males and females. Originally it was thought to be due to a single recessive gene but recent evidence indicates that it is a heterogenous disorder. In 1961, Kugelman and Van Scott incubated hair bulbs from oculocutaneous albinos in l-tyrosine or l-dopa. Subsequent microscopic examination revealed that, under these conditions, the hair bulbs of some albinos produced pigment while others did not. On the basis of this hair bulb incubation test, Witkop, Van Scott and Jacoby (1961) divided

the oculocutaneous albino population into two main groups and this categorization is now widely used in the classification of oculocutaneous albinism.

1) Tyrosinase negative (ty - neg) Oculocutaneous Albinos : after incubation, hair bulbs from these subjects do not produce pigment. Such individuals have no clinically detectable pigment in the skin, hair or eyes. The skin is usually of a milky-white colour; pigmented naevi and freckles are absent. Hair colour is snowy white, remaining unchanged throughout life. In oblique light eye colour varies from translucent grey to grey-blue (Witkop 1971; Witkop et al. 1974 and 1978). The physical appearance of these albinos does not vary with racial background (Witkop et al. 1978).

2) Tyrosinase positive (ty - pos) Oculocutaneous Albinos : after incubation, hair bulbs from these subjects do produce some pigment. Such individuals differ from ty-neg oculocutaneous albinos in that clinically there is some detectable pigment in the skin, hair and eyes. This pigment formation is, however, delayed so that in infancy ty-pos and ty-neg albinos may appear identical (Witkop et al. 1978). The amount of pigment accumulated depends on the age and racial background of the individual considered (Witkop 1971; Witkop et al. 1974). Consequently, an adult ty-pos Caucasian albino may resemble an adult ty-neg Caucasian while an adult ty-pos Negro may have the appearance of a blond Caucasian. Therefore, all descriptions of the

pigmentary characteristics of such albinos must be considered with reference to age and racial background. The skin colour may vary from pinky-white to cream; pigmented naevi and freckles may be present. At birth, the hair is usually white but can change to blond or even light brown. On transillumination the irides are diaphaneous with any obvious pigment occurring at the pupillary border and limbus. In accordance with the pigment accumulation, there is often a history of a change in eye colour from infancy such that in the adult this may vary from light blue to brown (Witkop 1971; Witkop et al. 1974 and 1978).

One other, much rarer form of oculocutaneous albinism was described by Nance, Jackson and Witkop (1970). The sufferers were found mainly in small inbred communities of Amish or Polish extraction and as a group are called yellow-mutant (YM) oculocutaneous albinos. They can be distinguished from both ty-pos and ty-neg albinos on the basis of the hair bulb incubation test. After incubation in l-tyrosine no pigment is produced but the addition of l-cysteine results in an intensification of yellow or red pheomelanin. Clinically, they may resemble ty-pos albinos and, like the latter group, their appearance depends on racial background. Skin colour is usually white and there is a slight but distinct tanning effect after exposure to sunlight. At birth hair is usually white but by about one year of age it acquires a distinct yellow cast. Eye colour may be blue in infancy but can change with age (Witkop 1971).

Further evidence for the hetereogeneity of this condition comes from the marriage of oculocutaneous albinos who subsequently produce normally pigmented offspring (Trevor-Roper 1952; Witkop, Nance, Rawls and White 1970). It was found that, in each case, one parent was a ty-neg albino while the other was of the ty-pos type. This indicates that genes at two separate loci are involved in the production of the two main forms of albinism and these genes are completely complementary in the double heterozygote (Witkop 1971).

The hair bulb incubation test is now used widely to differentiate between the two main types of albinism. However, Winder, Jay and Kissun (1976) found that the response to this test varies widely. An unequivocal negative response could not be found even in subjects who appeared clinically to be of the ty-neg type. It is also thought that the test may have little use on children under four or five years of age (Taylor 1978; Winder 1981).

The precise causes of oculocutaneous albinism are not yet clear. In 1908, Garrod, suggested that the condition was caused by an inborn error of metabolism lacking an intracellular enzyme for the synthesis of melanin. It was, therefore, assumed that the main cause was an absence of tyrosinase.

However, the hair bulb incubation test shows that there is tyrosinase activity in some oculocutaneous albinos.

In ty-neg albinos melanocytes are present in normal numbers but there is no evidence of tyrosinase activity in cytoplasmic structures and only immature melanosomes are present (Witkop, Hill, Desnick, Thies, Thorn, Jenkins and White 1979). Evidence suggests that this form of albinism is primarily caused by a lack of normal active tyrosinase (Witkop 1971; Witkop et al. 1974; King and Witkop 1976).

However, in ty-pos albinos the situation is not quite so simple. Mature melanosome production can be induced from the immature ones present by incubation in l-tyrosine or l-dopa. Hair bulbs contain moderate to large amounts of tyrosinase and hence the cause is not a lack of active enzyme (King and Witkop 1976). Serum levels of tyrosine and copper are normal (Witkop 1971; Witkop, White, Nance and Umber 1972) and there is no evidence for the presence of an inhibitor to melanogenesis in the serum (Witkop 1971; Witkop et al. 1972). King and Witkop (1976) found evidence for hetereogeneity among ty-pos albinos and it is therefore possible that more than one mechanism may be active.

In YM albinos melanocytes appear normal (Witkop et al. 1973). The cause of this condition is not known but there appears to be a defect such that only pheomelanin can be produced while eumelanin cannot be synthesised (Witkop et al. 1972).

1.2.2 Ocular albinism

In this condition the reduction in pigment is limited to the eye although there have been reports of a mild general hypopigmentary effect (Ohrt 1956). The most common form of this condition, an X-linked recessive trait, was first described by Nettleship (1909). A similar condition, associated with a protanomalous colour vision defect has been reported (Forsius and Eriksson 1964). However, Witkop (1971) considers that this condition may not be a distinct entity but due to the occurrence of both traits in the subjects examined. A third type of punctate ocular albinism, possibly with autosomal dominant transmission, has also been described (Bergsma and Kaiser-Kupfer 1974), and recently O'Donnell, King, Green and Witkop (1978b) reported ocular albinism occurring rarely as an autosomal recessive condition.

However, the most common form of ocular albinism is the X-linked type (O'Donnell, Hambrick, Green, Iliff and Stone 1976). Such a pattern of inheritance results in males only being affected while females act as carriers (Blach and Jay 1969). Ocular pigmentation is reduced but this may increase with age so that the final iris colour may range from blue to brown (Witkop et al. 1978).

Ocular albinism is thought to be more than simply an embryological variant of the oculocutaneous type as the genetic defect involves a different chromosome (Winder et al. 1976). Unusually large melanosomes have been found

after skin biopsies of sufferers (O'Donnell et al. 1976). These macromelanosomes appear to form from immature abnormal melanosomes distributed among those of a normal size. (Cortin, Tremblay and Lemagne 1981).

Consequently, althcugh the true cause of ocular albinism is unknown, it appears to result in a disturbance of the melanosome structure characterised by giant pigment granules (O'Donnell et al. 1976).

1.3 Ocular features of human albinism

In all of the main types of albinism discussed in 1.2., the eye is involved to a certain extent. Consequently, there are particular ocular findings shared by all forms of albinism. Table 1.1 summarises these common ocular features.

1.3.1 Reduced ocular pigmentation

Ocular pigmentation is reduced in all of the main forms of albinism. This pigment deficiency causes iris translucency and fundal palor.

As described in 1.2.1, the irides of ty-neg albinos appear diaphaneous and by transillumination there is no visible accumulation of pigment. In the pupil a prominent red reflex, caused by light penetrating the sclera, traversing the depigmented choroid and illuminating the fundus, can be seen. The fundus appears totally devoid of pigment, and

Table 1.1

The Typical Ocular Findings in Human Albinos

The common ocular features present in the main types of human albinism. (Adapted from Witkop 1971; Witkop et al. 1974, 1978; Carr and Siegel, 1979).

OCULAR FEATURE	TYPE OF ALBINISM		
	Oculocutaneous		Ocular
	Ty-neg	Ty-pos	
Iris colour	Blue to Grey	Blue to Brown	
Iris trans-illumination	Complete	Partial to complete	Partial
Fundal Pigmentation	Absent	Reduced	
Photophobia	Severe	Mild to severe	
Foveal Reflex	Absent in all types		
Visual Acuity	6/60 or less	6/9 to 6/60	
Nystagmus	Marked	Mild to marked	
High Refractive Errors	High incidence in all types		
Strabismus	High incidence in all types		

as a result, individual retinal and choroidal blood vessels can be seen clearly against the pale background (Witkop 1971; Witkop et al. 1974 and 1978).

Ty-pos albinos display a wide range in the degree of general pigmentation and this variation is reflected in the eye (Carr and Siegel 1979). As described in 1.2.1, pigmentation depends on age and racial background. Trans-illumination of the iris results in a cartwheel effect with pigment deposits visible at the borders.

A red pupil reflex is usually seen in all infants and, although this may remain in adult Caucasians, it may become less obvious in Negros and Indians. Fundal pigmentation is variable; in infants of all races it is usually grossly reduced. With age, a slight increase may be seen in Caucasians but the intensification of pigment is much greater in the dark races (Witkop 1971; Witkop et al. 1974 and 1978).

Similarly, the degree of pigment dilution in the eyes of ocular albinos depends on the general body pigmentation of the individual. As a result there is a wide variation in the amount of depigmentation found in this condition (Carr and Siegel 1979). The irides are often blue to brown and diaphanous.

Transillumination may be partial or complete and, although usually diffuse, it may show a cartwheel effect. Iris

pigmentation may increase with age but the amount of fundal pigment appears to remain unchanged (Witkop 1971). The peripheral fundus is pale but evidence of pigment may be seen at the posterior pole (O'Donnell et al. 1976; Carr and Siegel 1979).

Diagnosis of ocular albinism is often partially dependent upon the recognition of the above ocular features but this may prove difficult due to the variable expression. Cortin et al. (1981) reported iris translucency to be absent in two ocular albinos while O'Donnell, Green, Fleischman and Hambrick (1978a) emphasise the problem of diagnosing the condition in darkly pigmented races. In black albinos they found a lack of iris translucency and a tigroid or tessilated fundus appearance. In such cases, to confirm diagnosis, skin biopsies may be valuable.

1.3.2 Photophobia

The reduction in ocular pigmentation enables light to enter the albino eye not only via the pupil but also through the translucent ocular coats. This results in photophobia (Duke-Elder 1964; Witkop et al. 1974; Taylor 1978). The severity of this problem depends, of course, on the degree of ocular depigmentation and thus on the type of albinism. Hence, it is reported to be severe in ty-neg albinos, but mild to severe in ty-pos and ocular albinos (Witkop 1971; Witkop et al. 1978; Carr and Siegel 1979). In the latter two conditions the photophobia may decrease with age as

ocular pigmentation increases (Witkop 1971). One would presume that albinos would suffer great discomfort in bright light, particularly sunlight, but Fonda (1962) found the problem not to be as disabling as expected. He believed that albinos may simply adapt to their bright surroundings.

1.3.3 Reduced visual acuity

The major defect associated with albinism is a reduction in visual acuity (V.A.). Edmunds (1949) suggests that this is, on average, at the level of $^{6}/_{60}$ ($^{20}/_{200}$); Taylor (1978) gives a range of $^{6}/_{9}$ - $^{6}/_{60}$ ($^{20}/_{30}$ - $^{20}/_{200}$) for oculocutaneous albinos. However, the average range given by most authors for all types of albinism is $^{6}/_{36}$ - $^{6}/_{60}$ ($^{20}/_{120}$ - $^{20}/_{200}$) (Wallner and Rudens 1950; Gillespie 1961; Johnson, Gillan and Pearce 1971). The reason for such a wide variation in VA measures appears to be because acuity depends on the amount of ocular pigment and, therefore, on the type of albinism. Falls (1951); Witkop (1971); Witkop et al. (1973) and Carr and Siegel (1979) all believe that the greater the degree of depigmentation, the greater the visual loss. Consequently, ty-neg albinos tend to have low VA remaining constant, or even diminishing, with age (Witkop 1971; Witkop et al. 1974 and 1978) while that of ty-pos and ocular albinos falls within a wider range which may increase with age as pigment accumulates (Trevor-Roper 1963; Witkop 1971; Witkop et al. 1974, 1978).

Photophobia and light scattering may contribute to the VA

loss but it does not appear to play a major role as even in dim illumination the VA of oculocutaneous albinos does not improve significantly (Carr and Siegel 1979). A clue to the main cause of the VA loss is seen by ophthalmoscopy. The fovea appears hypoplastic, lacks hyperpigmentation and the normal reflex is absent. This is thought to be an almost universal finding in albinos (Witkop et al. 1974; Carr and Siegel 1979), although Witkop (1971) believes that the foveal reflex may be normal in approximately 10% of oculocutaneous albinos.

Edmunds (1949) postulated that albinos may be born with a normal foveal structure but over-stimulation by light may cause this area to atrophy. However, more recent microscopic examinations of albino eyes have revealed the true features underlying the abnormality.

Such studies have shown that in the central retina the ganglion cell layer retains its maximum 6 to 8 cell layer thickness with no apparent foveal pit (Naumann, Lerche and Schroeder 1976; O'Donnell et al. 1976). This finding was supported by Fulton, Albert and Craft (1978); they could find no evidence for a fovea in serial sections of the central retina, although there was some thinning of the nuclear layer. Neither a rod free area or typical cylindrical foveal cones could be found and instead the central cones resembled those found in the normal parafovea.

Therefore, there is an anatomical basis for the poor VA found in albinos in that the central retina lacks normal

foveal differentiation. O'Donnell et al.(1978a and b) found that the normal wreathing of the fovea by retinal vessels was absent in albino eyes while, in contrast, Gregor (1978) using fluorescein angiography, reported normal perifoveal vasculature. The latter author believes this may indicate that there is some form of specialisation within the macular area of albinos.

The cause of the foveal malformation is unknown. O'Donnell et al.(1978a) postulate that the normal relative hyper-pigmentation of the fovea, which is absent in albino eyes, may induce foveolar differentiation of the sensory retina. Carr and Siegel (1979) also believe that foveal development may be related to the degree of RPE melanization.

1.3.4 Nystagmus

This is found in all types of albinism (Fonda 1962; Duke-Elder 1964) and has been reported to be evident from birth (Johnson et al. 1971). The nystagmus may increase during near vision (Edmunds 1949) or on monocular fixation (Falls 1951). It can be accompanied by head-nodding, usually in childhood, (Falls 1951; Ohrt 1956; Witkop 1971; Witkop et al. 1974) and a head tilt is often acquired presumably to help to reduce the nystagmus particularly during reading (Johnson et al. 1971; Witkop et al. 1978; Taylor 1978). The type and severity of the nystagmus varies considerably but is commonly horizontal, rotatory or a combination of the two (Duke-Elder 1964; Johnson et al. 1971). The amount of

nystagmoid movement measured by Edmunds (1949) was in the range of 0.5 to 9.5mm; average 1.0mm. This author also found that most, but not all, albino subjects are unaware of their nystagmus.

The nystagmus is thought to be caused, primarily, by poor central fixation (Trevor-Roper 1963), which necessarily accompanies the poor foveal differentiation. Its severity has been related to the amount of depigmentation. Witkop (1971) observed that the greater the iris pigmentation, the lesser the degree of nystagmus. This is reflected in reports of a more severe defect occurring in ty-neg than in ty-pos or ocular albinos (Witkop 1971; Witkop et al. 1974, 1978). It is also apparent that in albinos who accumulate pigment with age, (ty-pos and ocular), the nystagmus may, as a consequence, reduce with age (Witkop et al. 1978).

1.3.5 Refractive errors

Refractive errors, often high, are reported as common in albinism. Some believe myopia to be the rule (Gillespie and Covelli 1963; Duke-Elder 1964) while others have observed the prescription to be neither consistently hypermetropic or myopic (Edmunds 1949; Wallner and Rudens 1950; Fonda 1962; Johnson et al. 1971; Taylor 1978). However, most authors agree a frequent occurrence of astigmatism (Edmunds 1949; Wallner and Rudens 1950; Ohrt 1956; Fonda 1962; Taylor 1978). As a result of the foveal defect discussed in 1.3.3, careful correction of the refractive

error may not actually cause a significant increase in VA but Taylor (1978) believes it is justified for the sake of vision outside the central retinal region. The subjective improvement obtained, however, is probably minimal; Edmunds (1949) found that many oculocutaneous albinos, particularly children, considered their spectacles more of a burden than an aid.

1.3.6 Strabismus

A high incidence of strabismus in albinos has been observed (Ohrt 1956; Fonda 1962; Johnson et al. 1971; Taylor 1978). Exotropia has been reported as more common than esotropia (Fonda 1962; Johnson et al. 1971) while others believe esotropia to be the rule, with a higher incidence in ty-neg than ty-pos oculocutaneous albinos (Witkop et al. 1974 and 1978). Taylor (1976) however, could not find any pattern, observing various types of squints in the albinos he studied.

1.3.7 Binocular vision

Witkop et al. (1978) using several methods, tested a group of albinos; all lacked binocular vision. This is supported by observations by Coleman, Sydnor, Wolbarsht and Bessler (1979); Creel, Spekreijse and Reits (1981a and b). The high incidence of strabismus in such subjects may, of course, influence these results (Coleman et al. 1979).

1.3.8 Visual fields

Peripheral visual fields have been reported as constricted in albinos (Edmunds 1949; Falls 1951; Fonda 1962; Duke-Elder 1964) while others have found them full (Falls 1951; Goodman, Ripps and Siegel 1965; Creel, Witkop and King 1974; Coleman et al. 1979). Relative or absolute central scotomata ranging from 1-6.5 degrees have been observed (Edmunds 1949; Falls 1951; Duke-Elder 1964).

1.3.9 Colour vision

Edmunds (1949) postulated that albinos are likely to have mild, generalised low colour discrimination simply because of their low V.A. Oculocutaneous albinos have been reported to display mild red colour vision defects similar to those found in protanomaly (Pickford 1951, 1958; Pickford and Taylor 1968; Taylor 1976). Such abnormalities are only identifiable with an anomaloscope; pseudo-isochromatic plates are too insensitive. Ocular albinos seem to display normal colour vision (Falls 1951; Fonda 1962; Goodman et al. 1965; O'Donnell et al. 1976) although Johnson et al. (1971) found an isolated subject with a deutan type defect.

1.3.10 Retinal functioning

The electroretinogram (ERG) has been reported to be normal in albino eyes (Fonda 1962; Goodman et al. 1965; O'Donnell et al. 1978b). In contrast, Tomei and Wirth (1978) observed

that it could be subnormal, while Krill and Lee (1963) found it to be of greater amplitude and shorter latency than in non-albinos. The latter authors attributed their results to the increase in light scatter present in albino eyes. Dodt, Copenhaver and Gunkel (1959) measured the relative spectral sensitivity of the photopic component of the ERG. A difference was found between deeply pigmented and albino eyes similar to the spectral reflection of blood.

The electro-oculogram (EOG) has been reported as normal (Gouras and Gunkel 1963; O'Donnell et al. (1978b) and super-normal (Reeser, Weinstein, Feiock and Oser (1970). A study by Gahlot and Hansen (1974) showed a generally low baseline, delayed light rise and early dark trough although the final EOG ratio was normal.

1.4 Carriers of human albinism

Carriers of oculocutaneous albinism are typically asymptomatic. Attempts to utilize iris translucency as indicative of the heterozygous state have met with varying degrees of success (Wirtschafter, Denslow and Shine 1973; Jay, Carruthers, Treplin and Winder 1976). The success of this method is dependent on race; translucency may be present in Caucasians but absent in Negros (Witkop et al. 1974). A biochemical technique of identifying ty-neg carriers has been developed although this is unsuccessful in ty-pos heterozygotes (King and Witkop 1977).

In X-linked ocular albinism the situation is very different. This condition is an example of intermediate sex-linked inheritance; homozygous males display the classical features of the condition while heterozygous females have only mild disorders (Duke-Elder 1964; Blach and Jay 1969). Carriers may be identified by iris translucency although this is not a constant feature (Falls 1951; Ohrt, 1956; Gillespie and Covelli 1963; Cortin et al. 1981). Fundal pigmentation is variable but characteristic findings are reported: cocoa-brown pigment clusters in the mid-periphery separated by areas of depigmentation. The macular area may also appear stippled (Falls 1951; Gillespie and Covelli 1963; Duke-Elder 1964; O'Donnell et al. 1976). The degree of expression of all these carrier features is dependent on general pigmentation and are therefore more pronounced in blond females (Gillespie and Covelli 1963). Other ocular functions appear to be normal (Gillespie 1961; Krill and Lee 1963; Goodman et al. 1965; Johnson et al. 1971; O'Donnell et al. 1976) although occasionally abortive symptoms of ocular albinism have been reported (Ohrt 1956; Johnson et al. 1971). More recently, results using skin biopsies have suggested that this may prove a more reliable method of identifying carriers (O'Donnell et al. 1976; O'Donnell et al. 1978a; Cortin et al. 1981). Carriers of autosomal recessive ocular albinism show none of the above ocular or skin biopsy findings (O'Donnell et al. 1978b).

1.5 Incidence of human albinism

The geographic distribution of albinism is widespread and

the frequency of its occurence varies with race (Duke-Elder 1964; Witkop et al. 1974, 1978).

Oculocutaneous albinism is thought to affect the sexes equally (Duke-Elder 1964) and most authors agree that its incidence in the general population falls between 1 in 18,000 to 1 in 20,000 (Witkop 1971; Witkop et al. 1974, 1978; Baraitser 1981). This frequency can increase in certain isolated populations; Baraitser (1981) quotes 1 in 5,000 among Nigerians concluding that in such cases it may be advantageous to be affected as albinos will be precluded from work in the hot sun.

The incidence of ocular albinism is not known. Witkop (1971) believes is to occur less frequently than oculocutaneous and, in a survey of partially-sighted schools in the U.S.A., Witkop et al. (1974) found 9% of students had some form of oculocutaneous albinism while 1% had ocular albinism.

1.6 Visual aids for albinos

There is no known cure for albinism. At the present, one is limited to providing advice to albinos and their families in the form of genetic counselling and help to albinos themselves, particularly for their ocular problems. Photophobia may be reduced by the use of tinted spectacles or contact lenses, particularly the painted haptic type (Edmunds 1949; Fonda 1962; Duke-Elder 1964; Taylor 1978). Low V.A. may be helped by the careful correction of any

refractive error present in conjunction with high reading additions or low vision aids if near vision is unsatisfactory (Fonda 1962; Taylor 1978).

CHAPTER TWO

THE VISUAL PATHWAY OF ALBINOS

In recent years it has become apparent that the organisation of the visual pathway in the albino animal differs from that of its normally-pigmented counterpart.

2.1 Historical background

Following work on interocular transfer in albino and hooded rats, Sheridan (1965) suggested that in the albino there could be a reduction in the number of uncrossed optic nerve fibres. This was subsequently verified anatomically by Lund (1965). Later, Giolli and Guthrie (1969) showed the existence of a similar reduction of uncrossed fibres in the albino rabbit. Guillery (1969) found evidence for an increase in the number of crossed fibres in the Siamese cat and he postulated that in this animal a misrouting was present such that fibres from the temporal retina, which would normally remain uncrossed, actually followed a crossed route. Creel (1971a) pointed out that the Siamese cat is regarded as an albino of the ty-pos type: (Creel, Henderson and Leventhal 1982a). Hence the possibility arose that a reduction of the uncrossed component in the visual pathway is characteristic of the albino trait.

Subsequent studies have revealed the presence of optic nerve fibre misrouting in a wide range of albino animals: the ferret (Guillery 1971); guinea pig (Creel and Giolli 1972); mink (Sanderson 1972); mouse (Guillery, Scott, Cattanach and Deol (1973); hamster (Guillery and Orsini - unpublished

observation cited by Kaas and Guillery 1973); white tiger (Guillery and Kaas 1973); monkey (Gross and Hickey 1980) and the ty-neg albino cat (Creel et al. 1982a).

Following work on mink, Sanderson, Guillery and Shackelford (1974) found that genes other than those at the albino locus could be associated with misrouting. Therefore, it would seem that, more precisely, it is a reduction in retinal pigmentation which is linked with the visual system anomaly.

Many albino animals and in particular the Siamese cat, have been subject to various forms of anatomical, electrophysiological and behavioural examinations in an attempt to fully investigate the abnormality. Consequently, misrouting will now be considered in greater detail in the Siamese cat. However, prior to this, a short description of the visual pathway of the normal cat will be given. In the subsequent sections the term 'normal' is used in reference to normally-pigmented, non-albinotic, animals. Particular attention will only be paid to those features of the cat visual system which have undergone investigation in the Siamese variety.

2.2 The visual pathway of the normal cat

The retina of the cat projects to two main structures; the dorsal lateral geniculate nucleus and the superior colliculus. Other projections are present, (Rodieck 1979), but these minor pathways will not be considered here. The dorsal lateral geniculate nucleus acts as the main relay station

for the transmission of information from the retina to the visual cortex. A diagrammatic representation of this pathway is illustrated in Figure 2.1.

2.2.1 Introduction

The cat possesses a relatively large eye ball with a broadly curved cornea and disproportionately large pupil (Blake 1979). At birth, the optical quality of the kitten eye is poor. This is mainly due to the presence of a vascular network engulfing the lens which is gradually absorbed during the first few weeks of life (Freeman and Lai 1978). Normal interocular alignment is not present at birth. Initially the eyes appear divergent and it is during the second month of life that the normal adult position is assumed (Sherman 1972). However, it does seem that the actual visual axes are not divergently misaligned (Olson and Freeman 1978). The V.A. of the adult cat is estimated to be about 6' arc ($^{6}/_{36}$) both monocularly and binocularly (Berkley and Watkins 1973; Packwood and Gordon 1975). The monocular visual field of the adult cat, measured behaviourally, is about 135 degrees along the horizontal meridian extending 90-100 degrees temporally and 30-45 degrees nasally (Sprague 1966; Packwood and Gordon 1975).

2.2.2 The retina

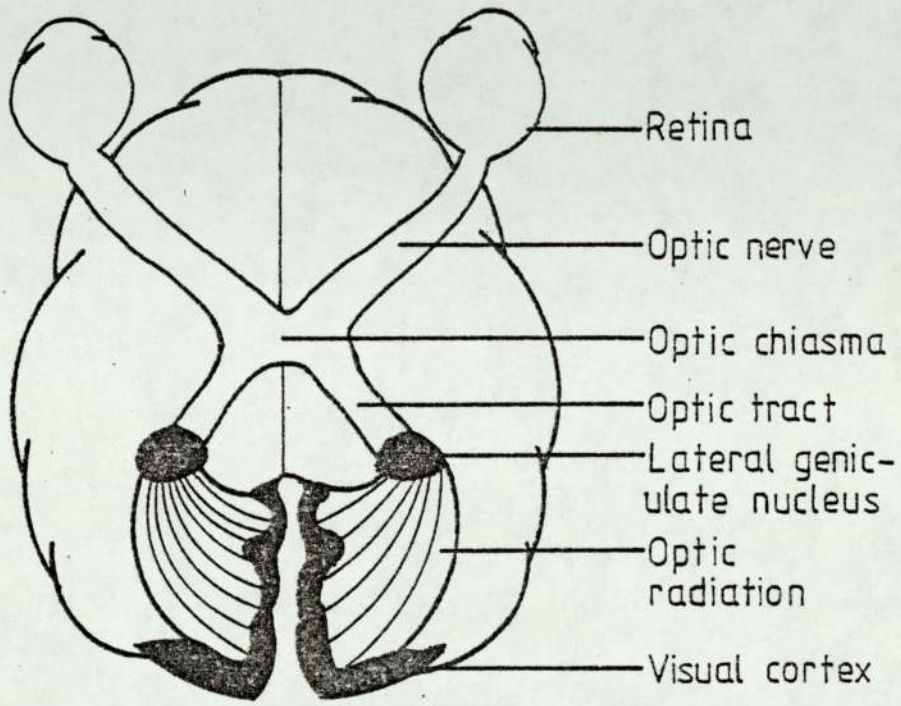
Examination of the fundus of the cat's eye reveals an optic disc, vascular system and an area centralis (Bishop, Kozak

Figure 2.1

The Retinogeniculocortical Pathway

A diagrammatic representation of the main visual pathway found in both the cat and the human.

(Adapted from Guillery 1974)


Retina
Optic nerve
Optic chiasma
Optic tract
Lateral genic-
ulate nucleus
Optic
radiation
Visual cortex

and Vakkur 1962b). The latter feature lies somewhat superior and lateral to the centre of the optic disc and is marked by an absence of visible blood vessels.

Microscopic examination of the adult cat's retina shows that below the choroid lies the tapetum lucidum. This is a reflective layer covering the greater portion of the upper part of the posterior pole of the eye (Donovan 1966; Glickstein 1969). Below the tapetum lies a single layer of pigment epithelium cells and beneath this the inner and outer segments of the rods and cones (Glickstein 1969). These receptors synapse with bipolar cells; cone bipolars then synapse directly with ganglion cells while rod bipolars must first contact amacrine cells which in turn synapse with ganglion cells (Kolb and Famiglietti 1974). Anatomically, the cat retina is immature at birth. The central region is more developed than the periphery and it is not until about nine weeks of age that a mature appearance is reached (Donovan 1966).

In the adult cat the density of cones and ganglion cells is highest in the area centralis (Steinberg, Reid and Lacy 1973; Stone 1965). The ratio of cones to ganglion cells is lowest in the area centralis and, as may be predicted, this is the site of maximum V.A. (Blake and Bellhorn 1978). In addition to the area centralis there is also an increase in the ganglion cell density along the horizontal meridian forming the so-called 'visual streak' (Stone 1965).

The ganglion cells are not homogenous with respect to their physiology or morphology. Kuffler (1953) described two types of ganglion cells; ON-centre and OFF-centre. Their receptive fields were found to be made up of two mutually antagonistic regions, a centre and a surround, one excitatory, the other inhibitory. The majority of retinal ganglion cells in the cat conform to this concentrically arranged centre/surround organization. Receptive field size varies with retinal eccentricity tending to be small in the area centralis and larger in the periphery (Wiesel 1960). Further studies have shown that ganglion cells can also be classified with respect to response properties independent of the centre/surround organization.

In 1966 Enroth-Cugell and Robson distinguished two classes of ganglion cells. On measuring the contrast sensitivity of individual units they found that one group of cells, X-cells, displayed approximately linear summation over their entire receptive field. A second group, Y-cells, showed non-linear summation. Later, Cleland, Dubin and Levick (1971) introduced the terms "sustained" and "transient" as a further classification of X- and Y-cells respectively.

Since this initial work the individual characteristics of these two types of cells have been examined. Only a summary of some of their major features is given here. Further details can be found in reviews by Lennie (1979); Rodieck (1979) and Stone, Dreher and Leventhal (1979).

X-cells are thought to comprise 40-50% of the total ganglion cell population and are concentrated particularly in the central retina. They have medium-sized soma and receptive fields and slow conducting axons. They respond poorly to rapidly moving stimuli.

Y-cells are thought to comprise only 5-10% of the cell population and, in relative terms, occur more frequently in the retinal periphery. Their soma and receptive fields are large; the axons thick and fast conducting. They respond well to rapidly moving stimuli.

A third type of ganglion cell has also been described. These W-cells (Stone and Hoffman 1972) are thought to comprise 50-55% of the cell population and are concentrated particularly in the visual streak. They have small to medium-sized soma with large receptive fields; their axons are very thin and slow conducting. They give a relatively poor response to rapidly moving stimuli.

Morphologically distinct cell classes have also been described. Boycott and Wassle (1974) identified three main types; the large α-cells and the somewhat smaller β- and γ-cells. A fourth type, termed δ-cells were infrequently seen. These cells have been linked with the physiologically described types such that α-, β- and γ-cells relate to Y-, X- and W-cells respectively (see Lennie 1979; Rodieck 1979; Stone et al. 1979 for a summary of the evidence).

The roles that the different ganglion cell classes play in visual perception are not yet totally clear. X-cells have small receptive fields and are concentrated in the area centralis. These features imply that these cells are important for high resolution vision (Blake 1979; Lennie 1979; Stone et al. 1979). Y-cells are more sensitive to fast moving objects than X-cells and therefore they may play a role in the discrimination of movement (Blake 1979; Rodieck 1979; Stone et al. 1979).

2.2.3 The optic chiasma

The ganglion cells unite at the optic disc and pass through the scleral coat of the eye to emerge as the optic nerve. As can be seen from Figure 2.1, the two optic nerves meet at the optic chiasma. It is at this site that partial decussation of the optic nerve fibres occurs. In general, fibres arising from the nasal retina cross over into the contralateral optic tract while the temporal fibres retain an ipsilateral projection. This organization results in visual information from each hemifield being transmitted to the opposite side of the brain. Phylogenetically, the ipsilateral fibres are more recent in origin than the contralateral ones and there is evidence that the nasal and temporal ganglion cells may differ in their properties (Stone, Leventhal, Watson, Keens and Clarke 1980). Within the general pattern of decussation described above it appears that each major ganglion cell type has a slightly different pattern of naso-temporal division. Stone and

Fukuda (1974) found the division to be most developed among X-cells; all cells nasal to the area centralis project contralaterally and all cells temporal to this site project ipsilaterally. Intermingling of ipsilaterally and contralaterally projecting cells occurs only within a small transition zone centred on the area centralis. All of the nasal Y- and W- cells project contralaterally but are also accompanied by 5% of Y-cells and 60% of W- cells arising in the temporal retina. Cooper and Pettigrew (1979a) confirmed these results and found that the contralaterally projecting temporal Y-cells project to the lateral geniculate nucleus whereas the temporal W-cells taking a crossed route terminate at another site, possibly the superior colliculus.

2.2.4 The dorsal lateral geniculate nucleus

From the optic tract fibres project mainly onto the dorsal lateral geniculate nucleus (LGN).

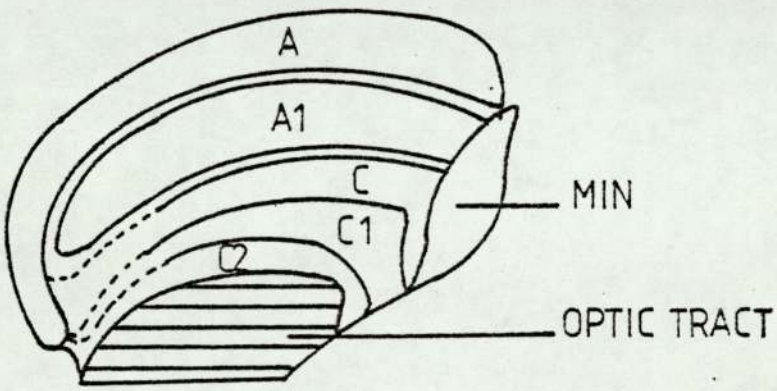
In section the LGN appears as a clearly laminated structure (Bishop, Kozak, Levick and Vakkur 1962a). This is illustrated in Figure 2.2. Classically, three layers have been described: lamina A dorsally, lamina B ventrally with lamina A1 lying between the two. Lamina B has subsequently been subdivided into laminae C, C1 and C2 (Guillery 1970). Each lamina receives afferents from only one eye. Fibres from the contralateral eye terminate in lamina A, those from the ipsilateral eye in A1. This pattern is repeated in layers

Figure 2.2

The Lateral Geniculate Nucleus (LGN) of the Normal Cat

This diagrammatical representation of a frontal section through the rostral third of the left LGN of a normal cat shows the laminar nature of this structure. Laminae A to C2, the optic tract and the medial interlaminar nucleus (MIN) are labelled.

(Adapted from Guillery 1970)


A
A1
C
C1
MIN
OPTIC TRACT

C and C1; the input to C2 is, as yet, unclear (Garey and Powell 1968; Guillery 1970; see Kaas, Guillery and Allman 1972 for a summary of the evidence).

The contralateral visual hemifield is represented in an orderly fashion within the LGN (Bishop et al. 1962a; Garey and Powell 1968; see Kaas et al. 1972 for a summary of the evidence). The upper field is represented posteriorly, the lower field anteriorly with an orderly progression from one to the other. The peripheral field is represented laterally, the central parts medially. This pattern extends throughout the geniculate layers so that cells within adjacent laminae receiving afferents from corresponding parts of the two retinae stand in register. Hence, a point in the visual field is represented as a line perpendicular to the geniculate layers along a 'line of projection' (Bishop et al. 1962a; Kaas et al. 1972, for a summary of the evidence). This arrangement is more easily understood if only two laminae, A and A1 are considered as is illustrated in Figure 2.3. All parts of the visual field are not equally represented within the LGN. The central region projects to a proportionately larger portion than does the periphery (Bishop et al. 1962a) and the superior retina has a larger representation than the inferior region (Garey and Powell 1968).

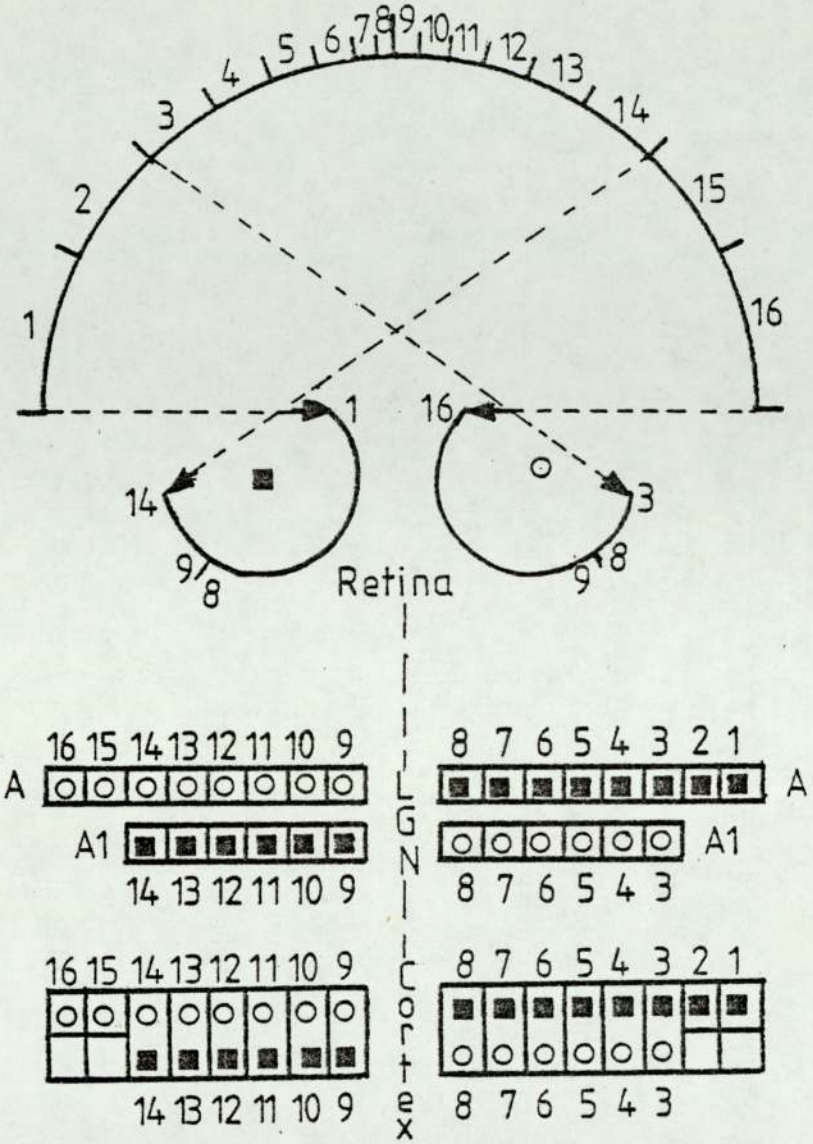
Each retina also projects to a region immediately adjacent and medial to the LGN; the medial interlaminar nucleus (MIN - see Figure 2.2). This structure is not clearly

Figure 2.3

A Schematic Diagram of the Retinogeniculocortical Pathway found in the Normal Cat

The visual field is divided into segments (1 - 16) and the mapping of these segments onto geniculate layers A and A1 is shown. The central region of the visual field (8 and 9) are represented at the medial margins while the peripheral parts are represented laterally: the remaining field is topologically arranged between these two margins. Visual field representations within the two geniculate layers can be seen to lie in register. Segments 1, 2, 15 and 16 represent the monocular crescents of the LGN. The systematic organisation found in the LGN is repeated in the cortex.

(After Guillery et al 1974; Guillery & Casagrande 1975b)


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
1
16
14
9
8
3
Retina
LGN
Cortex
A
A1
16 15 14 13 12 11 10 9
14 13 12 11 10 9
8 7 6 5 4 3 2 1
8 7 6 5 4 3

laminated but does receive a bilateral retinal projection (Garey and Powell 1968; Guillery 1970) and the visual field representation is a mirror image of that found in the main laminae (Garey and Powell 1968).

Geniculate cells have properties in common with those of the retina (Hubel and Wiesel 1961). Their receptive fields are concentrically arranged and tend to be smaller in size for cells originating in the central retina. In addition, individual cells are driven by one eye only. The retinal ganglion cell classes have their counterparts in the nucleus but the divisions are less clear (see Lennie 1979 for a summary of the evidence).

2.2.5 The superior colliculus

This is the second major structure onto which the retina projects. The superior colliculus (SC) is a laminated structure that can be divided into superficial and deep areas; only the former will be considered here. With this structure the visual hemifield is represented in an orderly manner (Garey and Powell 1968). The upper retina is represented laterally, the lower retina medially. The anterior region represents the central retina, the posterior part the periphery. In addition, the anterior tip receives an input from the contralateral temporal retina (Feldon, Feldon and Kruger 1970; Berman and Cynader 1972; Lane, Kaas and Allman 1974). The central retina is represented over a proportionately greater amount of the collicular surface than the periphery but, in contrast to that found in the LGN, the areas related

to the superior and inferior retinae are approximately equal in size (Garey and Powell 1968; Sterling and Wickelgren 1969). The cells of the SC differ from those of the LGN in that they are binocularly driven and some show directional sensitivity (Sterling and Wickelgren 1969). Both Y- and W-cells appear to project to the SC but there is no evidence of X-cell terminations (Hoffman 1972; Fukuda and Stone 1974).

2.2.6 The visual cortex

As illustrated in Figure 2.1, fibres from the LGN pass along the optic radiations and terminate in the ipsilateral cortex. Thirteen visual cortical areas have been described in the cat including six in the lateral suprasylvian area and four in areas 20 and 21 (Palmer, Rosenquist and Tusa 1978; Tusa, Rosenquist and Palmer 1979). However, only the three remaining areas, which receive the majority of geniculate fibres, will be considered here. Their anatomical positions are illustrated in Figure 2.4 and are identified as a) Area 17 (Striate cortex; Visual I) b) Area 18 (Visual II) and c) Area 19 (Visual III) (Hubel and Wiesel 1965).

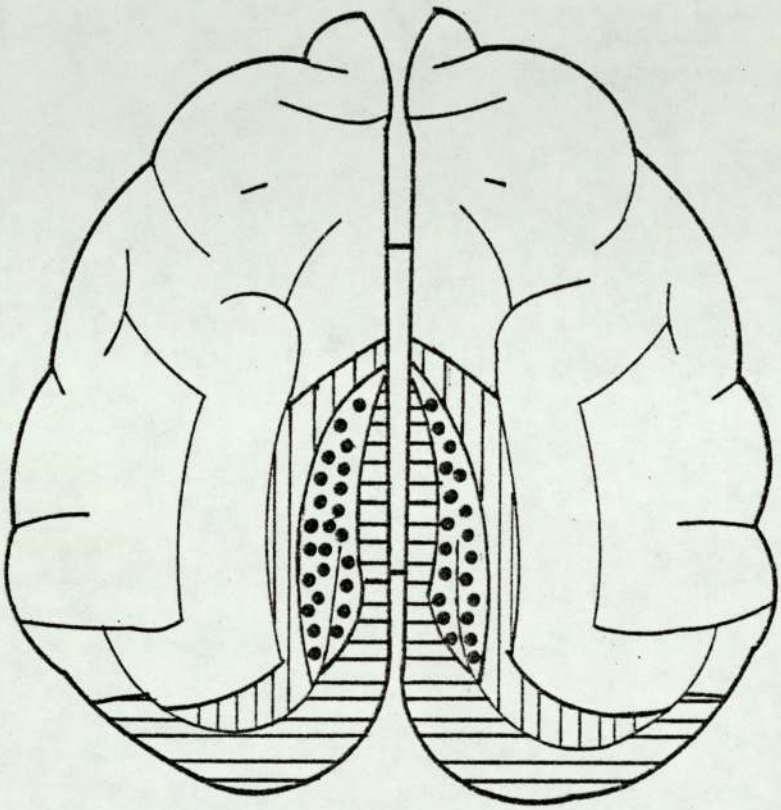
Of the three, area 17 covers the largest cortical surface area and it contains a representation of the entire contralateral hemifield (Tusa, Palmer and Rosenquist 1978). Areas 18 and 19 contain a similar but less extensive representation (Tusa et al. 1979). In all three, the representation of the central area occupies more cortical surface than that of the periphery (Tusa et al. 1978, 1979).

Figure 2.4

The Three Main Visual Areas of the Cat Visual Cortex

The relative positions of area 17 (Visual I, striate cortex), area 18 (Visual II) and area 19 (Visual III) are shown.

(After Sprague 1966)



= Area 17

= Area 18

= Area 19

The contralateral hemifield is represented in a systematic manner within the cortex (Garey and Powell 1967). This is shown diagrammatically in Figure 2.3. Cells from the anterior LGN project to the anterior region of areas 17 and 18 and, similarly, posterior geniculate cells project to the posterior cortex. The medial LGN projects to the lateral part of area 17; the lateral cells to the medial regions. The complementary arrangement is found in area 18; medial cells project medially, lateral cells, laterally. Consequently, the vertical meridian of the visual field is represented along the border of areas 17 and 18 (Hubel and Wiesel 1965; Garey and Powell 1967; Tusa et al. 1978). Area 19 contains an almost mirror image of the representation in area 18 (Tusa et al. 1979).

Although these cortical areas are often considered as separate units they are all interconnected. Area 17 projects to areas 18 and 19 on the same side (Hubel and Wiesel 1965; Garey, Jones and Powell 1968; Wilson 1968) and the two hemispheres are also interconnected via the corpus callosum. The latter connections mainly involve cells located at the 17/18 border and, hence, the representation of the vertical meridian of the visual field (Hubel and Wiesel 1967; Wilson 1968).

The cells in the cortex are far more complex than those found at the level of either the retina or LGN. After initial work by Hubel and Wiesel (1959, 1962, 1965) much attention has been paid to cortical cells and their

properties. Only certain features will be discussed here but further details can be found in Henry (1977) and Stone et al. (1979).

Three main groups have been described; simple, complex and hypercomplex cells (Hubel and Wiesel 1959, 1962, 1965). A major difference between these and the cells in the LGN lies in the fact that cortical cells do not possess concentrically arranged receptive fields. Instead the fields are elongated in shape so that the optimum stimulus is a straight contour at a particular orientation (Hubel and Wiesel 1959, 1962, 1965). This orientation specificity is a fundamental property of the cortical cells. In addition, a high proportion of the cells are binocularly driven; up to 84% in the striate cortex receive an input from both eyes (Hubel and Wiesel 1962, 1965). This is thought to form the basis for the fusion of images from the two eyes (Hubel 1982). Consequently, each cortical cell has two receptive fields, one associated with each eye, occupying corresponding positions in the two retinae (Hubel and Wiesel 1962, 1965). When corresponding parts of the two receptive fields are stimulated summation of the responses occurs. This property is thought to be important for binocular vision (Hubel and Wiesel 1962).

Initial work led Hubel and Wiesel (1962, 1965) to consider areas 17, 18 and 19 to form a hierarchical processing system whereby visual information passes from the LGN to area 17 and from there to areas 18 and 19 for successively

higher processing. However, recently, a more parallel processing system has been favoured whereby areas 17, 18 and 19 receive their principal input from the different classes of retinal ganglion cells (see Stone et al. 1979 for a summary of the evidence).

This short review of the visual pathway of the normal cat stresses the orderly manner in which it is arranged. It is organized such that a precise and systematic representation of the visual field is present at the level of the LGN, SC and visual cortex. This ensures that the cat perceives the world in a correct and unambiguous fashion.

2.3 The visual pathway of the Siamese cat

2.3.1 The retinogeniculate pathway

Anatomical studies by Guillery (1969) and later Kalil, Jhaveri and Richards (1971) showed that the LGN of the Siamese cat displays some unusual features. In the intermediate parts of the nucleus abnormal laminations were found; the lateral and medial sections appeared generally normal. Examination of fibre degeneration following monocular enucleation revealed that in the Siamese cat there was an increase in the input from the contralateral eye accompanied by a decrease in the ipsilateral component. The geniculate layers which in the normal cat receive only an ipsilateral input were found to receive both an ipsilateral and contralateral input in the Siamese cat. This

was interpreted as indicative of a possible misrouting of ganglion cell fibres at the optic chiasma such that some fibres from the temporal retinae, which normally remain uncrossed, actually terminate in the contralateral LGN (Guillery 1969).

This abnormal input was subsequently shown to arise from a vertical strip of retina, approximately 20 degrees in width, lying just temporal to the area centralis (Guillery and Kaas 1971; Hubel and Wiesel 1971).

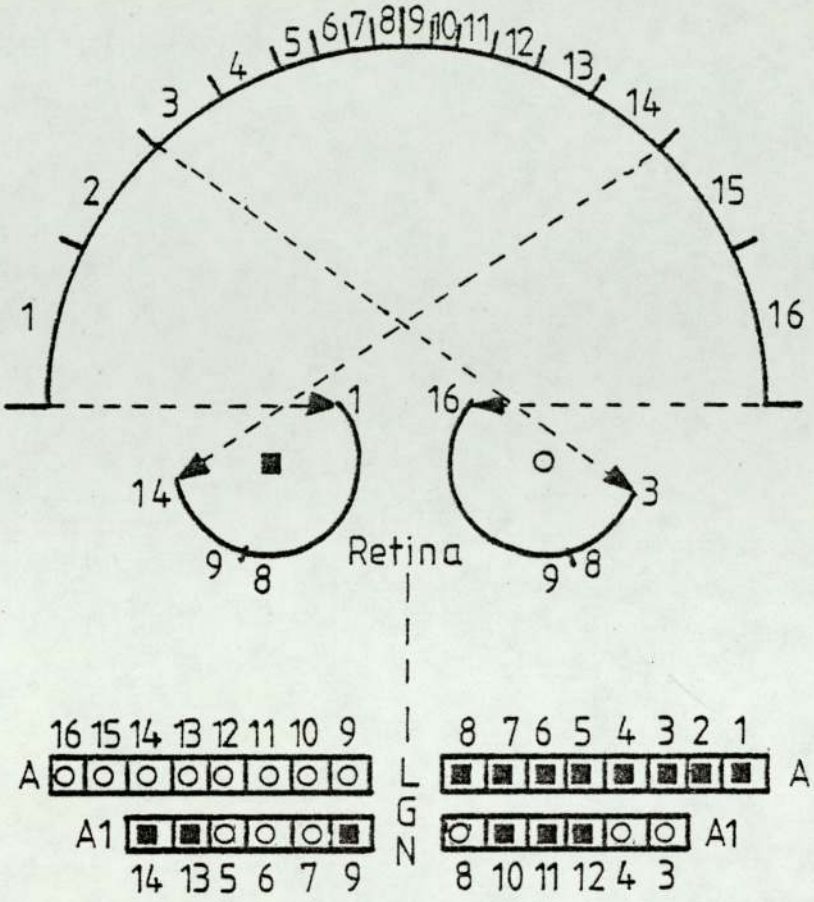
This misrouting necessarily disrupts the organization of the LGN described in 2.2.4, the consequences are illustrated in Figure 2.5. Again only two geniculate layers, A and A1, will be considered. The anomaly is more easily understood if only two laminae are shown; the nature of the misrouting in the C laminae and the MIN appears to be variable (Kalil et al. 1971; Guillery and Kaas 1971; Shatz 1977a). By comparing Figure 2.5 with Figure 2.3 it can be seen that in the Siamese cat the contralateral visual hemifield is represented in the normal fashion within lamina A but not in A1 (Guillery and Kaas 1971). In the most medial and lateral parts of A1 the representation is normal and the cells are in register with those in lamina A. These have been termed the "medial normal segment" (MNS) and the "lateral normal segment" (LNS) respectively. The MNS represents a group of ganglion cells which, despite their central location in the temporal retina, escape misrouting. The LNS represents the termination of cells in the temporal retina peripheral to the region from which the misrouted fibres arise. Between the two segments lies the termination

Figure 2.5

The Retinogeniculate Pathway of the Siamese Cat

The visual field is represented within lamina A in the normal fashion but in A1 it is disturbed. Segments 8 and 9 represent the medial normal segments (MNS) and 3, 4, 13 and 14 the lateral normal segments (LNS). Between these lie the abnormal segments representing the termination of misrouted temporal retinal fibres from the contralateral eye. The segments in laminae A and A1, no longer lie in register in this abnormal segment.

(After Guillery et al. 1974; Guillery & Casagrande 1975b)


1
2
3
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11
12
13
14
15
16
1
16
14
9
8
Retina
9
8
3
16 15 14 13 12 11 10 9
A
A1
14 13 5 6 7 9
L
G
N
8 7 6 5 4 3 2 1
A
A1
8 10 11 12 4 3

of the misrouted fibres which are, therefore, inserted in the site where the absent ipsilateral fibres would normally occupy (Hubel and Wiesel 1971). Within this "abnormal segment" (Guillery and Kaas 1971) the retina is represented in the normal order such that fibres originating in the central area project to the more medial parts of the LGN. However, as a consequence of this, the visual field is represented within the abnormal segment in a reversed order (Guillery and Kaas 1971; Hubel and Wiesel 1971).

The termination of the misrouted fibres in the Siamese cat LGN affects the normal organization of this structure and disrupts the systematic representation of the visual field within the nucleus. Again by comparing Figure 2.5 with Figure 2.3 it can be seen that within lamina A1 the visual field is represented in an interrupted fashion and, in parts, in a reversed order. Finally, because of the abnormal segment, the cells in adjacent layers in this part of this nucleus are no longer in register.

2.3.2 The geniculocortical pathway

If this pathway was arranged in the Siamese cat in a similar fashion to that found in the normal cat one would expect the cortex to receive a confused representation of the visual field since some regions would be mapped onto the wrong side of the brain. However, it appears that this pathway may be modified in the Siamese cat to somewhat compensate for the misrouting. Studies have revealed the

existence of two methods by which the Siamese cat deals with the anomalous projection.

Hubel and Wiesel (1971), using electrophysiological techniques found that in some Siamese cats a reorganization of the geniculo-cortical pathway could be present. The misrouted fibres, representing approximately 20 degrees of the ipsilateral visual hemifield, were found to be inserted along the border of areas 17 and 18, which in the normal cat receives a representation of the vertical meridian. The presence of this additional representation distorts the cortical topography such that the representation of a point in the contralateral visual hemifield is shifted from its normal position; medially in the case of area 17 and laterally in area 18. Within the anomalous projection the representation is the reverse of normal so that the reversal occurring in the LGN is corrected in the cortex. This arrangement is illustrated in Figure 2.6. Within this anomalous projection the cells were found to possess the normal simple, complex and hypercomplex properties. However, no binocularly driven units were found; cells were driven only by the contralateral eye. Even outside the abnormal segment cells appear to be aggregated into monocularly driven groups.

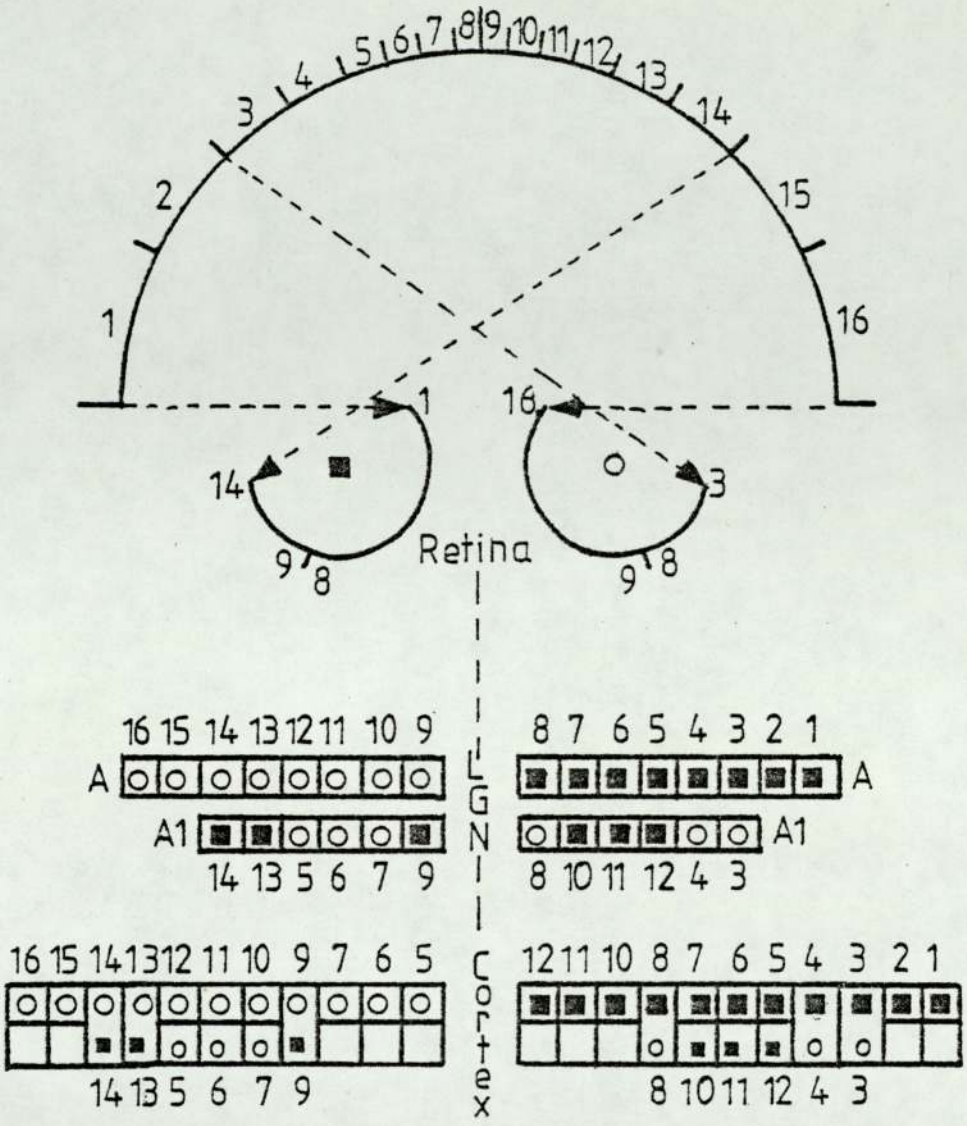
In contrast to these results, preliminary investigations by Kaas and Guillery (1972) suggested a somewhat different cortical arrangement in some Siamese cats. Further studies clarified their findings (Kaas and Guillery 1973). In one Siamease cat the cortical rearrangement reported by Hubel

Figure 2.6

The Retinogeniculocortical Pathway of a Boston Siamese Cat

The cortical representation of the visual field is disorganised. The abnormal LGN segments (5, 6, 7 and 10, 11, 12) are reversed and inserted in the part of the cortex which normally receives fibres representing the vertical meridian of the visual field. The smaller symbols represent a weaker cortical input.

(After Guillery et al 1974; Guillery and Casagrande 1975b)


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
1
16
14
3
9 8
9 8
Retina
LGN
Cortex
16 15 14 13 12 11 10 9
A
A1
14 13 5 6 7 9
8 7 6 5 4 3 2 1
A
A1
8 10 11 12 4 3
16 15 14 13 12 11 10 9 7 6 5
14 13 5 6 7 9
12 11 10 8 7 6 5 4 3 2 1
8 10 11 12 4 3

and Wiesel (1971) was found but in others the vertical meridian of the visual field was represented in its normal position at the 17/18 border. However, they found that the cortical input from the misrouted fibres was totally suppressed. This suppression, therefore, involved both misrouted and normally routed fibres. This arrangement is illustrated in Figure 2.7.

Consequently, the Siamese cat deals with the misrouted fibres in one of two ways with each providing an adequate solution to the abnormal representation of the visual field. The simplest method involves suppression of the abnormal input at a cortical level; the more sophisticated method involves a rearrangement of the abnormal input. Kaas and Guillery (1973) differentiated between the two types calling the former the "Midwestern" pattern and the latter the "Boston" pattern. The classification of Siamese cats into one of these groups is now widely used by investigators. The critical feature distinguishing the two types is the presence, in Boston cats, of a strip of cortex exclusively devoted to the representation of the ipsilateral visual field (Shatz 1977a).

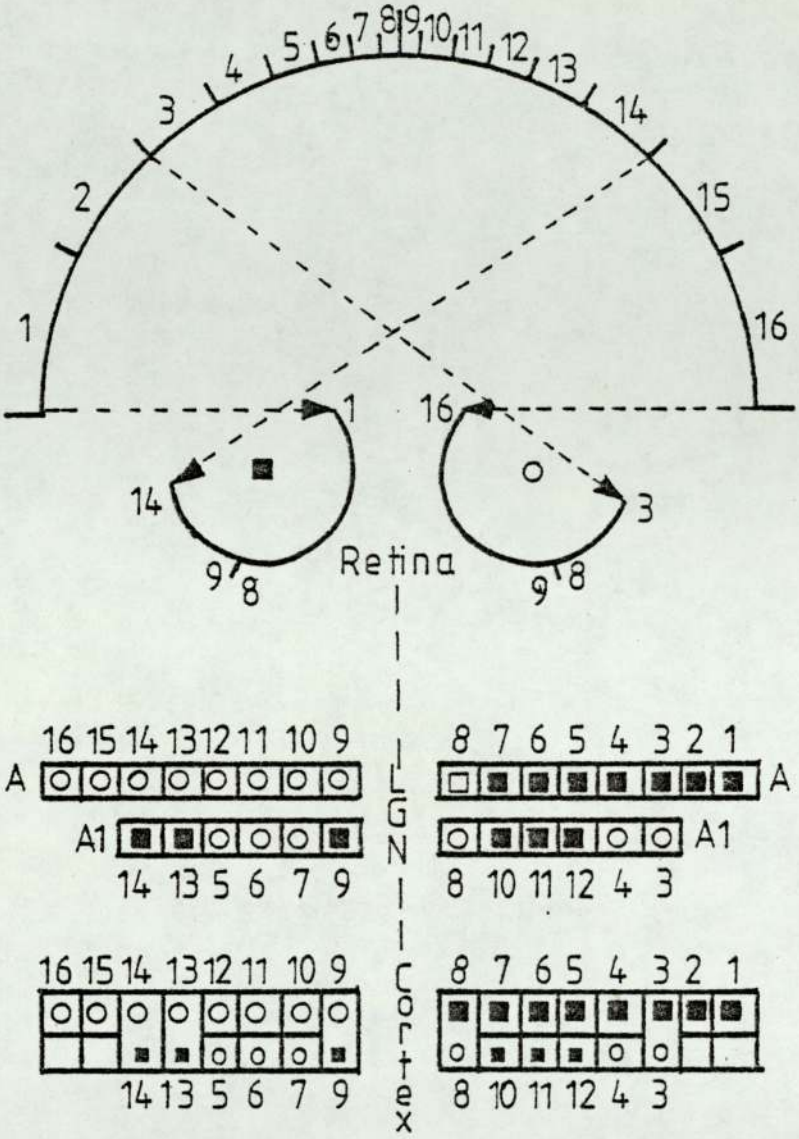
A distinction between the two patterns has also been made at the level of the LGN. Kaas and Guillery (1973) suggested that Boston cats may have a smaller MNS than Midwestern cats. If the Boston pattern was established in the cortex, a continuous and uninterrupted representation of the visual field could only be recreated in the absence of MNS. If the

Figure 2.7

The Retinogeniculocortical Pathway of a Midwestern Siamese Cat

The abnormal segments of the two LGNs project, without reversal, to the position expected from their sites in the LGNs. The smaller symbols represent a weaker input.

(After Guillery et al. 1974; Guillery & Casagrande 1975b)


1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
1 16
14 3
9 8 9 8
Retina
16 15 14 13 12 11 10 9
A
A1
14 13 5 6 7 9
8 7 6 5 4 3 2 1
A
A1
8 10 11 12 4 3
LGN
Cortex
16 15 14 13 12 11 10 9
14 13 5 6 7 9
8 7 6 5 4 3 2 1
8 10 11 12 4 3

latter were large, a more normal representation would be better achieved by suppression of the abnormal input. Subsequent studies have produced some evidence of this (Shatz 1977a).

Kaas and Guillery (1973) also proposed that callosal connections ought to be normal in Midwestern cats but, due to the additional representation at the 17/18 border, modified in Boston cats. Shatz (1977b and c) did find that in Boston cats callosal connections originated not only from the 17/18 border as in normal cats but from other cortical sites which actually represent the vertical meridian of the visual field.

2.3.3 The retinocollicular pathway

Although this pathway has not been so widely investigated as the retinogeniculocortical pathway, studies do suggest that misrouting occurs here also. Anatomical investigations by Kalil et al. (1971) and later Weber, Kaas and Harting (1978) showed an increase in the number of crossed fibre terminations in the Siamese cat superior colliculus. These misrouted axons appeared to originate from the contralateral temporal retina. Electrophysiological studies have also shown that there is a reduction in the number of binocularly driven cells in the SC, most only being activated by the contralateral eye (Berman and Cynader 1972; Lane et al. 1974).

2.3.4 The retinal ganglion cells

The distribution and properties of the different classes of ganglion cells have been studied in the Siamese cat.

Electrophysiological investigations have shown a normal proportion of X-cells but a decrease in the Y-cell population so that the ratio of Y-cells to X-cells is reduced compared to that found in the normal cat (Chino, Shansky and Hamasaki 1977, 1978; Shansky, Chino and Hamasaki 1981). This feature was found at all retinal loci outside 5 degrees from the area centralis; inside this the Y-cell to X-cell ratio was higher than normal (Chino, Shansky and Hamasaki 1980a). In addition, the responses of both classes were found to be reduced (Chino et al. 1977, 1978; Shansky et al. 1981) similar to that found in the immature retina of the normal cat (Chino, Shansky and Pizzi 1980b).

Anatomical studies have provided somewhat variable results. Stone, Rowe and Campion (1978b) found that the ganglion cell maps in Siamese cats, although variable, exhibited the same major features found in normal cats. However, in the area centralis the peak cell density was lower and the cells larger than found in normal cats. Medium-sized cells (possibly of the X-type) were also lacking from all retinal areas. These results thus provided no anatomical evidence for the reduction in Y-cells encountered by Chino et al. (1977, 1978) and Shansky et al. (1981). In contrast, Kicliter, Chino and Shansky (1980) found a reduction in the percentage of large cells (possibly of the Y-type) in the Siamese

compared to the normal cat.

Investigators have also tried to identify whether the typical Siamese cat misrouting affects the individual ganglion cell classes differentially. Lund (1975) originally postulated that the misrouting may be due to the anomalous projection of primarily Y-type ganglion cells. This hypothesis has subsequently received some anatomical support. Stone, Campion and Leicester (1978a) and Cooper and Pettigrew (1979b) found that the large (presumably Y-type) ganglion cells were more severely affected by the misrouting than the population as a whole. Marzi (1980) concluded the possible existence of an inverse relationship between cell size and the probability of being affected by the misrouting. Large, Y-cells, would be the most affected, middle-sized, X-cells, proportionally less affected while small, W-cells, the least affected.

2.3.5 Causes of misrouting in the Siamese cat

The cause or causes of the visual pathway anomaly in albino animals are not yet clear. Before the possibilities are discussed, two points are worth mentioning.

Originally it was thought that the misrouted fibres in the Siamese cat arose from a discrete patch of the retina 20 degrees temporal to the area centralis and questions were asked as to why this retinal region alone was affected. However, subsequent evidence has revealed that this retinal

localisation of the misrouted fibres may not be strictly accurate. Stone et al. (1978a) and Cooper and Pettigrew (1979b) found that temporal to the area centralis an intermingling of ipsilaterally and contralaterally projecting cells occurs in the Siamese cat. The proportion of ipsilaterally projecting cells appeared to increase with distance from the area centralis. Consequently, ipsilaterally projecting cells were found within 20 degrees temporal to the area centralis and contralaterally projecting cells beyond this region. Therefore, it does not appear that the misrouting is restricted to a localised area of the retina as originally proposed.

In addition, investigators also questioned why two types of misrouting in Siamese cats (Boston and Midwestern) should develop. However, recent work suggests that the Siamese cat population may not be so clearly divided. Cooper and Blasdel (1980) found that, on the basis of cortical recordings, they sometimes found it difficult to identify a cat as either of the Boston or Midwestern type. They concluded that there may not be two distinct Siamese populations but that it may be better to consider them as a single group in which the representation of the ipsilateral visual field in the cortex varies continuously between cats. Although this work throws some doubt on the Boston/Midwestern dichotomy, this terminology has been widely used by investigators and, therefore, will be referred to when necessary in subsequent sections.

Neither of the above findings, however, alters the fact that in the Siamese cat some fibres from the temporal retinae are misrouted at the optic chiasma with a profound effect on the representation of the visual field in the visual pathway. Several possible causes for the misrouting have been put forward by investigators. As yet we do not know what normally determines the projection of ganglion cell fibres and the extent of the defect is variable among Siamese cats (Guillery and Kaas 1971). The association of the misrouting with pigmentation abnormalities suggests that the two defects may be linked by genetic action at the common site of the neural crest (Creel 1971a). The primary, congenital neural abnormality is thought to be peripheral with all changes central to the optic chiasma occurring secondary (Guillery and Casagrande 1975b).

The existence of a mechanical block deflecting a group of fibres has been discussed (Guillery and Kaas 1971; Cooper and Pettigrew 1979b; Marzi 1980) and Lund (1975) has suggested that whatever causes some temporal W-cells in normal cats to take a crossed route, also affects the other ganglion cell classes in the Siamese cat.

Finally, Silver and Sapiro (1980) found that, during embryological development, the primitive eye stalk becomes transiently pigmented prior to and during migration of the initial optic axons. They suggest that during development melanin producing stalk cells may play a role in controlling the topographic pattern of optic fibres within the optic nerve.

Therefore, it is evident that future studies are necessary before the precise mechanism causing the misrouting is fully understood.

2.3.6 Strabismus in the Siamese cat

The presence of optic nerve fibre misrouting in the Siamese cat was regarded with great interest in the light of the fact that these animals are often cross-eyed (Hyde 1962). The development of a convergent strabismus would be advantagenous in that the nasal half of the retina would be favoured over the temporal half containing the misrouted fibres (Hubel and Wiesel 1971). Newborn Siamese cats appear to display a divergent ocular misalignment (Rengstorff 1976); any convergent strabismus is absent at birth but develops during the first six months or so of life (Hubel and Wiesel 1971; Blake and Crawford 1974).

Early studies also led to the suggestion that, because of the misrouting, Siamese cats should lack stereoscopic depth perception (Kalil et al. 1971) especially in view of the lack of binocularly activated cortical units (Hubel and Wiesel 1971; Cool and Crawford 1972). Support for this hypothesis was produced by Packwood and Gordon (1975) who found that behaviourally, unlike normal domestic cats who show stereoscopic vision, Siamese cats have no stereopsis. However, it is not thought that the lack of binocular units itself causes strabismus as these cells are lacking even in Siamese cats without an obvious strabismus (Hubel and Wiesel 1971; Cool and Crawford 1972). It has been suggested that

the squint does not cause the misrouting but is actually a result of the anomalous retinogeniculate projections (Guillery 1969; Guillery and Kaas 1971; Hubel and Wiesel 1971). Alternatively it has been thought that the strabismus may be due to the abnormal projections to the SC (Berman and Cynader 1972).

Kaas and Guillery (1973) believed that the organization of the LGN may be important in determining the development of the strabismus. They suggested that the critical factor may be the size of the MNS; since this segment receives fibres from the central retinal area, it is likely to be important for determining ocular alignment. Consequently, Siamese cats with a very small or absent MNS (which may also indicate a Boston type cat; see 2.3.2) would be more likely to be cross-eyed that those with a larger MNS (which may be of the Midwestern type; see 2.3.2). Shatz (1977a) did find that the one Midwestern cat examined had almost no squint and a much larger MNS than any of the Boston cats. However, within the latter group who displayed varying degrees of strabismus, there was no correlation between the size of this deviation and either the size of the MNS, LNS or the amount of ipsilateral visual field represented in the cortex.

The presence of strabismus has also been studied in relation to the retinal ganglion cell population in Siamese cats. Tucker (1978) found that the area centralis of strabismic cats contained a greater proportion of large-sized cells than in non-strabismic cats. Chino et al. (1978) and Kicliter et al. (1980) both found that the percentage of

large cells present was related to the size of any squint, the lower the percentage of large-cells, the greater the deviation. Later, Chino et al. (1980b) found a reduction in the number of binocularly driven cells in the Siamese cat cortex, although not as low as found by Hubel and Wiesel (1971); Cool and Crawford (1972), and that the number was inversely related to the size of the strabismus.

However, it must be pointed out that in the aforementioned studies investigators used differing methods of assessing ocular alignment. Often it is measured with the cat in an anaesthetised and paralysed state (Hubel and Wiesel 1971; Cool and Crawford 1972; Shatz 1977a; Chino et al. 1978, 1980b), by photographic techniques (Hyde 1962; Blake and Crawford 1974; Packwood and Gordon 1975; Rengstorff 1976) or simply by gross appearance or unknown methods (Guillery 1969; Guillery and Kaas 1971; Kaas and Guillery 1973; Tucker 1978; Kicliter et al. 1980). In addition much of the work emphasises the fact that Siamese cats display a convergent strabismus but, both orthophoric and divergent cats have been reported (Rengstorff 1976; Shatz 1977a). These two points, however, do not detract from the fact that Siamese cats can display an ocular misalignment which may be related to anomalies in their visual pathway.

2.3.7 The visual fields of the Siamese cat

Kaas and Guillery (1973) suggested that the results of cortical recordings in Midwestern Siamese cats would imply

that they have no vision in their temporal retinae. This correlated well with the work of Elekessy, Campion and Henry (1973) who found that, behaviourally, some Siamese cats seemed to have a virtual absence of vision on the nasal visual hemifield. These results were confirmed in Siamese cats of a definite Midwestern variety by Guillery, Casagrande and Oberdorfer (1974); Guillery and Casagrande (1975a, b). These authors extended the work of Elekessy et al. (1973) and found that raising such cats with vision limited to one eye resulted in the visual field of this eye being effectively increased resulting in a normal total field of approximately 135 degrees.

Guillery et al. (1974) postulated that the results of cortical recordings would suggest that Boston Siamese cats should have normal, full monocular visual fields and later studies showed this to be the case (Simoni and Sprague (1976). Antonini, Berlucchi, Marzi and Sprague (1979) found that after optic tract section the eye of Boston cats contralateral to the section was virtually blind while the ipsilateral eye retained a full visual field. This is in contrast to the results in normal cats who, after a similar tract section, display a contralateral hemianopia. However, some visual functioning was found to be present in the apparently blind eye of the above Boston cats. Marzi and Di Stefano (1979) found such eyes to still retain some capacity for simple pattern and light/dark discrimination. These results seem to indicate that the uncrossed fibres of these cats cannot subserve the vision necessary to perform

perimetry tests but can mediate simple visual discriminations. Marzi (1980) related this to the differential effects of misrouting on the different classes of ganglion cells. The lack of Y-cells in the uncrossed pathway may result in a difficulty in the discrimination of moving objects while the few uncrossed X- and W-cells may allow simple visual discriminations.

It has been suggested that measurement of monocular visual fields may be a simple way of differentiating between Boston and Midwestern cats (Guillery et al. 1974); this would prove a much easier method than the use of electrophysiological techniques.

2.3.8 The visual acuity of the Siamese cat

Very few investigators have studied VA and associated functions in the Siamese cat. Packwood and Gordon (1975) reported the VA to be similar to that in normal cats; 6' arc and this is believed to be a reflection of the normal X-cell population found in Siamese cat retinae (Chino et al. 1977, 1978). Blake and Antoinetti (1976) found contrast sensitivity to be reduced in Siamese compared to normal cats. This was taken as a reflection of the reduced responses of the ganglion cells in such animals (Chino et al. 1977). However, both these latter features have also been attributed by their authors as possibly caused by increased light scatter in the Siamese cat eye.

Little is known about the appearance of the Siamese cat area centralis. Shatz (1977a) did report that in some cats studied the area centralis could be clearly seen while in others it was poorly defined. Stone et al. (1978a) reported the area centralis to be "underdeveloped" in Siamese cats with the blood vessel pattern around this region less developed than in normal cats.

2.3.9 The Siamese cat and the human albino- a comparison

The Siamese cat displays some features that are common in human albinos. These include not only a reduction in pigmentation but the presence of strabismus, lack of stereopsis and the possibility of abnormalities in the central retinal area discussed in previous sections. In addition, nystagmus is occasionally reported in these animals (Creel 1971b; Cool and Crawford 1972; Kaas and Guillery 1973; Zeki and Fries 1980; Loop and Frey 1981). Because it appears that optic nerve fibre misrouting is linked with a reduction in retinal pigmentation as found in human albinos, the possibility arises that the Siamese cat visual pathway anomaly may be present in human albinos. The next section will discuss the organization of the visual pathway in the normal (normally-pigmented, non-albinotic) human in order to identify the impact that such a misrouting would have on the human visual system. Again, as in the section on the normal cat, only the parts of the visual pathway pertinant to the anomaly will be discussed.

2.4 The visual pathway of the normal human

2.4.1 Introduction

The human visual pathway follows a similar course to that illustrated in Figure 2.1. Compared to the human, the cat's eye has a greater light gathering capacity but the retinal image size of any object is some 33% smaller than that in the human (Blake 1979).

In contrast to the kitten, the ocular media of the human newborn is clear (Movshon and Van Sluyters 1981) and no consistent strabismus is present although it is said that the eyes move irregularly until 5-6 weeks of age (Walsh and Hoyt 1969). The normal visual acuity of the adult human eye is usually taken to be about 1' arc ($^{6}/_{6}$) (Duke-Elder 1962) and is often slightly improved under binocular viewing conditions (Barany 1946). The monocular, peripheral visual fields measured subjectively in the adult subject are approximately 100-110 degrees temporally, 60 degrees nasally, 70-75 degrees inferiorly and 60 degrees superiorly (Harrington 1976).

2.4.2 The retina

Examination of the human fundus reveals similar features to those found in the cat; an optic disc, vascular system and a central specialised area; the macula. The latter region can be distinguished by its lack of visible blood vessels

and slightly deeper pigmentation compared to the rest of the retina (Wolff 1976). Lying temporal and inferior to the centre of the optic disc, at the centre of the macular area, is a small pit called the fovea. This very specialised central area is absent from the eye of the cat (Bishop et al. 1962a). The region acts as a small concave mirror and thus produces the bright foveal reflex (Wolff 1976).

Microscopic examination of the retina shows that directly below the choroid lies a single layer of pigment epithelium cells followed by the inner and outer segments of the rods and cones. These receptors contact bipolar cells which, in turn, synapse directly with ganglion cells (Duke-Elder 1961a; Wolff 1976). There is no tapetum in the human eye; such a structure is absent from eyes with a true fovea (Duke-Elder 1958).

The retina of the newborn human is not fully developed. However, in contrast to the findings in the kitten, it is the central region that is poorly formed and the peripheral region that is well developed (Abramov, Gordon, Hendrickson, Hainline, Dobson and La Bossiere 1982).

In the adult human the foveal region contains no rod receptors, just tightly packed cones (Duke-Elder 1961a; Wolffe 1976). Hence, as in the cat, this central area is the region of maximum VA.

Compared to the cat very little is known about human

ganglion cells and their properties. Psychophysical evidence raises the possibility of the existence of fairly distinct movement - and shape-detectors in the human visual system. The properties of these are thought to resemble those of the Y- and X-cells in the cat retina (see Stone et al. 1979 for a summary of the evidence). Anatomical studies have shown that, although there are great variations in the sizes of human ganglion cells, their topographical organization seems to be basically the same as found in the cat and there is the possibility of similar differences between the properties of the nasal and temporal cells (Stone and Johnston 1981). At the fovea the ganglion cells are smaller and more uniform in size than in the periphery and there is some evidence of a visual streak (Stone and Johnston 1981). The latter authors hypothesise that the "ganglion cells comprise several groups at least analogous to the functionally specialised groups of ganglion cells described in the cat".

2.4.3 The Optic Chiasma

The ganglion cells unite at the optic discs to form the two optic nerves which, as in the cat, proceed to the optic chiasma. Here partial decussation of the fibres occurs and, generally, those originating from the nasal retina cross over into the contralateral optic tract whereas the ~~nasal~~ temporal fibres retain an ipsilateral course. The ratio of crossed to uncrossed fibres has been estimated to be 53:47 (Kupfer, Chumbley and Downer 1967). Accordingly, each

half of the visual field is represented in the opposite side of the brain.

From the optic tract fibres project to two main areas. The major projection is the LGN; a lesser component terminates in the SC.

2.4.4 The lateral geniculate nucleus

In section, the human LGN appears laminated. Classically, six layers have been recognised (Chacko 1949); layers 1 and 2 (magnocellular layers) and layers 3 to 6 (parvocellular layers). These are illustrated in Figure 2.8. By considering the number of layers present the nucleus can be divided into three segments: 1) a small, two layered segment representing the monocular part of the hemifield 2) a four layered segment where layers 1 and 2 continue as separate laminae while layer 3 fuses with layer 5 and layer 4 fuses with layer 6, 3) a segment containing all six layers (Chacko 1949; Kupfer 1962). Occasionally, even an eight layered segment may be present (Hickey and Guillery 1979). In accordance with that found in the cat, each layer is thought to receive its input from only one eye: layers 2, 3 and 5 receive ipsilateral fibres; 1, 4 and 6 contralateral fibres (Chacko 1949).

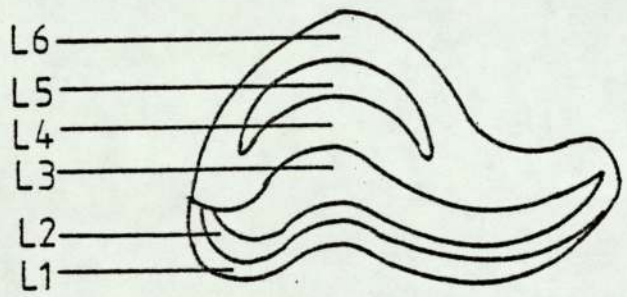
The central part of the visual field is represented in the caudal part of the nucleus (Kupfer 1962) where the full complement of six layers is present. This part of the visual field is represented over a disproportionately large part

Figure 2.8

The Lateral Geniculate Nucleus (LGN) of the Normal Human

A diagrammatic representation of a frontal section through the LGN of a normal human illustrating its laminar nature. Layers 1 to 6 (L1 - L6) are labelled. Layers 2, 3 and 5 receive fibres from the ipsilateral eye; 1, 4 and 6 from the contralateral eye.

(After Chacko 1949)


L6
L5
L4
L3
L2
L1

of the nucleus. Hickey and Guillery (1979) estimated that the central 15 degrees, although accounting for only 3% of the hemifield, is represented in over 50% of the geniculate volume.

The major difference between the human and cat LGN lies in the variability of the former. These variations are least marked in the part of the nucleus representing central vision (Hickey and Guillery 1979). In this region the laminae are clearly seen whereas in other parts the laminar arrangement may be more complex.

The "lines of projection" found in the cat LGN are less clearly defined in the human nucleus particularly in the more irregular parts. However, Hickey and Guillery (1979) believe that in the more regular regions, the projection lines may be identified by rows of nerve cells running perpendicular to the layers.

2.4.5 The superior colliculus

A minority (20-30%) of optic tract fibres terminate in other destinations than the LGN (Bernheimer 1899) and the majority of these are believed to pass to the SC and the pretectal regions. Little is known about the human SC but it is reported to have a laminar structure. Four laminae have been recognised with alternating cellular and fibre layers (Duke-Elder 1961b).

2.4.6 The visual cortex

As in the cat, the human LGN acts as the main relay station for visual information passing from the retina to the visual cortex. From the LGN fibres travel along the optic radiations and terminate in the ipsilateral visual cortex situated on the occipital lobe. Present knowledge of the organization of the visual areas in man is somewhat limited compared to the information available on the cat. Three areas on the occipital lobes have been described; area 17 (striate cortex); area 18 and area 19. The relative positions of these are illustrated in Figure 2.9. In primates, in contrast to the organization in the cat, the LGN seems to project exclusively to area 17 with areas 18 and 19 receiving afferents from this striate area (Wilson and Cragg 1967). At present it is not known if the human visual pathway compares with the primate in this respect.

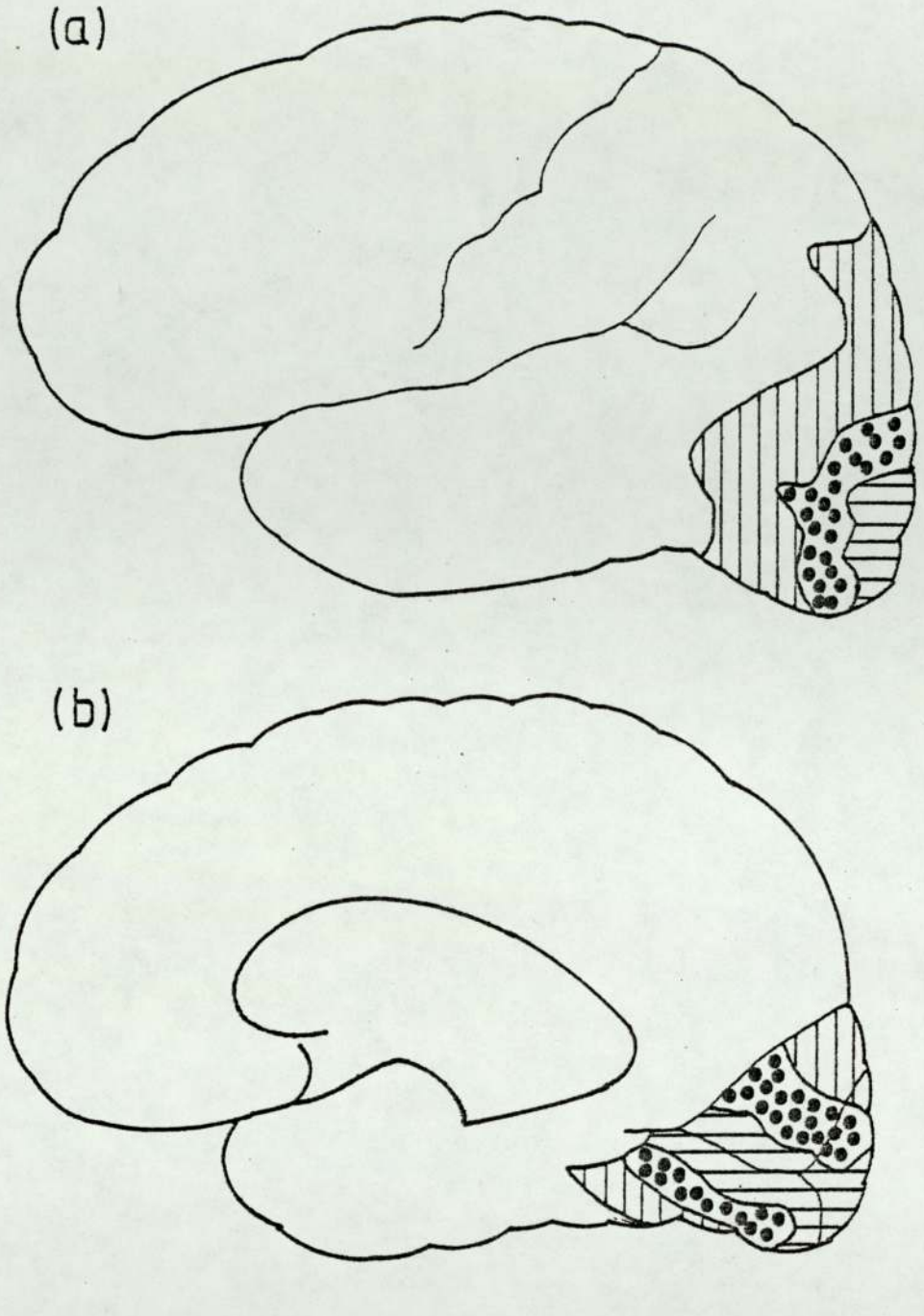
Much of the information available about the representation of the visual hemifield upon the striate cortex in the human has arisen from the analysis of visual field defects following brain injuries (Holmes 1919; Holmes 1945; Spalding 1952) and, more recently, the technique of cortical electrode implantation (Brindley and Lewin 1968; Dobelle, Turkel, Henderson and Evans 1979). Each hemisphere appears to contain a complete representation of the contralateral hemifield and, as found in the cat, the representation is arranged in a systematic fashion. The central area is represented at the occipital pole and the periphery further

Figure 2.9

The Visual Areas of the Human Cortex

The relative positions of areas 17, 18 and 19 are shown from both the lateral aspect (a) and the medial aspect (b).

(After Duke-Elder 1971)


(a)
(b)
= Area 17
= Area 18
= Area 19

anteriorly within the calcarine fissure. The upper field is represented below the fissure, the lower field above. This is illustrated in Figure 2.10. A disproportionate amount of the cortical surface is devoted to the representation of the central area; the central 10 degrees covers approximately one third of the surface (Whitteridge 1973).

Very little is known about the characteristics of single cells in the human cortex. Marg, Adams and Rutkin (1969) have recorded from implanted electrodes and examined a small number of receptive fields. The characteristics of these units seem to correlate quite well with findings in the cat. Many cells were found to be binocularly driven and, therefore, could be activated by stimuli presented to either eye in corresponding positions in the visual field.

2.5 Evidence for misrouting in human albinos

From the previous sections it can be seen that although we know very little about the visual system of the human compared to the cat and that some differences between the two do exist, the pathways have a similar systematic organisation. The contralateral visual hemifield is represented in an orderly fashion in the human LGN and cortex and, therefore, the presence of misrouting in human albinos would have the effect that some parts of the visual field will be represented in the wrong side of the brain.

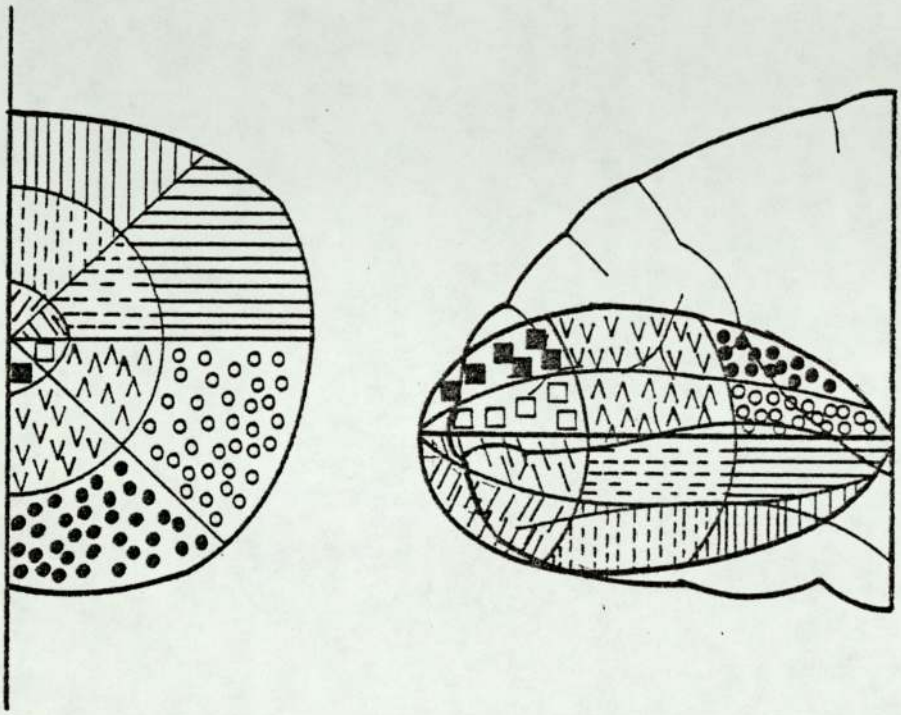
Anatomical evidence of such misrouting occurring in human

Figure 2.10

The Representation of the Visual Field in the Human Visual Cortex

The central part of the visual field is represented at the occipital pole and the periphery further anteriorly within the calcarine fissure. The lower and upper fields are represented above and below the fissure respectively. A disproportionately large area of the cortex is devoted to the representation of the central visual field.

(After Guillery, 1976)



albinos is very sparse. Guillery, Okoro and Witkop (1975) reported findings in a ty-pos albino. The LGN was smaller than usually found and rotated from its normal position. The two-layered segment was larger than normal and there were extensive fusions between parvocellular layers. In addition, the magnocellular layers were very irregular. It was concluded that the retinogeniculate pathway of this individual was abnormal and possible indicative of misrouting. A similar finding was also reported by Creel, King, Witkop and Okoro (1979a).

One method of demonstrating the presence of misrouting, which can be used in both animal and human subjects, is the recording of visually evoked cortical potentials. This method has been used to successfully identify the anomaly in albino rats (Creel, Dustman and Beck 1970); Siamese cat (Creel 1971a and b) and the albino guinea pig (Creel and Giolli 1972).

In both normally pigmented and Siamese cats flash visually evoked cortical potentials recorded over each hemisphere under binocular conditions were found to be similar: strong responses were obtained over each hemisphere. Under monocular conditions, (after unilateral enucleation), the normal cat still showed strong responses over both hemispheres, but the Siamese cat response showed hemispheric asymmetry. Over the hemisphere contralateral to the eye stimulated, high amplitude responses were recorded; over the ipsilateral hemisphere the primary response was diminished. These results, therefore, reflect the reduction in the

number of uncrossed fibres in the Siamese cat.

These results form the basis for identifying misrouting in human albinos. The development of the recording of visual evoked potentials in man will now be discussed.

CHAPTER THREE

3 VISUAL EVOKED POTENTIAL RECORDING IN MAN

This chapter will consider the method of recording visually evoked potentials (VEP) in man. The visually evoked cortical potential (VECP) and the visually evoked sub-cortical potential (VESP) will be described. The concluding section will consider how VEP techniques have been utilised to detect visual pathway misrouting in human albinos.

3.1 Historical background

Recording of the VEP in man developed from the technique of electroencephalography. In 1934, Adrian and Matthews demonstrated that electrical responses, elicited by regularly repeated flashes of light, can be recorded over the occipital cortex in the on-going electroencephalogram (EEG). The clinical use of this response is however, somewhat limited owing to the fact that less than 10% of the normal population show such activity in their EEG (Harding 1982). To be of practical use these responses must be extracted from the raw EEG. To this end, Dawson (1947) developed the method of superimposition whereby several responses are superimposed on a cathode ray oscilloscope. The resulting trace shows a wide baseline caused by the random on-going EEG; any deflections caused by the stimulus and time-locked to it are marked by their appearance or deflection of the baseline at the same point. However, real interest in VEP recording came with the advent of the averaging technique (Dawson 1951). This method operates

on two assumptions: 1) that the evoked potential is time-locked to the stimulus and 2) that the background noise in the EEG is random in nature.

A repetitive stimulus is presented and on each occasion the EEG is stored. Any common features slowly add together to produce a clear evoked response while the background noise slowly cancels out. The smaller the evoked potential and the greater the amplitude of the background EEG, the larger is the number of responses required to clearly define the VEP waveform. Consequently, the VECP is commonly recorded using an average of 50 or more responses but for the smaller amplitude VESP 500 to 700 responses are required.

The resultant VEP waveform is dependent upon the rate at which the stimulus is presented. On this basis two types of response are definable (Mackay and Jeffreys 1973; Regan 1975).

1) The transient VEP: this is polyphasic in waveform and produced by the repetition of the stimulus with an inter-stimulus interval of sufficient duration to allow the brain to settle to a somewhat undisturbed state.

2) The steady-state VEP: this is quite different from the transient response because a rapidly repeated stimulus is used. Initially a transient response is produced but this is successively reinforced resulting in a steady-state waveform that repeats at the same frequency

as the stimulus.

The two techniques are somewhat complementary and although the recording of steady-state potentials may be very rapid, it is the transient type of response which has been widely used in both normative and clinical studies. Therefore, the following sections will, unless otherwise stated, be considering transient VEPs only.

Investigators differ in the electrode sites used to record the VEP and also in the type of electrode linkage. With bipolar montages the potential is measured between two electrodes both assumed to be active. Such linkage may be useful for localising the source of VEP activity (Goff, Matsumiya, Allison and Goff 1969) but may allow the intrusion of artifacts or miss voltage changes that are similar to both electrodes (Vaughan 1966; Kinney 1977). With monopolar montages the potential is measured between an electrode placed over the site of activity (the active electrode) and a remote relatively indifferent electrode (the reference electrode). The latter should be placed in an inactive zone but such a location has not been found although common sites used are the ear or mid-frontal scalp regions. Consequently, to use the term "monopolar" recording is not strictly accurate in this situation; a more precise term is "reference" recording and this terminology will be used in subsequent sections.

The VEP waveform can be measured by different methods. The

latency of a component is usually expressed as the time interval between the onset of the stimulus and the occurrence of the component peak. Occasionally, interpeak latency is used. The amplitude of a component may be expressed using 'peak to peak' or 'peak to baseline' measures. In the former case the amplitude is measured relative to an adjacent, usually preceding, peak of opposite polarity. In the 'peak to baseline' method, a baseline must be determined and the amplitude of a component is measured relative to this baseline.

The interpretation of VEP potential distribution has been simplified by treating the electrical activity of the brain as an equivalent dipole within a uniform volume conductor (Vaughan 1969, 1974, 1982; Wood 1982). The surface potential at a given instant is assumed to approximate to that generated by an equivalent dipole (a small voltage source), although generally it is not single dipoles but sheets which are being considered. The dipoles may be defined in terms of their orientation, the two extremes being the radial and tangential types. Radial dipoles produce only one maximum positive or negative peak on the head. They lie under the site of maximum activity, oriented radially to the surface of the scalp. Tangential dipoles produce one positive and one negative peak on the head. These are separated by some distance but are of approximately equal amplitude with polarity reversal occurring at the mid-point. These dipoles are orientated tangentially to the scalp surface.

This equivalent dipole concept is now used to aid interpretation of scalp recorded VEPs.

The VEP has been recorded using a variety of evoking stimuli. Broadly speaking, they fall into one of two groups; luminance and pattern. The waveforms obtained under these different conditions will now be considered. Comparison of the VEPs obtained by different investigators is often very difficult. Varying types of averaging equipment have been used and, in addition, as seen in the previous discussion, studies differ in 1) site of electrodes 2) montage used: bipolar/monopolar and, in the latter case, the choice of reference 3) method of measurement of the resultant VEP 4) choice of stimulus: luminance/pattern. Within these categories variations in the actual stimulus parameters often occur. In the case of luminance, features that may be manipulated include intensity, colour, duration and rate of presentation. With patterned stimuli, in addition to the previous features, variations can occur in the choice of patterns used, size of the individual pattern units, total field size of pattern and the contrast between the pattern elements.

Therefore, the description of a typical, stereotyped VEP is difficult but the following section will attempt to show the waveforms generally accepted to be produced using different stimuli under controlled conditions. However, in all cases it must be remembered that manipulation of any of the previously described conditions may

alter the response.

Initially, the VEPs obtained in control subjects will be considered. These are subjects with normal V.A. ($^{6}/_{6}$ or better) and no known ophthalmological or neurological defects. The responses will also be considered with particular reference to how they may be altered in albinos. Consequently, the hemispheric contributions to binocular, monocular and, where appropriate, right-left half-field stimulation will be compared. As described in Chapter 1, albinism is usually accompanied by reduced VA and nystagmus. Therefore, the possible effects that these features may have on the VEP will be considered. The differences between the evoked responses of the two sexes will be described because albinism occurs in both males and females. In addition, because albinism is present in subjects of all ages, the changes occurring in the VEP simply due to changes in age will be considered.

3.2 The Luminance VECP

3.2.1 Introduction

Much of the early work on the human VECP utilised a bright flash filling the entire visual field as the stimulus. Other methods of luminance stimulation have been developed including sine-wave modulated light and Gaussion-noise-modulated light (Tweel and Verduyn Lunel 1965; Regan 1966; Tweel 1977; Spekreijse, Estevez and Reits 1977) and investigators have used Maxwellian

viewing systems (Armington 1964; Shipley, Jones and Fry 1966; Devoe, Ripps and Vaughan 1968) or very small flash stimuli in an attempt to record the VECP from localised retinal areas (Potts and Nagaya 1965; Eason, Oden and White 1967; Schreimemachers and Henkes 1968). However, the majority of luminance VECPs, particularly in clinical situations, have been recorded using a diffuse flash produced by a photostimulator situated a short distance from the subject so that the entire field is stimulated. This 'flash VECP' will now be considered in more detail.

3.2.2 The flash VECP waveform

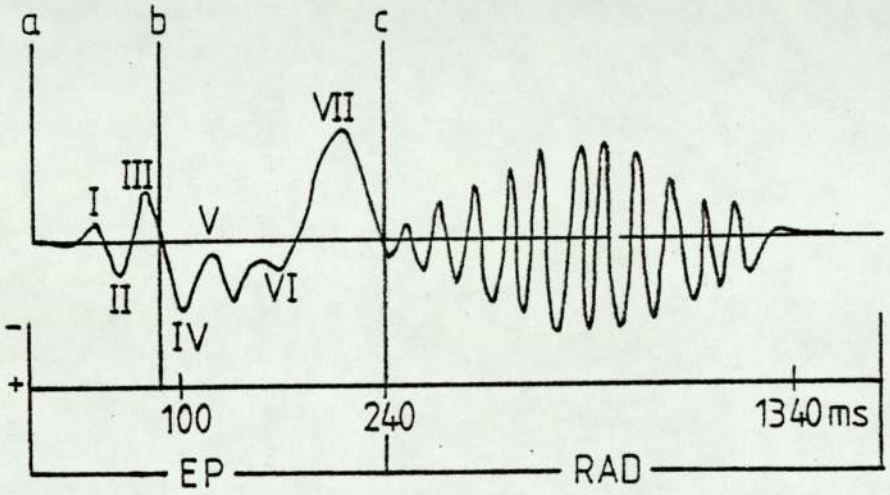
Bipolar montages were frequently used during early studies (Balen and Henkes 1960; Cobb and Dawson 1960) and a complete description of the VECP recorded with this electrode linkage was given by Ciganek (1961). A typical response recorded under these conditions is illustrated in Figure 3.1. The resulting waveform is divided into two constituents: a primary response occurring between 0 to 90ms (waves I-III) and a secondary response from 90 to 240ms (waves IV-VII). A rhythmic after-discharge completes the response. Ciganek (1961) considered the primary response to be specifically evoked by area 17 but the secondary response to be produced by more diffuse, non-specific pathways. The rhythmic after-discharge has been related to the on-going alpha activity in the EEG (Dustman and Beck 1963; Spehlmann 1965; Oosterhuis, Ponsen, Jonkman and Magnus 1969).

FIGURE 3.1

A typical flash visually evoked cortical potential obtained by bipolar recording in control subjects

The main peaks are labelled I-VII. The primary and secondary responses constituting the evoked potential and the rhythmic after-discharge are indicated

(After Ciganek 1961)



ab = Primary response
bc = Secondary response

EP = Evoked potential
RAD = Rhythmic after discharge

Although doubt was initially expressed concerning the existence of a standard VECP recorded from control subjects (Werre and Smith 1964) many investigators do believe that such a response is definable (Vaughan 1966; Ciganek 1969; Harding 1982). A typical response recorded using the reference method is illustrated in Figure 3.2 (Spehlmann 1965; Dustman and Beck 1966; Harding 1974; Borda 1977). The response is labelled by sequential designation of the peaks. Each peak is labelled with regard to its polarity (P-positive; N-negative) and its numerical position in the sequence.

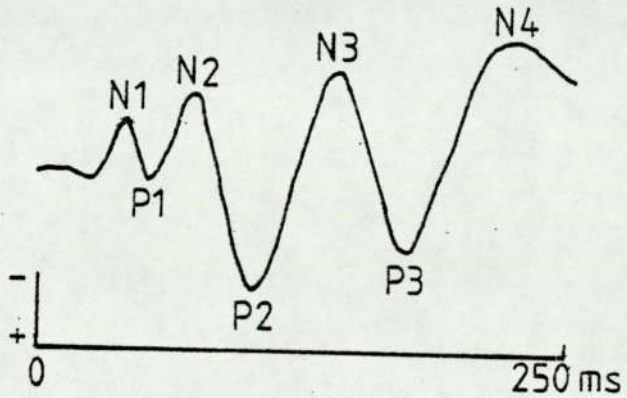
The most consistent and largest component is usually a positive wave (P2) at 80-120ms latency (Spehlmann 1965; Dustman and Beck 1965; Rietveld, Tordoir, Hagenouw, Lubbers and Spoor 1967; Rhodes, Dustman and Beck 1967; Harding 1974). The early components of the response (between 0 to 300ms) are reliable and stable in a subject over a period of time (Dustman and Beck 1963) and it is this part of the response which is usually used to define the VECP waveform; particularly, the latency of the P2 component and its amplitude measured from the peak of the preceding negative (N2) component. Differences between subjects may occur in the part of the response occurring after 300ms (Dustman and Beck 1963; Spehlmann 1965) and this is a further reason why the initial waves are usually the only ones considered. Of the two measures, latency and amplitude, it is the latter which shows the greater variability both within and between subjects

FIGURE 3.2

A typical flash visually evoked cortical potential obtained by reference recording in control subjects

The peaks are sequentially designated according to polarity. The major positive component, P2, is found to occur between 100-120ms and its amplitude is usually measured relative to the peak of the preceding N2 component.

(After Harding 1974)


N1
N2
N3
N4
P1
P2
P3
−
+
0
250 ms

(Schreinemachers and Henkes 1968; Vaughan 1966, 1969; Lewis, Dustman and Beck 1972; Aunon and Cantor 1977).

The recorded flash response is not a result of current spread from the electroretinogram (ERG) or from other artifacts (Cobb and Dawson 1960; Katzman 1964; Goff et al. 1969) and that it originates from the cortex has been confirmed by the comparison of recordings obtained from both the scalp and the cortex (Katzman 1964; Rayport, Vaughan and Rosengart 1964).

The early part of the response is best recorded from electrodes placed over the occiputs (Cobb and Dawson 1960; Vaughan, Katzman and Taylor 1963; Spehlmann 1965; Gastaut, Regis, Lyagoubis, Man and Simon 1967; Goff et al. 1969; Vaughan 1969). This region receives its major projection from the central region of the visual field and it is therefore believed that the flash VECP primarily reflects activity of the central retina (Vaughan and Katzman 1964; Vaughan 1966; Riggs 1969; Nakamura and Biersdorf 1971). This activity may be represented by radially located dipoles located at the occipital pole (Vaughan 1969; Vance and Jones 1980).

The binocular VECP tends to have a larger amplitude than the monocular response although the amount of addition varies greatly between subjects (Bartlett, Eason and White 1968; Perry, Childers and McCoy 1968; Ciganek 1970; Borda 1977). The binocular response is also said to have

a shorter latency than the monocular responses (Borda 1977). When recordings are made over each hemisphere in control subjects, the two monocular responses tend to be very similar although hemispheric asymmetries and asynchronies are quite common under both binocular and monocular conditions. It has been reported that with monocular stimulation the contralateral hemisphere shows the greater response (Vaughan and Katzman 1964; Jacobson, Hirose and Suzuki 1968), although some believe this to be only significant in very young babies (Groth, Weled and Batkin 1970). The limits of hemispheric asymmetry and asynchrony in control subjects are usually accepted to be 50% and 6ms respectively (Vaughan et al. 1963; Vaughan and Katzman 1964; Kooi, Guvener and Bagchi 1965; Oosterhuis et al. 1969; Harmony, Ricardo, Otero, Fernandez, Llorente and Valdes 1973). Any such asymmetries or asynchronies are stable and if any waves are absent over one hemisphere compared to the other, it is usually limited to the very early components (Harmony et al. 1973).

3.2.3 The flash VECP. Effects of visual acuity and nystagmus

The flash VECP is unaffected by the refractive state of the subject; induced refractive errors in control subjects do not alter the latency or amplitude of the response (Spehlmann 1965; Dustman and Beck 1969; Dustman, Schenkenberg, Lewis and Beck 1977; Harding 1982). The normal flash stimulus fills the entire visual field and

therefore it is unlikely that small changes in eye position during recording will affect the response; light entering the eye at any angle will be scattered providing adequate stimulation. Indeed, flash VECPs have been recorded successfully in subjects with simple congenital nystagmus in the absence of albinism (Meienberg, Hemphill, Rosenberg and Hoyt 1980).

3.2.4 The flash VECP. Effects of age and sex

The flash VECP can be recorded early in life. The waveform tends to be more simple than that found in adults and it shows great fatiguibility (Ellingson 1960; Hrbek and Mares 1964). The response may be very variable particularly with regard to amplitude (Ellingson 1966; Hrbek and Mares 1964; Groth et al. 1973; Marcus 1977). The first major wave seen is a positive component peaking at around 185ms (Hrbek and Mares 1964; Ellingson 1966; Ferris, Davis, Dorsen and Hackett 1967; Ellingson, Lathrop, Danahy and Nelson 1973; Harden 1982; Vries-Khoe and Spekreijse 1982). Later other waves appear resulting in a more complex response (Ferris et al. 1967; Harden 1982) and gradually the latency of the major positive component reduces (Ellingson 1960, 1966; Ferris et al. 1967; Marcus 1977; Harden 1982). Hence, the waveform begins to resemble that found in the adult although differences are still present until about two years of of age (Vries-Khoe and Spekreijse 1982).

Even when the adult type response is established, changes in waveform do occur with age. The amplitude of early components increases from infancy to about seven years of age and subsequently reduces until thirteen years. An abrupt increase in the amplitude of all components follows with stabilisation at about sixteen years (Dustman and Beck 1966, 1969; Dustman et al. 1977). The amplitude then remains fairly stable throughout adult life up to about sixty years of age, after which the early components (particularly P1) again increase while the later waves may or may not reduce (Dustman and Beck 1966, 1969; Harding 1974; Cose, Vitelli, Gozzoli, Corona, Ceroni and Calliecor 1982; Harding 1982) although all these changes seem to gradually begin in middle age (Schenkenberg, Dustman and Beck 1971; Dustman et al. 1977). These changes in response amplitude are also somewhat linked to the sex of the subject considered. In childhood, males show larger amplitude components than females but the reverse is thought to be true after puberty (Schenkenberg et al. 1971; Dustman et al. 1977). The latencies of the components are, as previously discussed, longer in infancy but, having reached adult values, remain stable until middle age when they begin to increase (Dustman and Beck 1969; Dustman et al. 1977).

3.3 The Pattern VECPs

3.3.1 The patterned flash VECP

Following the successful recording of VECPs to changes in

luminance alone, attempts were made to evoke responses using patterned stimuli.

Spehlmann (1965) originally recorded the VECP with a flash stimulus illuminating a checkerboard of alternating black and white squares. Although other pattern types have been tried: gratings (Rietveld et al. 1967; White 1967); radial lines or concentric circles (White 1969) and polka dots (Harter 1971) it was checkerboards that were most widely used and it appears that it is the presence of acute or right-angles that is important for evoking the response (Rietveld et al. 1967).

This patterned flash response shows a negative peak at around 100ms, a positive at 180-250ms and an after-discharge (Spehlmann 1965; Rietveld et al. 1967; Harter and White 1968, 1970; White 1969; Harter 1970). The amplitude of the response is dependent upon the check size used and is said to be maximal with checks between 10-20' arc in size; both larger and smaller elements cause an amplitude reduction (Rietveld et al. 1967; White 1969; Harter and White 1970; Harter 1970).

A major difference between patterned flash and pure flash responsesis that the former is affected by the refractive state (and hence V.A.) of the subject. Induced refractive errors in control subjects cause the amplitude of the response to reduce (Spehlmann 1965; Harter and White 1968; White 1969) although this effect is dependent

upon the check size used. The larger the checks the less is the response affected by lenses (Harter and White 1970).

Both Spehlmann (1965) and Harter (1970) believed that the major part of the patterned flash response is generated by the central area of the retina.

3.3.2 Other forms of patterned stimulation

The use of patterned flash stimuli advanced the technique of VECP recording but this type of stimulus is not ideal. The presentation of the pattern is accompanied by a change in luminance and, therefore, the resulting response is likely to consist of a combination of the responses to both the pattern and the change in luminance. Because of this problem methods have been devised whereby a patterned stimulus may be presented with the total amount of light falling on the eye remaining constant. Two main forms of pattern presentation have been developed:

1) pattern reversal - the stimulus, for example a black and white checkerboard, is presented such that bright and dark elements interchange rhythmically. Therefore, both sets of checks have the same mean intensity.

2) pattern appearance-disappearance - the stimulus, again for example a checkerboard, is presented and then disappears to leave a blank field. The intensities of the two sets of checks are equal during half the stimulus period.

The responses to both pattern reversal stimuli (Armington, Corwin and Marsetta 1971; Ristanovic and Hajdukovic 1981) and pattern appearance-disappearance stimuli (Spekreijse, Tweel and Zuidema 1973; James and Jeffreys 1975; Jeffreys 1977; Smith and Jeffreys 1978) have been found to be greater using alternate black and white checks rather than stripes. Therefore, only the responses to the former, most commonly used in studies, will be considered further.

In control subjects such pattern responses are believed to be optimum using check sizes of between 10-20' arc (Spekreijse 1966; Regan and Richards 1971; Spekreijse and Estevez-Uscanga 1972; Spekreijse et al. 1973; Spekreijse 1980) although often larger checks in the region of 40-70' arc are used in both clinical and normative studies.

These pattern responses are thought to be larger than the flash responses of many subjects and are generally believed to be more reliable (Tweel 1977). The stimuli have the advantage that discrete parts of the visual field can be stimulated without the problem of stray light encountered when this is attempted with flashed stimuli (Harding, Smith and Smith 1980). Consequently, the following sections will involve a description of the responses obtained with half-field stimulation, particularly applied to right-left field stimulation and not the vertical half-fields. The topographical scalp distribution of both the full-field and half-field responses is often analysed during the recording of these type of patterned VECPs

using transverse and longitudinal rows of occipital electrodes.

3.4 The Pattern Reversal VECP

3.4.1 Waveform

Using reference recording, the pattern reversal VECP of control subjects is dominated by a positive (P) deflection with a peak latency of around 100ms (P100) both preceded and followed by negative deflections (Halliday and Michael 1970). The typical waveform recorded under such conditions is shown in Figure 3.3. The response is usually described on the basis of the latency of the P100 component and its amplitude measured from the peak of the preceding negative wave. Comparable to that found with flash stimuli, the latency of P100 is a less variable measure than its amplitude (Michael and Halliday 1971). The P100 component is believed to result from stimulation of the central retina (Blumhardt, Barrett, Halliday and Kriss 1978; Halliday, Barrett, Blumhardt and Kriss 1979). The response is thought to be of extrastriate (area 18 and/or 19) origin reflecting the activity of a surface positive dipole source (Halliday and Michael 1970; Michael and Halliday 1971).

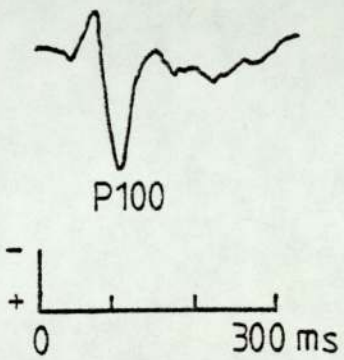
In control subjects the monocular full-field responses are usually fairly symmetrically distributed over the two cortical hemispheres with the maximum P100 amplitude usually occurring at the midline (Blumhardt and Halliday 1979;

FIGURE 3.3

A typical pattern reversal visually evoked cortical potential obtained by reference recording in control subjects

The response can be seen to be dominated by a positive component of 100ms latency (P100)

(After Kriss and Halliday 1980)


P100
−
+
0
300 ms

Onofrj, Bodis-Wollner and Mylin 1982; Kriss, Carroll, Blumhardt and Halliday 1982). Both the amplitude and latency of the P100 component tend to be similar whichever eye is stimulated (Celesia and Daly 1977; Kriss et al. 1982) and although hemispheric asymmetries and asynchronies are found, these tend to be similar whichever eye is stimulated with no preference for either hemisphere (Blumhardt, Barrett and Halliday 1977; Kuroiwa and Celesia 1977; Streletz, Bae, Roeshman, Schatz and Savino 1981).

Although half-field responses can be recorded using pattern reversal stimuli, the scalp topography of the resulting potential is not easily predicted on the basis of anatomical considerations. One would expect that selective half-field stimulation should result in lateralisation of the response over the contralateral hemisphere. Using occipital bipolar montages this is indeed the case (Cobb and Morton 1970; Shagass, Amadeo and Roemer 1976; Barrett, Blumhardt, Halliday, Halliday and Kriss 1976b) but with the more usual reference recording, the response is often characterised by a maximal P100 amplitude over the ipsilateral hemisphere (Barrett, Blumhardt, Halliday, Halliday and Kriss 1976a and b; Shagass et al. 1976). This 'paradoxical lateralisation' has been found to occur consistently in control subjects such that the maximum response is recorded by midline and ipsilaterally placed electrodes (Barrett et al. 1976a and b) and has been confirmed by other groups of investigators (Harding et al. 1980; Lith, Henkes and Vijfvinkel-Bruinenga 1980; Onofrj et al. 1982). The

response recorded over the contralateral hemisphere is somewhat variable (Barrett et al. 1976b; Blumhardt et al. 1977) but often shows components of opposite polarity to those recorded ipsilaterally (Blumhardt et al. 1978). It is thought that this lateralisation is due to the fact that the cortical generators responsible are largely situated on the medial and posterio-medial surfaces of the cortex where the neurons are transversely oriented. In this situation, the electrodes on one side of the head are best placed to record potentials arising from the medial surface of the opposite lobe (Barrett et al. 1976a and b). Other explanations, such as callosal transfer have been put forward (Beauchamp, Matthews, Small and Stein 1976) but it has been shown, using both patients and dipole localisation methods, that the response recorded from the ipsilateral hemisphere is generated in the contralateral hemisphere (Blumhardt et al. 1977; Blumhardt and Halliday 1979; Wood 1982).

However, the degree of ipsilateral lateralisation does seem somewhat dependent on the electrode sites and stimulus parameters, particularly the field size used. Barrett et al. (1976b) found that with very small fields the response is less well lateralised and may even show a contralateral predominance. Later Harding et al. (1980) and Holder (1980) confirmed that with small sized fields contralateral lateralisation can be obtained using reference recording and widely spaced occipital electrodes. This is probably because the generators responsible for these small field

responses are situated at the occipital pole and therefore more radially oriented and point more directly towards the overlying scalp electrodes. A discussion of this problem can be found in Halliday, Holder and Harding (1980).

3.4.2 The pattern reversal VECP. Effects of visual acuity and nystagmus

As found with patterned flash VECPs, the pattern reversal response is sensitive to accurate focusing of the pattern. Induced refractive errors in control subjects cause a reduction in the amplitude (Collins, Carroll, Black and Walsh 1979) and an increase in the latency (Collins et al. 1979; Harding 1982) of the P100 component. Similar changes can be found with voluntary defocusing and inaccurate fixation (Uren, Stewart and Crosby 1979). Eye movements during recording can produce an amplitude reduction or abnormally shaped response (Uren et al. 1979) and, indeed, congenital nystagmus, without albinism, produces abnormal pattern reversal responses (Creel et al. 1981a).

3.4.3 The pattern reversal VECP. Effects of age and sex

The amplitude of the P100 component is greatest in childhood (Shaw and Cant 1981) but gradually reduces up to teenage with, thereafter, very little change with age (Celesia and Daly 1977; Snyder, Dustman and Shearer 1981; Halliday, Barrett, Carroll and Kriss 1982). The latency

of P100 increases with age (Celesia and Daly 1977; Stockard, Hughes and Sharborough 1979; Halliday et al. 1982) beginning at about twenty years of age (Snyder et al. 1981; Sokol, Moskowitz and Towle 1981) although this effect seems dependent on the check size used (Sokol et al. 1981).

In childhood, females tend to show a larger P100 component than males (Snyder et al. 1981). After this some report no effect of sex on amplitude (Celesia and Daly 1977; Snyder et al. 1981) while others believe that in adulthood, females show the greater response (Shaw and Cant 1981; Halliday et al. 1982). In the adult years females are believed to possess shorter P100 latencies than males (Stockard et al. 1979; Halliday et al. 1982).

3.5 The pattern appearance-disappearance VECP

3.5.1 Waveform

A checkerboard stimulus appearing for a short duration of time (such as 25ms) evokes a response using reference recording consisting of three components. These are; a positive component peaking at 65-80ms; a prominent negative wave at 90-120ms and a later, positive wave at 160-180ms (Jeffreys 1970; Jeffreys and Axford 1972a and b). These components have been called CI, CII and CIII respectively and are believed to be mainly due to the appearance of the pattern (Jeffreys 1970; Jeffreys and Axford 1972a; Spekreijse and Estevez-Uscanga 1972). If

the pattern is presented for a longer period of time (at least 100ms) a response to the disappearance of the pattern can also be seen. This consists of a sharp positive deflection followed by a decay (Spekreijse and Estevez-Uscanga 1972). This late positive wave has become known as the 'OFF' response. A typical pattern appearance-disappearance VECP found in control subjects under such conditions is shown in Figure 3.4.

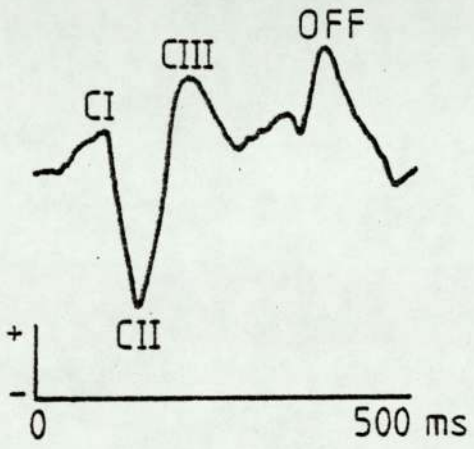
It has been postulated that CI originates from the striate cortex (area 17) located mainly on the medial surface of the occipital lobes in and around the calcarine fissure, while CII originates from the extrastriate cortex (areas 18 and/or 19) mainly on the external surfaces of the occipital lobes, both being a reflection of the activity of a basically surface negative dipole source (Jeffreys 1970; Jeffreys and Axford 1972a and b). However, other sites of origin have been proposed (Lesevre and Joseph 1980; Drasdo 1980; Lesevre 1982). CIII is also thought to be of extrastriate origin but from a different site to that producing CII (Jeffreys 1977). The 'OFF' response is thought to be identical to the P100 component of the pattern reversal response and possibly of extrastriate origin (Estevez and Spekreijse 1974; Kriss and Halliday 1980). CII is thought to be mainly foveal in origin with CI containing little contribution from the central retina (Jeffreys and Axford 1972a and b; Spekreijse et al. 1977). CI is believed to be a contrast specific component but CII and CIII are thought to be more contour specific

FIGURE 3.4

A typical pattern appearance-disappearance visually evoked cortical potential obtained by reference recording in control subjects

The response is dominated by a negative (CII) component. CI and CIII precede and follow this peak respectively. The response is completed by a positive-going OFF response

(After Spekreijse and Estevez-Uscanga 1972)


OFF
CIII
CI
CII
+
-
0
500 ms

(James and Jeffreys 1975; Jeffreys 1977; Spekreijse et al. 1977).

Binocular and monocular stimulation produce VECPs of similar form and magnitude. CI may have a slightly greater amplitude binocularly and CII and CIII a slight increase in latency under monocular conditions (Jeffreys and Axford 1972b, Jeffreys 1977).

Although the topographic distribution of the components over the scalp can differ between subjects, half-field stimulation has been found to produce systematic changes in the distribution. CII does not seem to lateralise over the scalp (Jeffreys and Axford 1972a; Lesevre and Joseph 1980; Lesevre 1982) but CI does lateralise over the contralateral hemisphere with a reversal of polarity at the midline (Jeffreys and Axford 1972a; Shagass et al. 1976; Jeffreys 1977; Kriss and Halliday 1980; Drasdo 1980). In accordance with the 'OFF' response being identical to the pattern reversal P100 component, the former lateralises over the ipsilateral hemisphere (Kriss and Halliday 1980). With half-field stimulation, the amplitudes of the two half-field responses are very similar and some authors believe that the pattern appearance-disappearance VECP lateralises more clearly over the scalp than the pattern reversal response (Shagass et al. 1976).

3.5.2 The pattern appearance-disappearance VECP. Effects of visual acuity and nystagmus

Induced refractive errors in control subjects cause a reduction in the amplitude of CII and CIII (Jeffreys 1977; Chelva and Lith 1982). As CII is contour specific it is thought to be particularly sensitive to defocusing. A ¼ dioptre miscorrection is said to halve the amplitude of this component (Spekreijse 1980) and similarly, defocusing lenses increase its latency (Harding 1982). CI is more resistant to defocusing such that stronger defocusing lenses are needed to produce a similar amplitude reduction to that obtained with lower powered lenses when considering components CII and CIII (Jeffreys 1977).

3.5.3 The pattern appearance-disappearance VECP. Effects of age and sex

The pattern appearance-disappearance VECP in infants consists of a single, large amplitude, positive component of peak latency 150-190ms (Spekreijse 1978). Gradually, the amplitude and latency of this wave reduce and the response becomes more sharply defined (Spekreijse 1978). The positive component, thought to be CI, which occurs in isolation in infants suggests that they lack the foveal contrast mechanism (Vries-Khoe and Spekreijse 1982). This simple type of waveform continues until about four years of age after which a negative, CII, component gradually develops and thereafter begins to dominate the

response (Spekreijse 1978; Vries-Khoe and Spekreijse 1982). However, it is not until puberty that the typical adult-type waveform is acquired (Spekreijse 1978; Vries-Khoe and Spekreijse 1982).

3.6 Summary

The previous Sections have described the major type of VECPs recorded in experimental and clinical situations. In the former studies pattern VECPs (in particular those to pattern reversal and pattern appearance-disappearance stimuli) are undoubtedly advantageous. Their stimulus parameters can be manipulated, recordings can be made from discrete portions of the visual field and arrays of occipital electrodes allow the distribution of the response over the scalp to be investigated. Pattern reversal and pattern appearance-disappearance stimuli are both used widely and are favoured by different investigators although it must be remembered that they do not give complementary information (Creel et al. 1981a and b). The main disadvantages of pattern VECPs are that during their recording they require subject co-operation and the wearing of any refractive error correction. These factors often preclude their use in such subjects as the demented, infants, comatose patients, malingerers and those who cannot or will not co-operate for any reason. In these circumstances a more robust test, such as that provided by the flash VECP, is desirable (Vaughan and Katzman 1964; Bianchi and Lauri 1974; Borda 1977; Harding 1974, 1980, 1982).

Although the flash VECP may show greater inter-individual variability than that obtained using either pattern reversal or pattern appearance-disappearance this can be overcome in clinical situations. By using the patient as his own control one can compare the responses from the two eyes (Jacobson et al. 1968; Schreinemachers and Henkes 1968; Thompson and Harding 1978; Bianchi and Lauri 1974; Borda 1977) or the two hemispheres (Jacobson et al. 1968; Oosterhuis et al. 1969; Borda 1977).

In conclusion, the development of VECP recording has provided us with a technique of investigating the visual system of man. Different stimuli may be used to evoke the responses and the limitations of each method must be considered. By careful selection of the appropriate stimulus, maximum information can be obtained appropriate to the condition under investigation.

3.7 The Visually Evoked Subcortical Potential

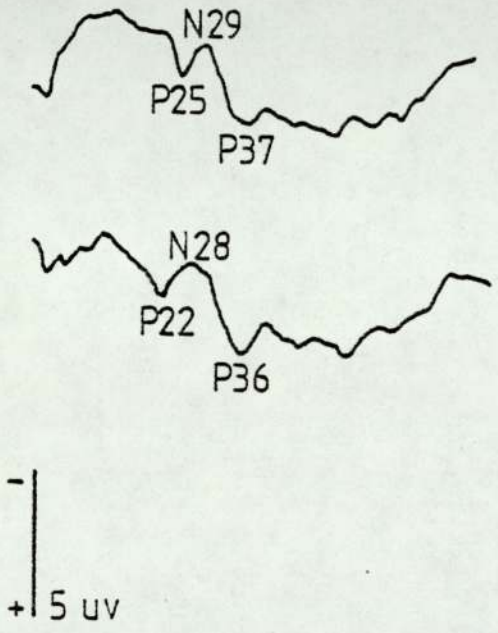
Early components of the human VEP have undergone little investigation probably because of their minute amplitude, intersubject variability and poor repeatability. However, Harding and Rubinstein (1980a) described a small amplitude, short latency, triphasic wave recorded using high intensity flash stimuli in conjunction with a large number of averages (usually 500-700). This early component they called the visually evoked subcortical potential (VESP) and is illustrated in Figure 3.5.

FIGURE 3.5

The typical visually evoked subcortical potential recorded in control subjects

The response is a small amplitude, triphasic, positive-negative-positive wave of short latency.

(After Rubinstein and Harding 1981)


N29
P25
P37
N28
P22
P36
-
+
5 uv

The response is best recorded from electrodes situated at a high mastoid position referred to the vertex and is present in 96% of control subjects (Harding and Rubinstein 1982). The VESP is present bilaterally on both binocular and monocular stimulation and is seen as a positive-negative-positive complex of latencies 20-23ms, 26-28ms and 34 ms respectively, but of very small, 1-2uV amplitude (Harding and Rubinstein 1980a, 1981). During monocular stimulation the VESP undergoes a bilateral reduction in amplitude (Harding and Rubinstein 1980, 1981).

Work on both control subjects and patients with known lesions suggests that the VESP is independent of the ERG, optic nerve and visual cortex, but is post chiasmal in origin (Harding and Rubinstein 1980b, 1981, 1982; Rubinstein and Harding 1981). Its most likely origin is, therefore, either the thalamus or optic radiation, the obvious site being the LGN (Harding and Rubinstein 1980a).

The VESP shows good repeatability in subjects (Harding and Rubinstein 1980b, 1981), and as found with most VECPs, the latency of the components, particularly that of the late positive, is a more reliable measure than the response amplitude (Harding and Rubinstein 1980b, 1981, 1982).

To date VESPs have generally been elicited using flash stimuli and, under these conditions, it is unlikely that induced refractive errors or the presence of nystagmus

alter the response.

The work so far described has used a young adult population in which males and females show similar VESP latencies (Harding and Rubinstein 1981, 1982). Little work has concentrated on the effect of age on the response but preliminary studies suggest that significant alterations do not occur (Rubinstein 1981).

The VESP thus provides a new tool for investigating the human visual pathway providing additional information to that obtained from the VECP. The use of flash stimuli enable it to be used on a similar wide range of subjects to that that can be studied using the flash VECP.

3.8 The VECP in human albinos

The recording of the scalp VECP has provided successful in identifying optic nerve fibre misrouting in human albinos similar to that seen in albino animals. Different evoking stimuli have been used with varying degrees of success.

The flash VECP was first used to study oculocutaneous albinos (Creel et al. 1974) and later ocular albinos (Creel, O'Donnell and King 1978). In both cases, binocular responses showed the same hemisphere symmetry seen in normally-pigmented control subjects. However, monocular stimulation revealed significant hemispheric asymmetries in 70% of albinos which was not seen in normal, control

subjects. This asymmetry, of similar severity in oculo-cutaneous and ocular albinos (Creel et al. 1978), was characterised by the absence, attenuation or reversal in polarity of one or more VECP components over the hemisphere ipsilateral to the eye stimulated. These waveform changes were usually seen in the components occurring in the first 125ms of the response (Creel et al. 1974; 1978) while the later components were little affected (Creel 1979). Typical results are shown in Figure 3.6. These hemispheric asymmetries seen on monocular stimulation were thought to be greater than those seen in normal subjects with one eye enucleated (Creel et al. 1974; Creel 1979; Creel, King, Witkop and Okoro 1979a) and often as severe as those seen in patients with a hemianopia or a localised unilateral scotoma affecting 20 degrees of the horizontal visual field (Creel et al. 1974; Creel 1979; Creel, O'Donnell, King and Witkop 1979b).

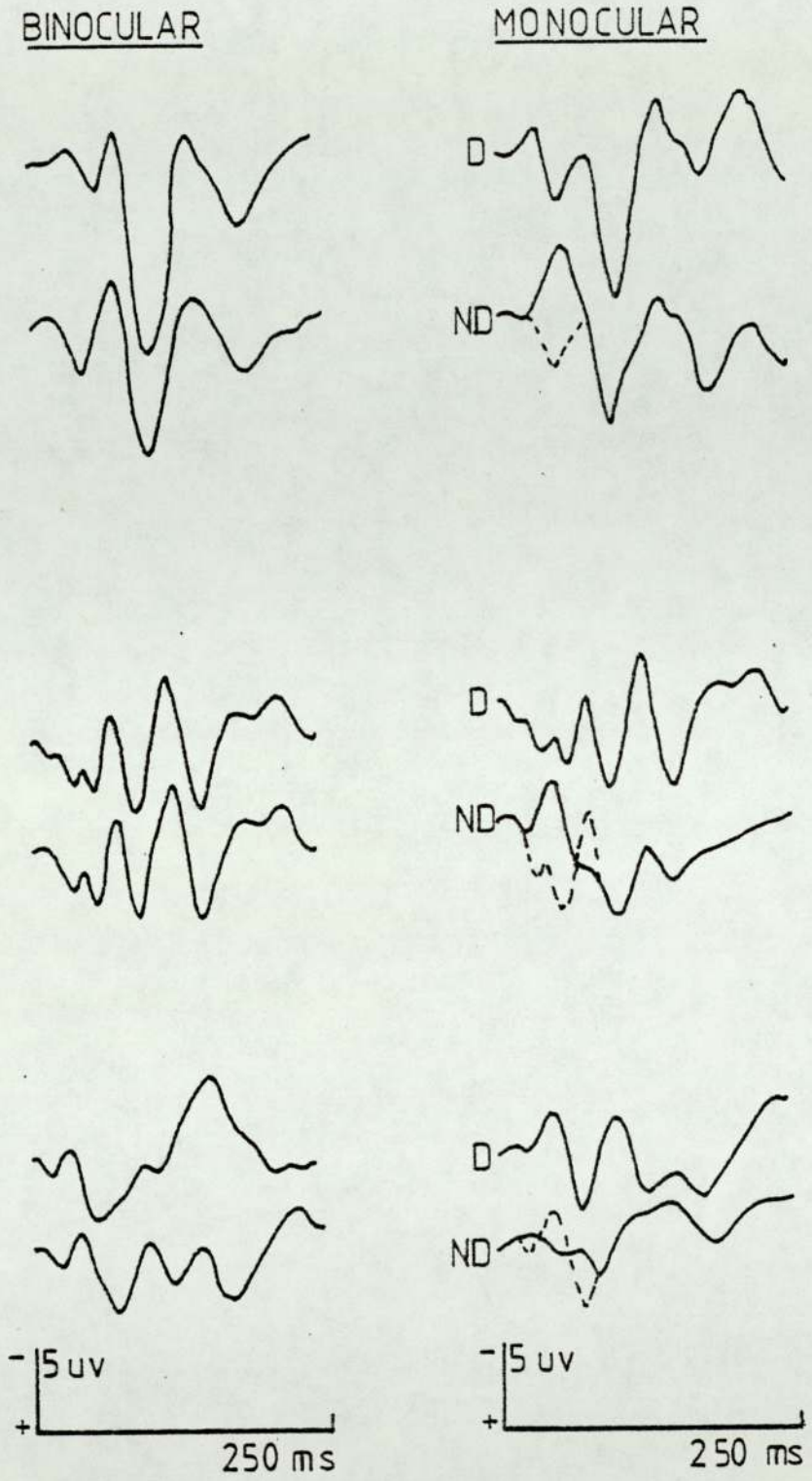
The critical feature distinguishing the albinos from normal control subjects is the change in the VECP symmetry seen when moving from binocular to monocular stimulation and, indeed, binocular responses may show asymmetry in albino subjects but this can become symmetrical on monocular stimulation (Creel 1979). It was found that the changes in the VECP waveform on monocular stimulation could be different depending on the eye used. Stimulation of one eye may greatly disrupt the response while the potential recorded from the other eye may be minimally affected.

FIGURE 3.6

The flash visually evoked cortical potential in human albinos

The binocular and a single monocular response, recorded from both hemispheres (O1-A1 and O2-A2) of three albinos are shown. Response D represents that of the hemisphere receiving decussated optic nerve fibres and ND that receiving non-decussated fibres. Components missing from the ND evoked potential are indicated by the dotted lines

(After Creel et al.1974)


BINOCULAR
MONOCULAR
D
ND
D
ND
D
ND
- 5 uv
+
250 ms
- 5 uv
+
250 ms

Similar results in oculocutaneous albinos using flash stimuli were reported by Taylor (1978). Again monocular responses showed delay or attenuation over the hemisphere ipsilateral to the eye stimulation, but this author considered these monocular changes to be an inconsistent feature in albino subjects.

Therefore, the flash VECP seemed to prove successful in identifying misrouting in 70% of human albinos. In order to try and improve this success and further investigate the misrouting, pattern responses were used.

Patterned flash stimuli have been used in a small number of studies. Creel (1979) reported patterned flash to produce similar results to pure flash while Creel et al. (1979a) believed flash to be a superior stimulus in the identification of misrouting than patterned flash using 15' checks. Coleman et al. (1979) used patterned flash using 14' checks in oculocutaneous and ocular albinos and reported similar monocular hemispheric asymmetries to those obtained with flash. On binocular stimulation albinos showed no significant asymmetries while on monocular stimulation approximately 77% of albinos showed larger response amplitudes over the hemisphere contralateral to the eye stimulated. The ipsilateral components were reduced in amplitude, absent or occasionally of reversed polarity. Similar to the results found using flash, the components in the first 125ms were found to be most affected by the hemisphere asymmetry.

These results are illustrated in Figure 3.7. These authors used small sized stimuli, (field size 5^{o}), presented eccentrically in an attempt to determine the site of decussation in the temporal retina of the albino subjects, i.e. the point beyond which the fibres retain their normal ipsilateral projection. Within 15 degrees of the central retinal area, responses showed the contralateral predominance seen on full-field monocular stimulation. Temporal to this area a qualitatively different response was found with a change to ipsilateral lateralisation. Using these eccentric stimuli the results were very variable and outside 45 degrees into the temporal retina, the responses were greatly attenuated. However, the authors did interpret these results as possibly indicative that the misrouted fibres arise in human albinos, as found in Siamese cats, from a patch of the temporal retina about 15 to 20 degrees from fixation; fibres outside this area were thought to have normal ipsilateral projection.

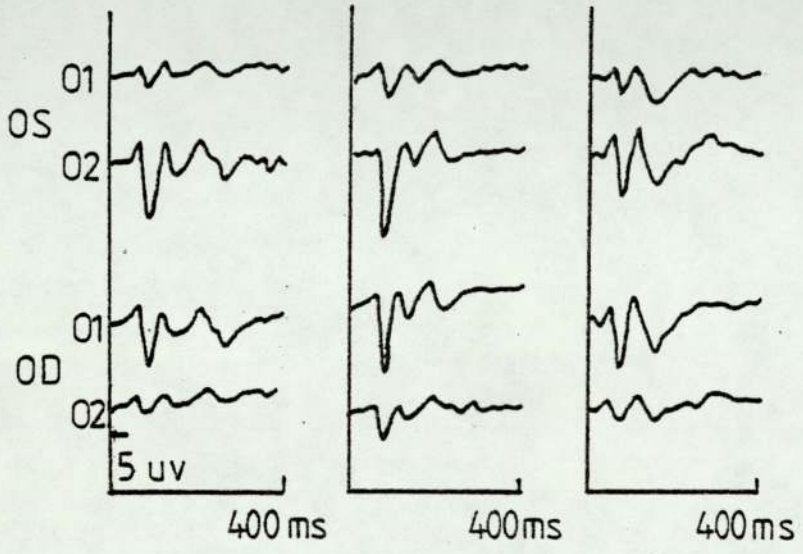
Creel (1979) reported that pattern reversal stimuli produce essentially the same results as flash and patterned flash in albinos. More detailed studies were performed by Carroll, Jay, McDonald and Halliday (1980a) and Jay and Carroll (1980). They investigated the cortical topography of the response to 50' checks in both oculocutaneous and ocular albinos. In all albinos studied monocular responses showed hemispheric asymmetries not seen in normal control subjects. However, two different types of results were obtained. In one group of subjects, (Group I), P100 was found to lateralise over the hemisphere

FIGURE 3.7

The patterned flash visually evoked cortical potential in human albinos

The right (OD) and left (OS) eye responses of three albinos are shown. Components are larger over the hemisphere contralateral to the eye stimulated. Field size 10 degrees x 10 degrees, check size 14'. Ear lobe reference

(After Coleman et al.1979)


OS
O1
O2
OD
O1
O2
5 uv
400 ms
400 ms
400 ms

ipsilateral to the eye stimulated but in a second group of subjects, (Group II), P100 was maximal contralaterally (see Figure 3.8). One individual studied showed a mixture of the two responses. Temporal half-field stimulation showed similar scalp distributions to the full-field responses of each subject indicating that the whole field waveform is dominated by the response of the crossed fibres. The latency of the P100 component in albino subjects was found to fall within the normal range but the amplitude was greatly reduced (approximately 1.5uV in albinos, but 14uV in control subjects).

Carroll, Jay, McDonald and Halliday (1980b) extended this work. Again, two groups of albinos (Groups I and II) could be differentiated on the basis of the lateralisation of the full-field monocular response. In Group I temporal half-field stimulation again lateralised ipsilaterally as found in control subjects but Group II showed the opposite lateralisation to normal with P100 maximal contralaterally (see Figure 3.9). Nasal half-field stimulation also produced differences in the responses from the two subject groups. Group I showed little or no P100 on stimulation of this half-field whereas in Group II a nasal half-field response was obtained and had an almost identical distribution to the full-field or temporal field responses (see Figure 3.9).

The discovery of this dichotomy within the pattern reversal responses of albino subjects was interpreted by

FIGURE 3.8

The full-field pattern reversal visually evoked cortical potential in human albinos

The left eye responses are shown. (a) shows the grand average of 5 albino subjects showing Group I type lateralisation; P100 is distributed ipsilateral to the eye stimulated. (b) shows the grand average of 9 albino subjects showing Group II type lateralisation; P100 is distributed contralateral to the eye stimulated.

Field size 16 degree radius, check size 50'

(After Jay and Carroll 1980)

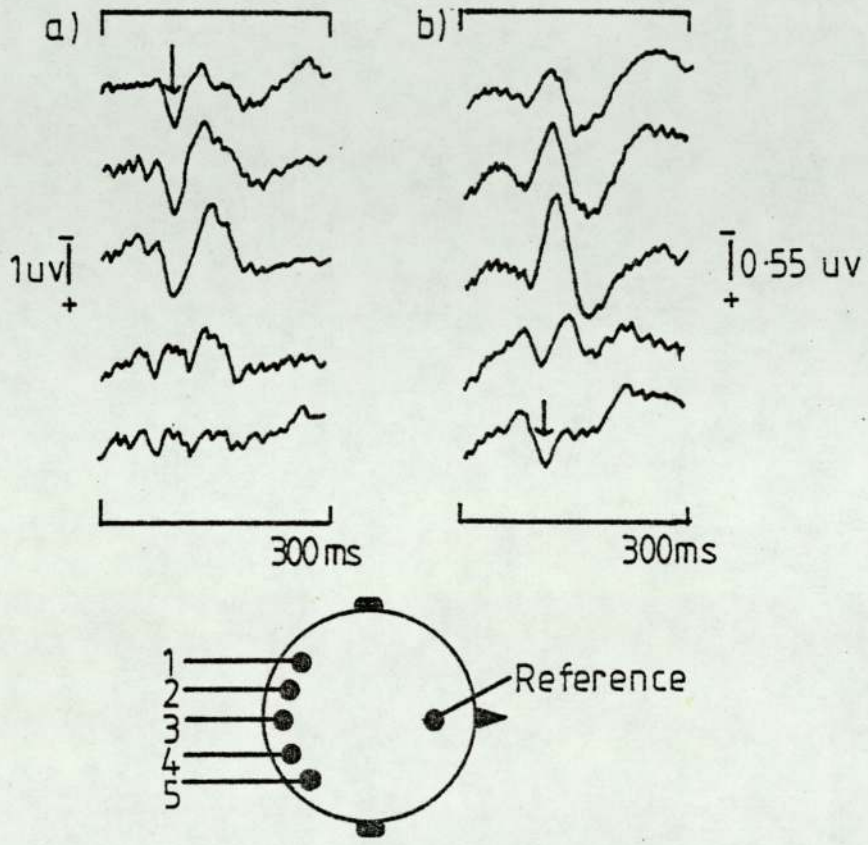

a)
b)
1uv
0·55 uv
300ms
300ms
1
2
3
4
5
Reference

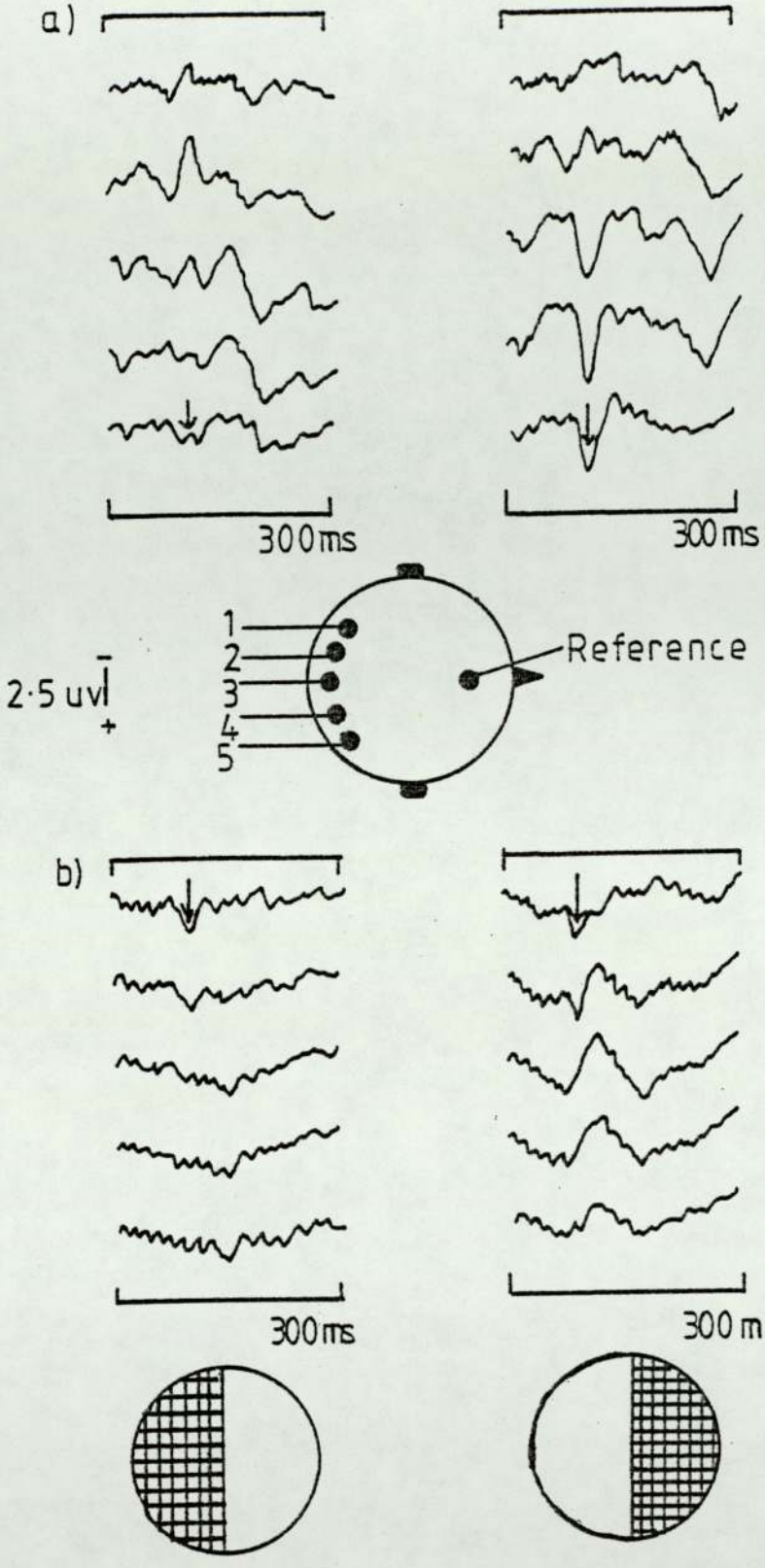
FIGURE 3.9

The half-field pattern reversal responses in human albinos

a) The temporal and nasal half-field responses of the right eye of a Group I type albino. The temporal half-field response shows the same lateralisation as the full-field response i.e. ipsilateral. The nasal half-field is said to show a negativity at these ipsilateral channels
b) The half-field responses of the right eye of a Group II type albino. Both the temporal and nasal half-field responses show the contralateral lateralisation found in the full-field response.

Field size 16 degree radius, check size 50'

(After Carroll et al.1980b)


a)
300ms
300ms
2·5 uv
1
2
3
4
5
Reference
b)
300ms
300ms

Carroll et al. (1980b) in terms of the Midwestern and Boston classification found among Siamese cats. Group I showed normal ipsilateral distribution of the temporal half-field response, indicating that the generator site of this response was at its normal site on the postero-medial surface of the contralateral occipital lobe (see Figure 3.10). Therefore, in this group, the representation of the temporal field was considered to be not shifted from its normal position. In addition, Group I also showed an attenuated nasal half-field response which was thought to be indicative of suppression. Group II, on the other hand showed a temporal half-field response that is more likely to arise because the generators are situated further laterally than in normal subjects and Group I albinos on the outer convexity of the lobes (see Figure 3.10). This was interpreted as indicating a shift of the representation in the cortex of this part of the visual field. In addition, nasal half-field responses could be elicited in these subjects. Therefore, Carroll et al. (1980b) postulated that Groups I and II may be analogous with the Midwestern and Boston Siamese cats respectively. They believed that the one subject displaying both Group I and Group II type features may represent a human equivalent of the Siamese cats found to display both Midwestern and Boston characteristics.

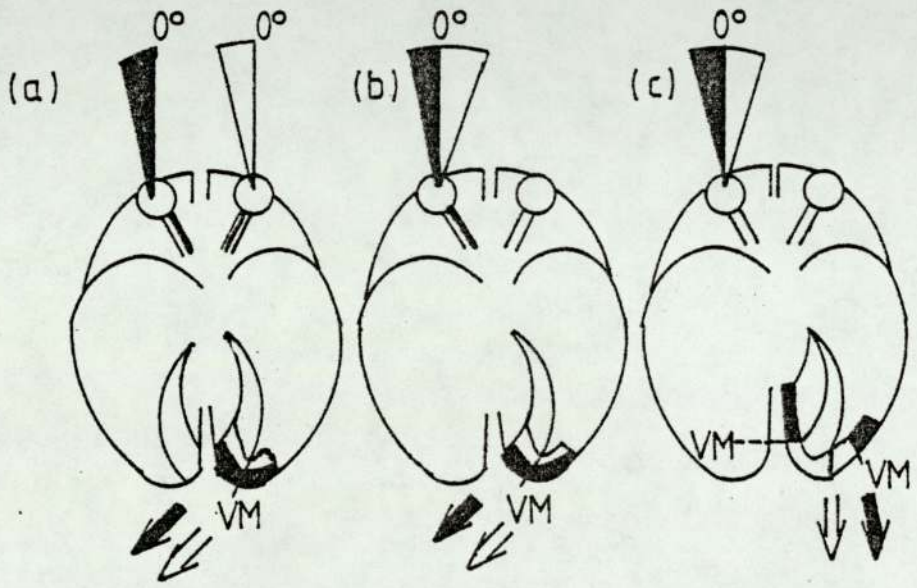
Therefore, the pattern reversal VECP provided a further method of identifying misrouting in human albinos. The main problem encountered with this type of stimulus is the

FIGURE 3.10

Cortical generator sites in Group I and II type albinos to half-field pattern reversal stimulation

The arrows indicate the direction of the P100 recorded after half-field stimulation in a) normal subjects; b) Group I type albinos and c) Group II type albinos. VM = vertical meridian; in a) and b) this also identifies the border of Areas 17 and 18 but in c) the VM is moved away from the 17/18 border. This is used to explain how Group I type albinos may be representative of the Midwestern pattern seen in Siamese cats and Group II the Boston pattern (see text for further details)

(After Carroll et al.1980b)


(a)
0°
0°
VM
(b)
0°
VM
(c)
0°
VM
VM

very small amplitude of the responses recorded. Carroll et al. (1980b) believed this to be a reflection of reduced VA in albino subjects and also because of a bilateral reduction in the number of functional generator units within the visual cortex. This reduction in amplitude was reported to often make identification and measurement of the P100 component difficult in some albino subjects (Carroll et al. 1980b) and Creel et al. (1981a and b) found that half of the oculocutaneous and ocular albinos studied showed virtually no P100 component (Figure 3.11). When it was present, it was very small and did not show clear monocular hemispheric asymmetries. They found that the most important factor determining this poor pattern reversal response was the presence of nystagmus (Creel et al. 1981b).

Using pattern appearance-disappearance stimuli misrouting has been detected in 90% of oculocutaneous and ocular albinos (Creel et al. 1981a and b) and this is believed to be a superior indicant than the response obtained with either flash, patterned flash, pattern reversal and noise-modulated-light stimuli (Creel et al. 1981a and b).

These authors used 50 or 70' checks because these were found to be the optimal size for eliciting pattern responses in albinos. The typical albino pattern appearance-disappearance VECP showed a large CI often followed by poor CII and CIII components. In accordance with the pattern reversal responses obtained, very poor

'OFF' responses were found. On monocular stimulation, CI clearly lateralised over the hemisphere contralateral to the eye stimulated. This asymmetry was confirmed by using bipolar recordings between two occipital electrodes, one located over each hemisphere (see Figure 3.11). Using this technique, in normal control subjects, the response recorded between the two electrodes was almost identical on binocular and monocular stimulation. In albinos, however, the response was found to reverse polarity when changing the eye stimulated (Figure 3.11).

In an attempt to locate the decussation point in the albino temporal retina, small (6 degree) stimulus fields were presented at eccentric retinal locations (Creel et al. 1981b). In most albinos, the decussation line was found to be some 10 to 20 degrees from fixation although there was a certain amount of variation in the precise location. Beyond 20 degrees the responses were found to be so reduced in amplitude that components could not be reliably identified.

The nature of the results obtained using monocular full-field pattern appearance-disappearance stimuli and an array of occipital electrodes was further investigated by Apkarian, Reits, Spekreijse and Van Dorp (1983). Two methods of analysis were used:

1) Qualitative; visual inspection of the potential distribution across the scalp and a reverse in sign of the

FIGURE 3.11

The pattern appearance-disappearance and pattern reversal visually evoked cortical potential in human albinos

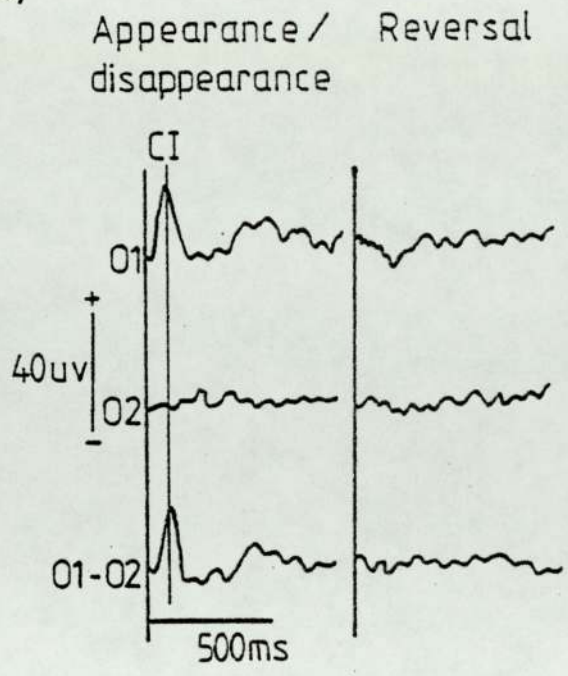
a) The full-field response of the right eye of an ocular albino is shown. There is an absence of a pattern reversal response while pattern appearance-disappearance produces a simple response on the left hemisphere which is also clearly seen in the bipolar O1-O2 trace.

b) Shows the binocular and monocular responses to pattern appearance-disappearance in an ocular albino. Only the bipolar O1-O2 responses are shown. The first component (arrowed) reverses polarity when stimulation is changed from one eye to the other.

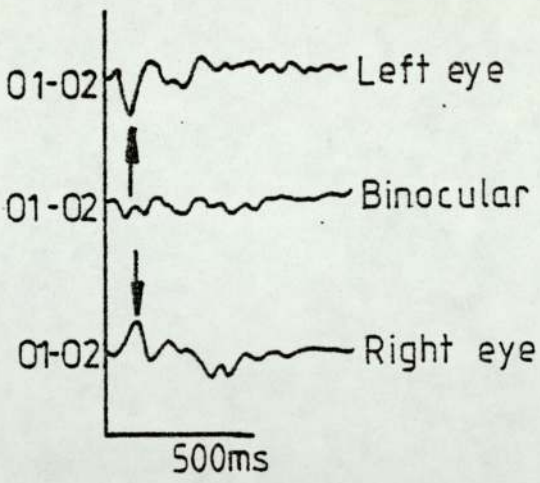
Field size 20 degrees, 50' checks, reference electrode in (a) is linked ears

(After Creel et al.1981b)

a)


Appearance / disappearance
Reversal
CI
O1
+
40uv
-
O2
O1-O2
500ms

b)


O1-O2
Left eye
O1-O2
Binocular
O1-O2
Right eye
500ms

difference potential from a left minus right hemisphere response following left and right eye stimulation.

2) Quantitative; estimation of the peak of the potential distribution across the array of electrodes at every time instant of the response.

It was found that by obtaining both right and left eye responses, the presence of misrouting as reflected by hemisphere asymmetry could be detected by visual inspection alone. Confirming earlier results, (Creel et al. 1981a and b), a bipolar derivation between electrodes to the right and left of the midline provided an additional indication of the lateralisation.

Quantitative analysis showed that the degree of asymmetry in the albinos was highly significant and, using their stimulation conditions, restricted to a narrow time window of the response between about 80-110 ms.

Further investigations showed that the most reliable asymmetry occurred with 55' checks and a relatively large stimulus field (20 degrees x 15 degrees). Under these conditions misrouting was identified in all of the albinos examined with no false positive results occurring in control subjects.

Young albinos (aged one to sixteen years) have also been examined using pattern appearance-disappearance stimuli

(Apkarian, Reits, Spekreijse and Van Dorp 1982). Monocular asymmetries were found and the latency changes with age suggested that the waveform develops in albino children in a similar way to that found in the normally-pigmented.

In conclusion, the VECP does appear to successfully identify misrouting in human albinos.

Different evoking stimuli have been used with varying degrees of success necessarily leading to some disagreement among investigators.

The preceding section forms the basis of the study now to be described. The VESP has not been used to examine the albino visual pathway by any previous investigators. This technique provides an additional method of identifying misrouting in human albinos at a site in the visual pathway before the visual cortex is reached. Thus, the following study will also describe the application of the VESP to albino subjects.

CHAPTER FOUR

4 METHODOLOGY

The following chapters describe work undertaken at the Clinical Neurophysiology Unit, The University of Aston in Birmingham, from October 1980 to February 1983, although the majority of the experimental data was acquired between July 1981 and October 1982.

4.1 Aims and predictions

The major part of this work was directed towards the detection of optic nerve fibre misrouting in human ocular and oculocutaneous albinos by the use of VEP techniques. Different evoking stimuli were used with the aim of identifying the most reliable method of showing the existence of such an anomaly. The studies were intended to confirm and extend existing work in this field by the recording of both VECPs and VESPs. In addition, certain psychophysical measures were made for comparison with the VEP data.

Before investigations began the VEP and psychophysical tests to be undertaken were considered and certain predictions made regarding the possible outcome of such investigations. These predictions took into account the previous work performed on human albinos and Siamese cats. The VEPs recorded and the psychophysical tests used fell into the following categories:

1) The flash VECP

It was considered necessary to include this test because of its robustness and wide applicability for use in subjects of all ages. Unlike pattern, flash VECPs have the advantage of being recordable in the presence of poor V.A. as is commonly found in albinos.

These VECPs were to be recorded over the two cortical hemispheres. It was predicted that any misrouting should manifest itself in the form of an asymmetry or asynchrony of the responses recorded over the hemispheres on monocular stimulation. The response should lateralise in the form of an increase in amplitude or decrease in latency over the hemisphere contralateral to the eye stimulated leading to a change in lateralisation when stimulation is changed between the two eyes. Statistical analysis of individual component latencies and amplitudes should reveal the most reliable measure indicative of misrouting.

2) Pattern VECPs

It was considered necessary to record these using both pattern reversal and pattern appearance-disappearance stimuli because both have been reported to be successful in detecting misrouting. The use of both methods should enable a decision to be made as to which of the two evoking stimuli is the most reliable and effective in

albinos and which method most clearly indicates optic nerve fibre misrouting. The topographical distribution of the potential over the scalp can be recorded on both binocular and monocular stimulation using an array of occipital electrodes. In addition, such stimuli, unlike flash, enable the recording of half-field responses. The use of such a technique should allow confirmation that the monocular full-field response is dominated by the crossed optic nerve fibres and therefore most closely resemble the temporal rather than the nasal half-field response from that eye.

3) The flash VESP

VESPs were recorded primarily because these small potentials have not been previously studied in albinos. Since the VESP is believed to have a post-chiasmal but sub-cortical origin it offers an opportunity of detecting the typical albino misrouting at a site in the visual pathway prior to the level of the cortex.

These responses were to be recorded from bilateral sites and the predicted outcome was similar to that expected using the flash VECP. Due to the preponderance of crossed optic nerve fibres in albinos, the response should lateralise on monocular stimulation over the channel contralateral to the eye stimulated. Therefore, as suggested with the flash VECP, the lateralisation should change sides as stimulation is moved from one eye to the other.

4) Psychophysical tests

In addition to the recording of the previously described evoked potentials, it was thought necessary to perform certain psychophysical tests.

Measurement of distance V.A. is essential because this is normally reduced in albinos. This should be recorded after correction of any refractive error (particularly as high prescriptions are reported to be common among the albino population) and is important when recording pattern VECPs which can be affected by induced refractive errors and reduced V.A.

The presence of any nystagmus and/or strabismus was to be noted as a high incidence of these features is also reported in human albinos.

In addition, it was believed that the monocular visual fields of the albinos studied should also be assessed in view of the gross hemianopic defects reported in some Siamese cats. It seemed only necessary to develop a simple method of assessing visual functioning along the horizontal meridian of the visual fields. Such a procedure should reveal the presence of any gross visual field defects concomitant to those found in Siamese cats as well as enabling the test to be performed easily and fairly rapidly on subjects falling into a wide age range.

The following sections describe how all these tests were utilised in the examination of the albino subjects taking part in the presented study.

4.2 The recording of VEPs

4.2.1 Electrode placement

Flash VECPs were recorded from two occipital electrodes O_1 and O_2 referred to C_3 and C_4 respectively (10/20 system; Jasper 1958). The sites of the active electrodes were chosen because of their symmetrical placement about the midline of the scalp and because they allow the responses from the two cortical hemispheres to be recorded separately. The reference electrode sites were chosen because of their relative inactivity with regard to the flash VECP and because, as will be seen later, many of the albinos examined in this study were young children. In subjects of this age, reference electrodes at these positions have been found to be useful (Harding in Halliday, Holder and Harding 1980).

Pattern VECPs were recorded using different electrode placements depending on the type of stimulus used.

Pattern reversal VECPs were recorded from a horizontal array of five electrodes placed on the posterior scalp region. A midline electrode was positioned 5cm above the inion with additional electrodes placed 5 and 10cm lateral to this site on both sides of the scalp. Such

a montage was chosen because much of the work on pattern reversal VECPs has used such placements (Blumhardt et al. 1978; Blumhardt and Halliday 1979; Kriss and Halliday 1980), including the work performed on human albinos (Carroll et al. 1980a and b; Jay and Carroll 1980).

Pattern appearance-disappearance VECPs were also recorded from a horizontal array of electrodes but at sites slightly lower on the scalp than those used for pattern reversal recording. A midline electrode was placed 10% above the inion (O_z) with lateral electrodes placed 10% to either side (O_1 and O_2 10/20 system; Jasper 1958). In addition, two further lateral electrodes were placed 10% to either side of O_1 and O_2 at sites which will be called O_3 and O_4. These active electrodes were chosen primarily because identical sites have been used in the study of these evoked potentials in human albinos (Creel et al. 1981a and b).

During both pattern reversal and pattern appearance-disappearance recordings all of the active electrodes were referred to a common midfrontal electrode at F_z (10/20 system; Jasper 1958). A common reference aids interpretation of the responses obtained from an array of active electrodes and F_z is relatively inactive with respect to the VECP. The albino subjects studied using patterned stimuli did not include the very young children and therefore F_z, which may record artifacts in younger subjects, should be a reliable reference site (Harding in

Halliday, Holder and Harding 1980).

During the recording of both flash and pattern VECPs the use of the ears as reference sites was avoided. Although electrodes at these positions are often used by investigators it has been found that the ears are not necessarily inactive with respect to the VECP (Michael and Halliday 1971; Lehtonen and Koivikko 1971).

The flash VESPs were recorded from two electrodes, one behind each ear, at a high mastoid position. A common reference at the vertex, C_z, (10/20 system; Jasper 1958) was used throughout. These electrode positions were chosen as much of the work on the VESP has involved similar placements and they have been found to be optimal for VESP recording (Harding and Rubinstein 1980a).

In all VEP recordings an electrode attached to the forehead acted as an earth.

The electrodes montages so far described were those commonly used during the routine VEP recordings in albinos and control subjects. On some occasions additional electrodes were used at different sites; these will be described as necessary in the appropriate sections.

4.2.2 Stimulation equipment

Flash stimulation for both VECP and VESP recordings was provided by a Grass PSII photostimulation with the stroboscope

situation 50cm from and directly infront of the subject's eyes. At this distance the front of the stroboscope subtended approximately 15.5 degrees. Setting 2 (1363 nits) was used for VECP recording presented at a flash rate of normally 1.8 per second although in the babies studied this was usually reduced to one per second. The flash intensity was kept constant in all recordings in order to avoid any changes in VECP waveform due to alterations in flash intensity. Setting 8 (3939 nits) was consistently used for the VESP. To record this response reliably a higher intensity flash is necessary compared to that used for VECP recordings (Harding and Rubinstein 1980a) and, since a large number of responses need to be averaged, (Harding and Rubinstein 1980a), a fairly high repetition rate of 5 flashes per second was used in order to keep the recording time to a minimum.

Pattern reversal stimulation was provided by a Nicolet T.V. system with the screen placed directly infront of and one metre away from the subject's eyes. At this viewing distance the screen subtended 11 degrees vertically and 14 degrees horizontally. Half-field stimulation could be provided by the stimulator itself by blanking off half of the screen resulting in a half-field size of 11 degrees vertically and 7 degrees horizontally. Throughout the recordings the subject's attention was directed towards a centrally placed small circular red fixation dot subtending 28' arc. If necessary, in subjects with very reduced VA, the size of this spot was increased.

A black and white checkerboard was used reversing at a rate of 2 reversals per second. Usually the pattern was made up of individual checks each subtending 50' arc primarily to allow comparison with previous work on albinos (Carroll et al. 1980a and b; Jay and Carroll 1980) although occasionally 2 degree checks were substituted. The luminance of the black checks was 9 candelas per square metre and the white checks 240 candelas per square metre; contrast 93%.

Pattern appearance-disappearance stimulation was provided by a SC Electronics grating generator T221 linked to a Hitachi video monitor situated 110cm directly infront of the subject's eyes. At this distance the screen subtended 18 degrees horizontally and 14 degrees vertically. Subject fixation was maintained during the recording of full-field responses by a small circular red fixation dot subtending 25' arc centrally placed on the screen. As in the case of pattern reversal stimulation, the size of this spot was increased as necessary. Using this equipment half-field stimulation could not be produced by internal blanking off of half the screen. Consequently, these conditions were achieved by the placement of two additional red fixation dots on the vertical edge of the screen but at the same level as the centrally placed spot. In this way half-field VECPs could be recorded by directing the subject's fixation to one of these dots. Again, the size of these additional fixation marks was increased as necessary.

Fifty minute black and white checks were routinely presented. This check size has been shown by Creel et al. (1980a and b) to be optimal for evoking responses in albinos and its use in this study allows comparison of the results obtained with those of other authors (Creel et al. 1980a and b; Apkarian et al. 1983). A Research Machines 380Z computer was used to trigger the stimulator to produce checks of approximately 80% contrast appearing for 100 ms followed by a blank field of the same mean luminance (100 candelas per square metre) for 400ms.

4.2.3 Averaging equipment

All of the VEPs recorded were averaged by a Nicolet Pathfinder II. For the VECP the first 500ms of the response was averaged enabling the earlier and most reliable part of the response to be clearly seen. For the recording of VESPs only the first 50ms was averaged because these responses have very short latencies and should be easily seen within this time window.

Filter settings used during averaging were different depending on whether a VECP or VESP was being recorded. In the former case a bandpass of 0.5 to 30Hz was used, but for VESP recording it was changed to 30-500Hz.

During VECP recording a total of 50 responses were usually averaged although occasionally this number was increased to one hundred. Routinely 500 to 750 responses

were averaged to allow clear definition of the VESP.

All of the evoked potentials were stored on floppy discs and plotted out after recording was completed. The resulting waveforms were then measured using the averager's internal cursor.

Throughout all VEP recordings a constant but fairly bright room illumination was used.

This was primarily to allow observation of the subjects during recordings so as to ensure that adequate fixation was maintained and, in the case of the children examined, they were actively encouraged to retain such fixation.

4.3 Psychophysical testing

4.3.1 Distance visual acuity

Where possible binocular and monocular VAs were measured in each subject. In the older children and adults a 6m Snellen chart was used, but in younger children whose response to this test was unreliable or where the alphabet was not known adequately, the Sheridan-Gardiner test, again used at 6m, was performed. In all cases the V.A. was measured in a brightly lit room the level of illumination of which was kept constant. Care was taken that each subject was, if necessary, wearing an accurate up-to-date, distance refractive error correction to

ensure that the V.A. recorded was the best achievable. If any refractive error was present the correction was worn during VEP recordings.

4.3.2 Nystagmus and Strabismus

The presence or absence of nystagmus was noted in each subject. No precise measurements of its speed and size were made but by visual inspection it could usually be determined whether the movement was horizontal, vertical, rotatory or mixed in nature.

The presence fo strabismus was also investigated using a cover test and/or Hirschberg test (Cashell and Duran 1974). If any squint was found its direction and approximate size was noted.

4.3.3 Visual fields

The visual fields were investigated using a Carl Zeiss Jena bowl perimeter. A simple method of combined kinetic and static perimetry was used. It was hoped that by using such a technique any gross defects would be picked up without precluding the test from being performed by young children in whom the use of perimetry often leads to problems of boredom and fatigue. Initially, the peripheral limits of the visual fields along the horizontal meridian were determined for each eye.

The largest test target (IV : 16 square mm) was used at its maximum intensity (4 : 1500asb) with one eye occluded and the subject comfortably positioned in the head rest, attention was directed towards the central fixation spot on the posterior pole of the bowl. This fixation was maintained and constantly checked throughout the investigation. The large bright target was then advanced from the extremes of both the nasal and temporal sides of the field along the horizontal meridian. The subject was asked to respond when they became aware of the target by simply saying "Yes". This exercise was repeated to assess the accuracy of the response. Using this technique the extreme limits of the peripheral visual fields were established. The intensity of the target was then reduced to its minimum level (1 : 50asb) and the entire horizontal meridian of the visual field examined within the limits previously found. The subject was told that the target would disappear and then appear somewhere along the horizontal meridian; if they were aware of the appearance they were again asked to respond with the answer "Yes". To produce this effect the target was extinguished and made to appear randomly at sites at 10 degree intervals along the horizontal meridian, avoiding the blind spot, until the entire field had been investigated. If the subject's response was positive the position and level of brightness of the target when seen was noted on the standard visual field chart used with this instrument. Any dubious responses were checked repeatedly and if necessary after a positive answer was thought

doubtful the subject was asked to point to where they thought the target was appearing. If, even after repeated checking the target was not seen at a certain place or places in the field, the intensity of the target was increased by one step (2 : 150asb) and those points repeated. This process was repeated increasing the target intensity where necessary (3 : 500asb; 4 : 1500asb) and the chart marked with the level of illumination necessary to see the target at that position. If any gross field defects were found using this method the entire peripheral visual fields of both eyes of the subject were examined using the more conventional kinetic perimetry method. The larger, high intensity target (4 : 1500asb) was advanced from the periphery until a positive answer resulted and this was repeated along all the meridians of the visual field and the chart marked appropriately.

4.4 Subject sources

The albinos examined in the study came from a variety of sources. Some were known to the Ophthalmic Optics department through contact lens and low vision aid clinics while others were referred from the Birmingham and Midland Eye Hospital and the Coventry and Warwickshire Hospital. The majority, however, were attending partially-sighted schools in the Birmingham area namely Priestly Smith School, George Auden School and Braidwood School. All of the subjects attending had been previously diagnosed

as an ocular or oculocutaneous albino by an ophthalmologist.

To allow statistical analysis of the results obtained it was necessary to also examine a group of normal subjects; hereafter referred to as 'control subjects'. These were all volunteers with normal distance VA (6/6 or better with a refractive correction if necessary) with no known ophthalmological or neurological defect. These control subjects were all sex and, as near as possible, age matched with the albinos examined. This precaution is necessary because of the differences in VEP waveforms found between the sexes (Dustman and Beck 1969; Schenkenberg et al. 1971; Celesia and Daly 1977; Dustman et al. 1977; Stockard et al. 1979; Shaw and Cant 1981; Snyder et al. 1981; Halliday et al. 1982) and the changes that occur with age (Dustman and Beck 1966, 1969; Celesia and Daly 1977; Dustman et al. 1977; Spekreijse 1978; Stockard et al. 1979; Shaw and Cant 1981; Snyder et al. 1981; Sokol et al. 1981; Halliday et al. 1982; Vries-Khoe and Spekreijse 1982).

4.5 Experimental procedure

The experimental procedure used varied slightly depending on whether the subject being examined was a control or albino subject and, in the latter case, whether a child/adult or baby. Consequently, the procedure will be described for these groups separately.

4.5.1 Albino children and adults

Before examination commenced the type of albinism diagnosed was noted and the age and sex of the subject recorded. The distance binocular and monocular VAs (with refractive correction if necessary) were measured and the presence of nystagmus and strabismus investigated. Directly following this the VEPs were recorded.

Each subject was seated, the scalp measured and the appropriate electrode positions marked with a coloured pencil. Silver/silver chloride electrodes were then attached to the scalp with collodion glue with the exception of the earth electrode which was attached to the forehead with the aid of a double sided sticky pad and tape. On each occasion the scalp was measured and the electrodes attached by the same examiner and particular care was taken to ensure lateral and vertical symmetry of electrodes so that mispositioning could not interfere with the results. The electrodes were then filled with electrode jelly and the scalp abraded with a blunt needle to achieve an inter-electrode resistance of 10KOhms or less. Special care was taken to maintain equality of electrode resistance throughout the recordings so that differences between electrode resistances could not affect the results.

Subjects were then comfortably seated in a moderately lit room and recording commenced. When performed, pattern

responses were the first to be recorded. Initially, binocular responses were recorded followed by individual monocular full-field and half-field responses. Laterality of occlusion was varied between subjects. On monocular stimulation the non-stimulated eye was carefully occluded with cotton wool and a black patch to prevent light entering that eye. If for any reason the response obtained was considered unreliable or of doubtful waveform the recording was repeated, not immediately, but towards the end of the examination.

Following this the flash VECP and VESP were recorded. In each case binocular and monocular responses were examined. As in the case of pattern VECPs, laterality of occlusion was varied between subjects and care was taken to adequately occlude the non-stimulated eye. Any unreliable or dubious responses were repeated.

After recording was completed the electrodes were removed with acetone and finally the visual fields, if examined, were investigated.

4.5.2 Albino babies

It was not possible to measure the VA of these babies but the presence of nystagmus and strabismus was noted by gross observation. Only flash VECPs and VESPs were recorded in these subjects using a procedure similar to that described for the children and adults.

The scalp was measured and marked by the same examiner but the electrodes were not glued but taped to the scalp. The electrodes were filled with jelly and the scalp gently abraded to give an equality of electrode resistance. During the recordings the baby was usually lying on the mother's knee and she often gently restrained the baby's hands to prevent the electrodes from being pulled off.

For VECP recording a flash intensity of 2 was used presented with a flash rate of one or less per second. For VESP recording exactly the same stimulator parameters were used as in the children and adults. It was decided that, since VESPs have not previously been examined in babies, it would be unwise to alter parameters.

In all cases binocular and monocular responses were recorded and always repeated to provide some idea of the stability and reliability of the response. If the child became very active or tearful examination was ceased until a quiet state was regained.

No visual field testing was performed on the babies.

4.5.3 Control subjects

The distance binocular and monocular VAs (corrected if necessary) were measured in these subjects to ensure that they were of an adequate level (6/6 or better).

All these subjects underwent the appropriate VEP recordings concomitant with that necessary after examination of the albino subject to whom they were matched.

The procedure used was identical to that used in the albino children and adults. Visual fields were not examined in these subjects primarily because we were only interested in the presence of any gross field defects in the albinos.

The next Sections will describe the results obtained in all these forms of investigation.

CHAPTER FIVE

5 RESULTS I : PSYCHOPHYSICAL FINDINGS

This Chapter will describe the albinos examined during this study and the results obtained from the psychophysical tests employed. The following Chapters will then consider the evoked potential findings in these albino subjects and their controls.

5.1 Albino subjects : general features

A total of 26 albinos were examined. Three were young babies under one year of age and, as no matched controls were obtained for comparison with these subjects, their results will be considered separately in Chapter 8.

Table 5.1 lists the remaining 23 albinos studied. In this table each albino is given a subject number and hereafter will be referred to by this number. Twelve of the albinos were of Asian origin, the remaining 11 Caucasian. Hair bulb testing of the oculocutaneous albinos was not available and therefore it was not possible to differentiate between ty-pos and ty-neg types. Five females were examined all having been diagnosed as possessing oculocutaneous albinism. Of the remaining 18 males, 14 were oculocutaneous and 4 ocular albinos. The ages of the subjects ranged from 5-35 years (average 13.4 years). All these details are summarised in Table 5.1.

Table 5.1

The General Features of the Child and Adult Albinos Studied

Each albino is given a subject number. The type of albinism, sex and age of each albino is shown. Those of Asian origin are marked with a *; all of the remaining albinos were Caucasian.

SUBJECT NUMBER	TYPE OF ALBINISM	SEX	AGE (YEARS)
1*	OC	F	20
2*	OC	M	21
3	OC	M	9
4*	OC	M	11
5*	OC	M	16
6*	OC	F	6
7*	OC	F	8
8*	OC	F	12
9	OC	M	16
10	OC	M	11
11	OC	M	27
12	OC	M	9
13	OC	M	5
14*	OC	F	9
15*	OC	M	8
16	OC	M	6
17*	OC	M	21
18*	OC	M	20
19*	OC	M	5
20	O	M	14
21	O	M	14
22	O	M	35
23	O	M	6

Key:
* = Asian
OC = Oculocutaneous albinism
O = Ocular albinism
M = Male
F = Female

5.2 Visual acuity

The binocular and monocular VAs of 22 subjects could be measured. Unfortunately, subject 16, a 6 year old male oculocutaneous albino would not co-operate with either the Snellen or Sheridan Gardiner test so no reliable measure of his VA was possible.

The VAs of the albinos ranged from 6/12 to 2/60. Twelve subjects had equal monocular VAs and, in these cases, the binocular acuity was equal to or slightly superior to the monocular value. Ten subjects had unequal monocular VAs, and, in these cases, the binocular acuity was either equal to or slightly superior to that of the better eye. The levels of acuity recorded in each subject are summarised in Table 5.2.

5.3 Nystagmus

Only one subject showed no visible nystagmus (see Table 5.2). However, this was subject 16 whose VA could not be recorded. No precise measurement of nystagmus was made, but gross observation showed that its size and speed varied greatly among the albinos. In some subjects it was very fine and rapid while in others it was slow and pendular. The movement usually became more prominent on the covering of one eye. The nystagmus almost always contained a horizontal movement with, in some subjects, a second rotatory component.

Table 5.2

The V.A.s of the Albino Subjects

The binocular and monocular V.A.s of each albino are given. These ranged from 6/12 to 2/60. The V.A.s of albino 16 could not be obtained, this was the only subject of the group in whom no visible nystagmus was detectable. (See text for details).

SUBJECT	VISUAL ACUITY		
	R.EYE	L.EYE	BINOC
1	6/60	6/60	6/60
2	6/60	6/60	6/60
3	6/36	6/36	6/36
4	5/60	5/60	6/60
5	6/60	6/60	6/60
6	6/36	6/18	6/18
7	6/18	6/18	6/18
8	6/18	6/18	6/18
9	6/36	6/24	6/24
10	6/60	6/60	6/60
11	6/60	6/36	6/36
12	6/36	6/36	6/36
13	6/24	6/36	6/24
14	6/60	6/36	6/36
15	6/24	6/60	6/24
16**	----	----	----
17	6/60	6/60	6/60
18	5/60	4/60	6/60
19	2/60	2/60	2/60
20	6/36	6/12	6/12
21	6/18	6/18	6/18
22	6/24	6/18	6/18
23	6/60	6/36	6/36

KEY: R.EYE = Right Eye
L.EYE = Left Eye
BINOC = Binocular
** = Visual acuities not obtainable. Only subject with no visible nystagmus.

5.4 Strabismus

Eight (35%) of the albinos were thought to display a strabismus. The types and approximate sizes of these squints are detailed in Table 5.3. There was no consistency in the direction of the deviation; five showed convergence (one alternating) and three divergence. The approximate sizes ranged from 5-25 degrees.

5.5 Visual fields

The visual fields of 14 albinos were examined. The results are summarised in Table 5.4.

During the early part of the study attempts were made to measure the visual fields of all the subjects examined but it soon became evident that the results obtained from the younger children (5-6 years of age) were inconsistent and unreliable. Future examination of the visual fields of children of this age was, therefore, abandoned. This problem also occurred in the testing of subject 15 who, although aged 8 years, did not give reliable responses. Of the older albinos on whom visual field testing was not performed, subjects 1 and 2 posed communication problems and subject 22, one of the first albinos to be examined electrophysiologically, was to return later for visual field testing but, unfortunately, in the meantime he moved out of the Birmingham area and was lost to further testing.

The visual fields of the remaining albinos were considered

Table 5.3

Strabismus Observations in the Albino Subjects

Eight albinos were thought to display a stabismus although, as the table shows, there was no consistency regarding the direction or the size of the deviation.

SUBJECT	STRABISMUS	
	TYPE	SIZE (Degrees)
1	X	X
2	X	X
3	X	X
4	LCS	20
5	X	X
6	RDS	5
7	X	X
8	X	X
9	X	X
10	LDS	25
11	RCS	5
12	LCS	15
13	X	X
14	RDS	10
15	X	X
16	X	X
17	X	X
18	X	X
19	X	X
20	X	X
21	ACS	15
22	X	X
23	RCS	20

KEY:
X = No Strabismus found
RCS = Right Convergent Strabismus
LCS = Left Convergent Strabismus
RDS = Right Divergent Strabismus
LDS = Left Divergent Strabismus
ACS = Alternating Convergent Strabismus

Table 5.4

Peripheral Visual Field Observations
in the Albino Subjects

These were measured in 14 albinos. Only one subject (Number 20) showed a gross defect in the form of a nasal hemianopia with central sparing and some temporal constriction in the right eye. (See text and Figure 5.1 for details).

SUBJECT	VISUAL FIELD	
	RIGHT EYE	LEFT EYE
1	---	---
2	---	---
3	FULL	FULL
4	STC	FULL
5	SNC	FULL
6	---	---
7	FULL	FULL
8	FULL	FULL
9	SNC	FULL
10	STC	STC
11	FULL	FULL
12	FULL	FULL
13	---	---
14	STC	STC
15	---	---
16	---	---
17	FULL	FULL
18	FULL	FULL
19	---	---
20	N.HEM	FULL
21	STC	STC
22	---	---
23	---	--

KEY:

--- = Test not performed or results unreliable.
FULL = Horizontal limits of visual field within normal range.
STC = Slight temporal constriction along horizontal field.
SNC = Slight nasal constriction along horizontal field.
N.HEM = Nasal hemianopia with central sparing.

'full' along the horizontal meridian if the extreme limits fell either outside or within 10 degrees inside the normal visual field. Only when the limits were reduced by greater than 10 degrees were the visual fields considered constricted. Using the large, bright target (4.1V) the average visual field measures approximately 90-100 degrees temporally and 60 degrees nasally (Harrington 1976). The above criterion for abnormality avoids the classification of very small constrictions from the normal limits as a sign of an abnormal field especially as the purpose of the test was to identify gross defects. This method is also adequate for comparison with the study of Carroll et al. (1980b) who investigated VECPs and the peripheral visual fields using the cruder confrontation test.

Of the 14 albinos, 7 were found to have full fields in both eyes while 6 showed some constriction in one or both eyes. In the latter subjects the defects were considered only slight in nature as in no case was the constriction greater than 20 degrees either temporally or nasally. In 4 subjects it was the temporal field that appeared constricted and in 2 it was the nasal field.

In all of the aforementioned 13 albinos there was, using our method, no difference between the sensitivities of the nasal and temporal fields. Within the limits of their horizontal fields they could all positively and consistently report the appearance of the low intensity (1:50asb) target.

One subject, number 20, a 14 year old male ocular albino did, however, show a much grosser defect setting himself apart from the above 13 albinos. The visual field of his left eye was full but the extent of his visual field along the horizontal meridian of his right eye was greatly reduced giving the impression of a nasal hemianopia. The entire visual fields of both eyes were then examined using the conventional kinetic method; the results are shown in Figure 5.1. The visual field of the left eye was indeed full and within the normal limits in all meridians but the right eye showed a distinct nasal hemianopia with central sparing and some constriction of the temporal field.

Consulting Table 5.2 it can be seen that this subject had unequal monocular VAs, that of the right eye (6/36) being lower than that of the left (6/12). Ophthalmoscopic examination of both eyes revealed no obvious reason for such a visual field finding and the ophthalmological records of the subject again showed no known cause. On questioning, the subject was aware of the field loss and, as far as he knew, it had always been present.

5.6 Summary

1) Of the 23 child and adult albinos examined the VAs of 22 could be measured. The levels of acuity fell within the range of 6/12 to 2/60.

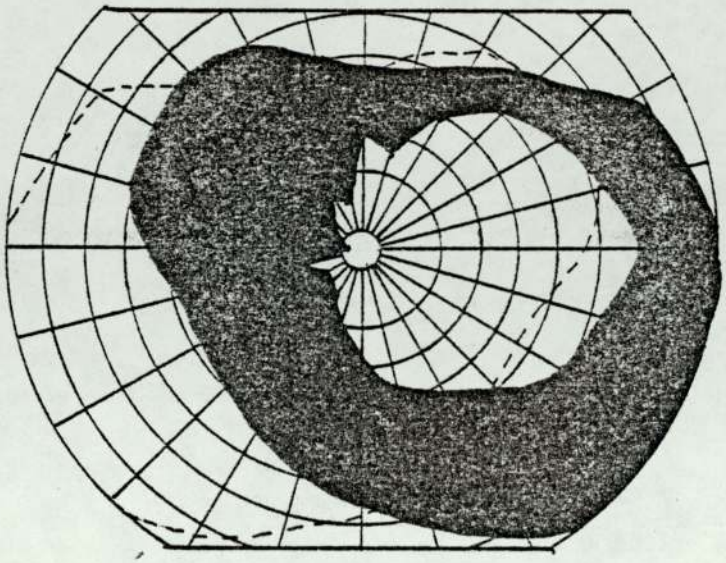
2) Nystagmus was present in all but one of the albinos.

Figure 5.1

Peripheral Visual Fields of Albino 20

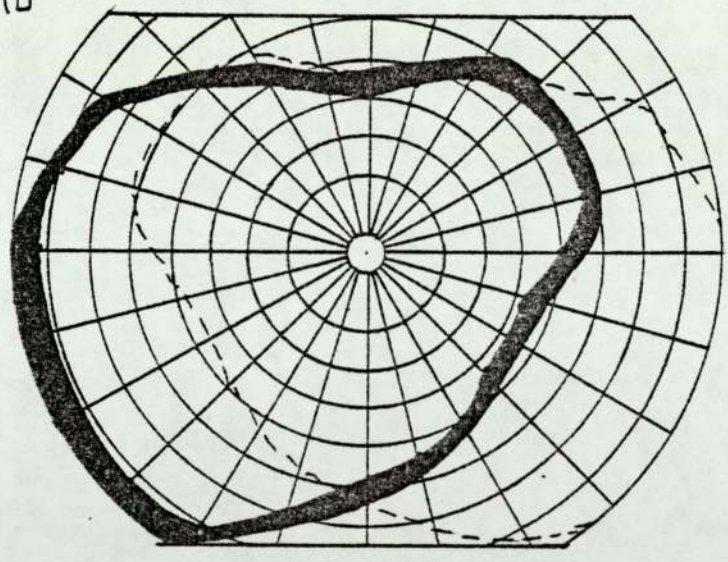
This was the only albino of those tested by perimetry who was found to display a major peripheral field defect. As shown, that of the left eye was full but the right had a nasal hemianopia with central sparing in conjunction with some constriction of the temporal field.

(a



Target = IV:4 (16 mm^2; 1500 as b)

(b



3) Eight of the albinos were thought to have a strabismus; both convergent and divergent squints of varying sizes were found.

4) The visual fields of 14 albinos were examined. Only one subject displayed a major visual field defect in the form of a nasal hemianopia of the right eye with central sparing and some constriction of the temporal field. Of the remaining 13 subjects, the horizontal limits of their visual fields were within the normal range and, using the simple static perimetry test employed, no detectable differences were found between the sensitivities of the nasal and temporal retinae.

CHAPTER SIX

6 RESULTS II : VISUALLY EVOKED CORTICAL POTENTIALS

This Chapter will describe the results obtained during examination of the child and adult albinos and their controls using flash and pattern VECPs.

6.1 Treatment of data

One of the main aims of this study was the identification of misrouting in albinos using VECP recording techniques. This abnormality should manifest itself by lateralisation of the VECP over the contralateral hemisphere on monocular stimulation. By considering the latencies and amplitudes of the VECP components one should see a shortening in latency or increase in amplitude over the contralateral hemisphere or an increase in latency or reduction in amplitude over the ipsilateral hemisphere on monocular stimulation. In order to show whether this indeed does occur for each VECP component, two methods of dealing with the raw data were developed.

1) The calculation of a Cx value for each component measure in each subject. Cx is defined as the average amount that a VECP component lateralised contralaterally on monocular stimulation. In the case of latency it was calculated by how many milliseconds a component lateralised contralaterally on monocular stimulation. Similarly for the amplitude it was calculated by how many microvolts a component lateralised contralaterally on monocular stimulation. In every subject the values of Cx for the two eyes

were added together and divided by two to give an average value for the particular component measure in that subject. A positive Cx value thus represents contralateral lateralisation and a negative Cx ipsilateral lateralisation on monocular stimulation. A Cx of zero will result if no consistent monocular hemispheric lateralisation is present. The greater the positive or negative Cx value, the larger is the amount of contralateral or ipsilateral lateralisation respectively. Using group data the mean Cx value and its standard error (S.E.) can be calculated for each component measure in both albinos and controls for comparison.

The major advantage of this method lies in the fact that any consistent asymmetries or asynchronies occurring between the two hemispheres or eyes in any subject will be cancelled out. The existence of possible hemisphere or eye effects are considered in the following section.

2) Analysis of variance

Two-way analysis of variance (ANOVA) was performed on the raw data obtained in both the albinos and their control subjects. This involved comparing both the latencies and amplitudes of individual components over both hemispheres on binocular and monocular stimulation. Using this method one can ascertain whether there is any significant interaction between the hemisphere over which the VECP lateralises and the eye of stimulation and whether the results are of a significant level using critical value tables. The results obtained can also be represented graphically.

The critical value tables used throughout are those of Murdoch and Barnes (1982).

Both of the above methods of dealing with the raw data rely on consistent identification of components over both hemispheres on binocular and monocular stimulation. If a component could not be identified in one or more responses that subject could not be included in statistical analysis. In addition, the results of subject 20, who displayed a monocular nasal hemianopia were not included in any such statistical analysis. The existence of such a gross field loss should affect the VECP waveform and lateralisation independent of any lateralisation due to albinism (Harding 1977; Harding et al. 1980; Holder 1980; Onofrj et al. 1982; Blumhardt, Barrett, Kriss and Halliday 1982) and therefore, the results obtained in this subject will be considered separately at the end of each section.

Matched control subjects were obtained for all of the remaining 22 albinos; the average age of these controls was 14.1 years. These controls will be referred to by the number of the albino to whom they are matched followed by the letter 'C'. Hence, subject 10C is the control subject matched to albino subject 10.

The results obtained using flash and patterned stimuli will now be considered.

6.2 The flash VECP

Three early components of the flash VECP are usually identifiable; P1, N2 and P2. Therefore, it was considered advantageous to consider these components in detail. The absolute latencies of the three components and the peak-to-peak amplitudes of P1N2 and N2P2 were measured. These measures are illustrated in Figure 6.1. Each component measure will now be considered in turn.

6.2.1 P1 latency

A P1 component could be identified over each hemisphere on binocular and monocular stimulation of both eyes in all of the control subjects but only 17 (77%) of the albinos. In the remaining 5 (23%) P1 was absent in one or more of the above conditions; the subjects displaying this feature are shown in Table 6.1 and the responses of such a subject are illustrated in Figure 6.2. This shows the VECPs of albino 4; a P1 component can be identified over both hemispheres on binocular stimulation but its appearance in the monocular responses is inconsistent.

Table 6.1 shows the calculated P1 latency Cx values in the albinos and their matched controls. Among the albino group Cx ranged from +35.0ms to -17.5ms and within the controls from +5.5ms to -9.5ms.

Ten (59%) of the 17 albinos showed a positive Cx value

Figure 6.1

The Flash VECP Parameters Measured in the Study

A typical flash VECP waveform is shown with the peaks P1, N2 and P2 labelled. During the study the latency of these components and the P1N2 and N2P2 amplitudes were measured for analysis.

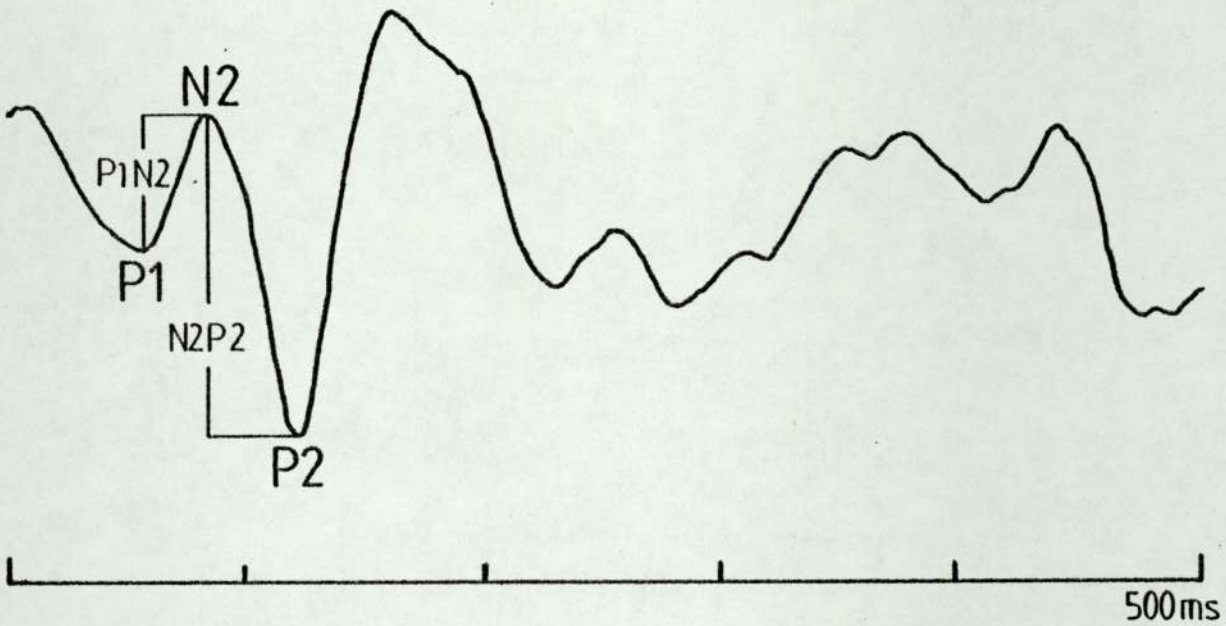

N2
P1N2
P1
N2P2
P2
500ms

Table 6.1

The Cx Values for P1 Latency

The calculated Cx values (in ms) for the latency of component P1 in the flash VECP are given for each albino and his matched control. The values in five subjects are omitted because of the inconsistency of the component in the VECPs of the albinos examined. (See text for further details).

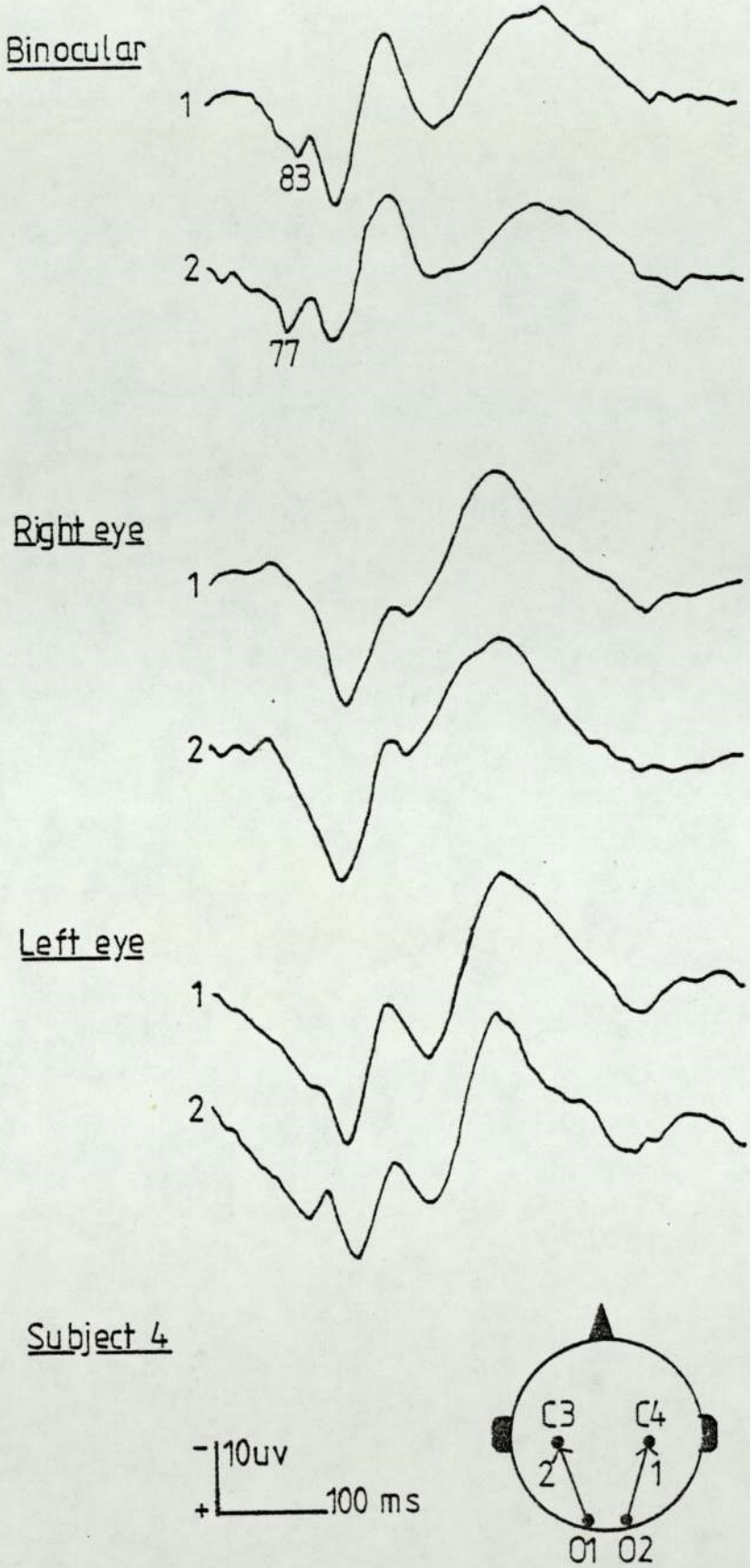
SUBJECT	Cx (P1 LATENCY)	
	ALBINO	CONTROL
1	+5.5	+2.0
2	0	-1.5
3	-14.5	+0.5
4	-	-
5	+1.5	+0.5
6	+2.5	0
7	-	-
8	+33.0	+5.5
9	-2.0	+3.0
10	+2.5	+1.0
11	-3.5	-2.0
12	-17.5	-9.5
13	-14.5	-2.5
14	-	-
15	+4.0	-5.5
16	-	-
17	+3.5	-1.0
18	-8.5	+1.0
19	+13.5	+0.5
21	-	-
22	+1.5	+4.5
23	+4.5	+1.5

Key: - = No P1 component consistently identified in the albino examined, hence control value not given.

Figure 6.2

The Flash VECPs of an Albino Subject Showing an Inconsistent P1 Component.

The flash VECPs of albino subject 4 are shown. A P1 is seen over both hemispheres on binocular stimulation but appears inconsistently on stimulation of the two eyes independently. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).


Binocular
1
83
2
77
Right eye
1
2
Left eye
1
2
Subject 4
10uv
100 ms
C3
C4
2
1
O1
O2

and 6 (35%) a negative value. Only one subject (6%) had a Cx of zero. Within the control group one (6%) showed a zero Cx value while 10 (59%) showed a positive Cx and 6 (35%) a negative value.

Therefore, among both the albino and control groups, P1 lateralised both ipsilaterally and contralaterally on monocular stimulation. In some control subjects Cx had quite a large positive or negative value. Figure 6.3 shows the responses of subject 12C in whom P1 lateralises ipsilaterally (Cx = -9.5ms) on monocular stimulation. In contrast, Figure 6.3 also shows the responses of subject 22C in whom Cx = +4.5ms indicating monocular contralateral lateralisation.

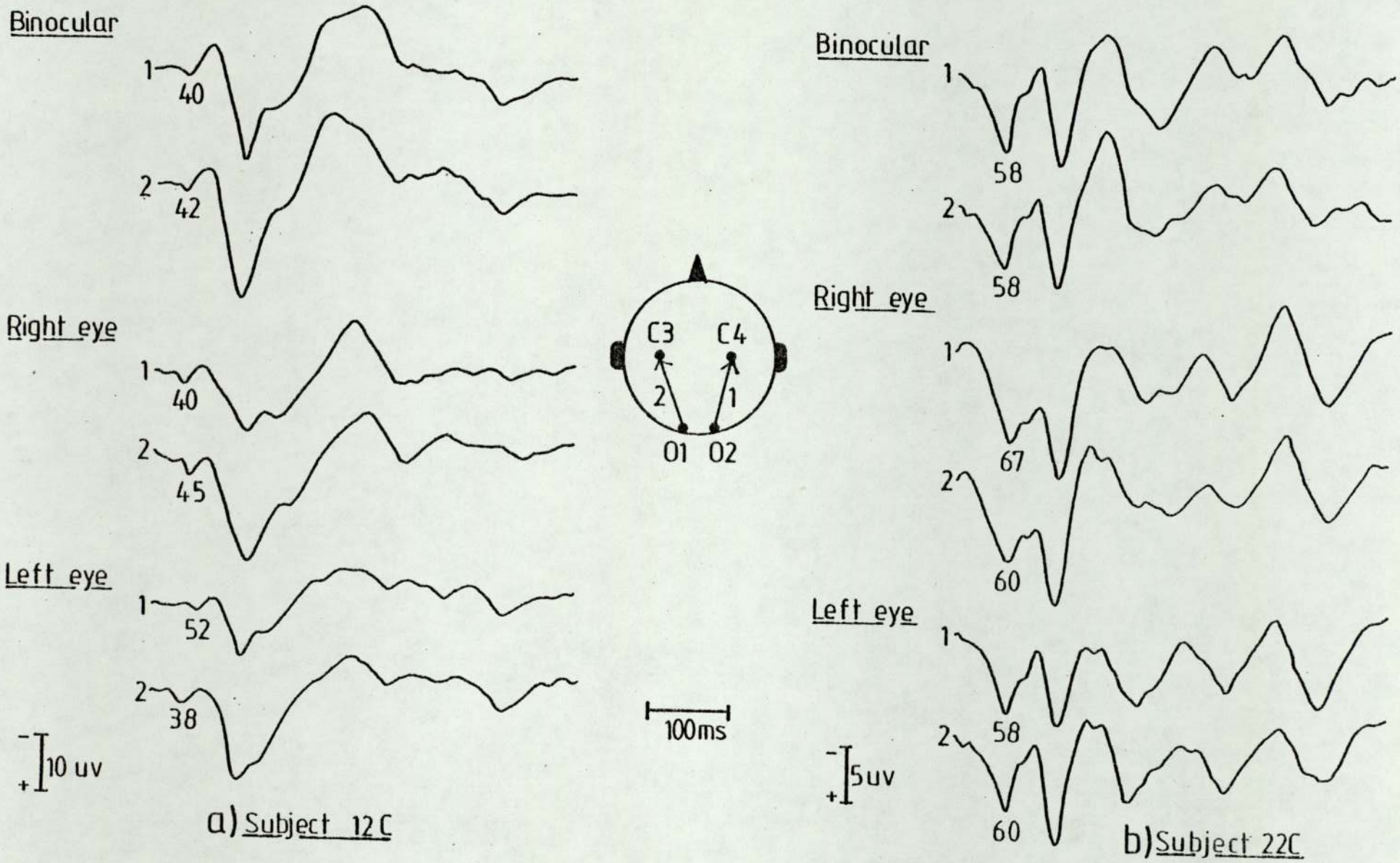
As shown in Table 6.1, among the albinos there was a similar diversity of Cx values. Subject 2 was the exceptional case in whom P1 showed no lateralisation on monocular stimulation resulting in a Cx of zero. The responses of this subject are shown in Figure 6.4. In all other albinos a variable amount of lateralisation was present. Figure 6.5 shows the gross contralateral lateralisation found in subject 8 (Cx = +33.0ms). This, however, is an extreme example; in other subjects the amount of contralateral lateralisation was of a more modest level; Figure 6.6 illustrates such a case. This shows the responses of subject 17 in whom Cx = +3.5ms.

In contrast, some albinos showed ipsilateral monocular

Figure 6.3

The Flash VECPs of Control Subjects 12C and 22C with P1 Labelled

The binocular and monocular VECPs are shown with the latency of the P1 component over each hemisphere labelled. In (a) Cx = -9.5 ms indicating ipsilateral lateralisation on monocular stimulation. However, in (b) Cx = +4.5 ms indicating contralateral lateralisation. (Flash intensity 2, 1.8 flashes per seconds, 50 sweeps).



a) Subject 12C

b) Subject 22C

Figure 6.4

The Flash VECPs of Albino Subject 2 with P1 Labelled.

The latency of the P1 component over both hemispheres on binocular and monocular stimulation is given. The resulting Cx value is zero indicating that there was no consistent lateralisation of this component on monocular stimulation. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).

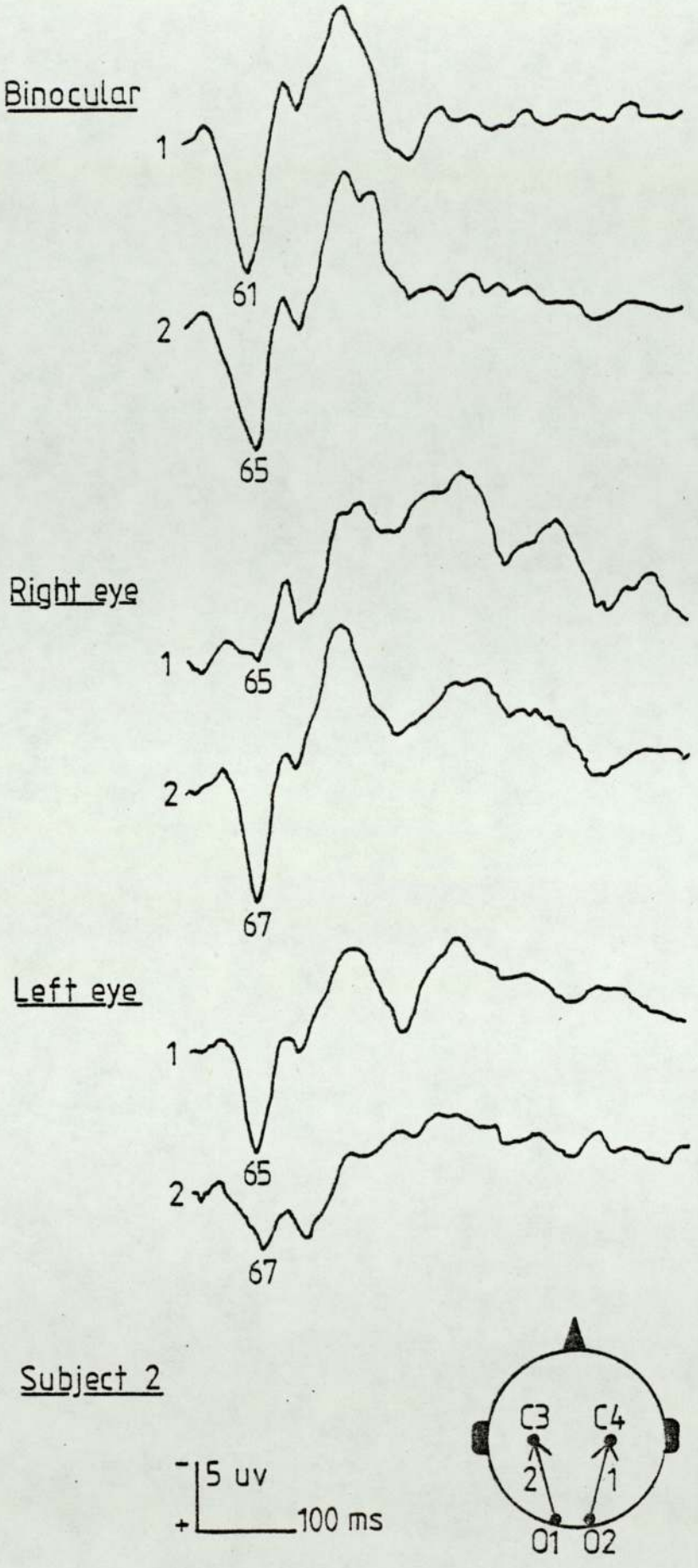

Binocular
1
61
2
65
Right eye
1
65
2
67
Left eye
1
65
2
67
Subject 2
5 uv
100 ms
C3
C4
2
1
O1
O2

Figure 6.5

The Flash VECPs of Albino Subject 8
with P1 Labelled

The latency of the P1 component over each hemisphere on binocular and monocular stimulation is given, the resulting Cx value for this component is +33.0 ms. This subject, therefore, showed an extreme amount of contralateral lateralisation on monocular stimulation. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).

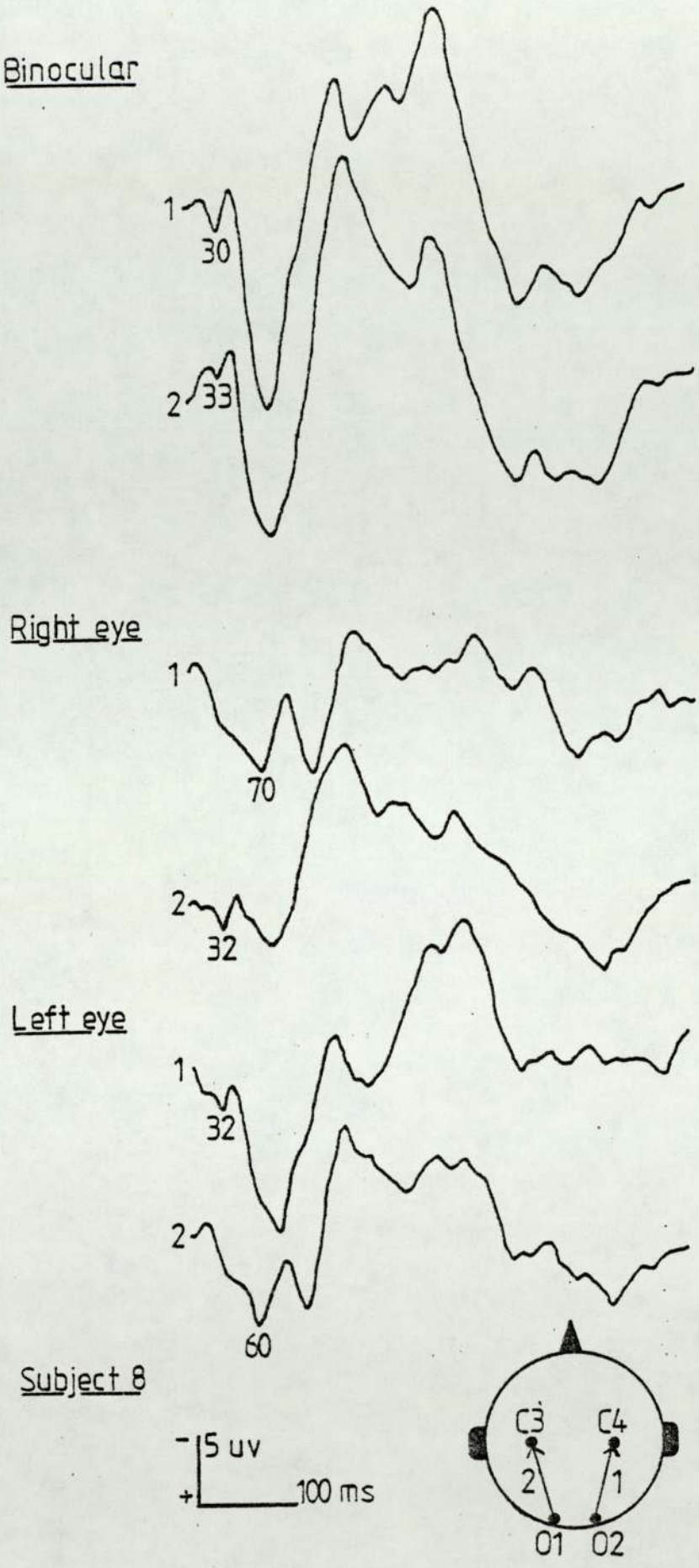
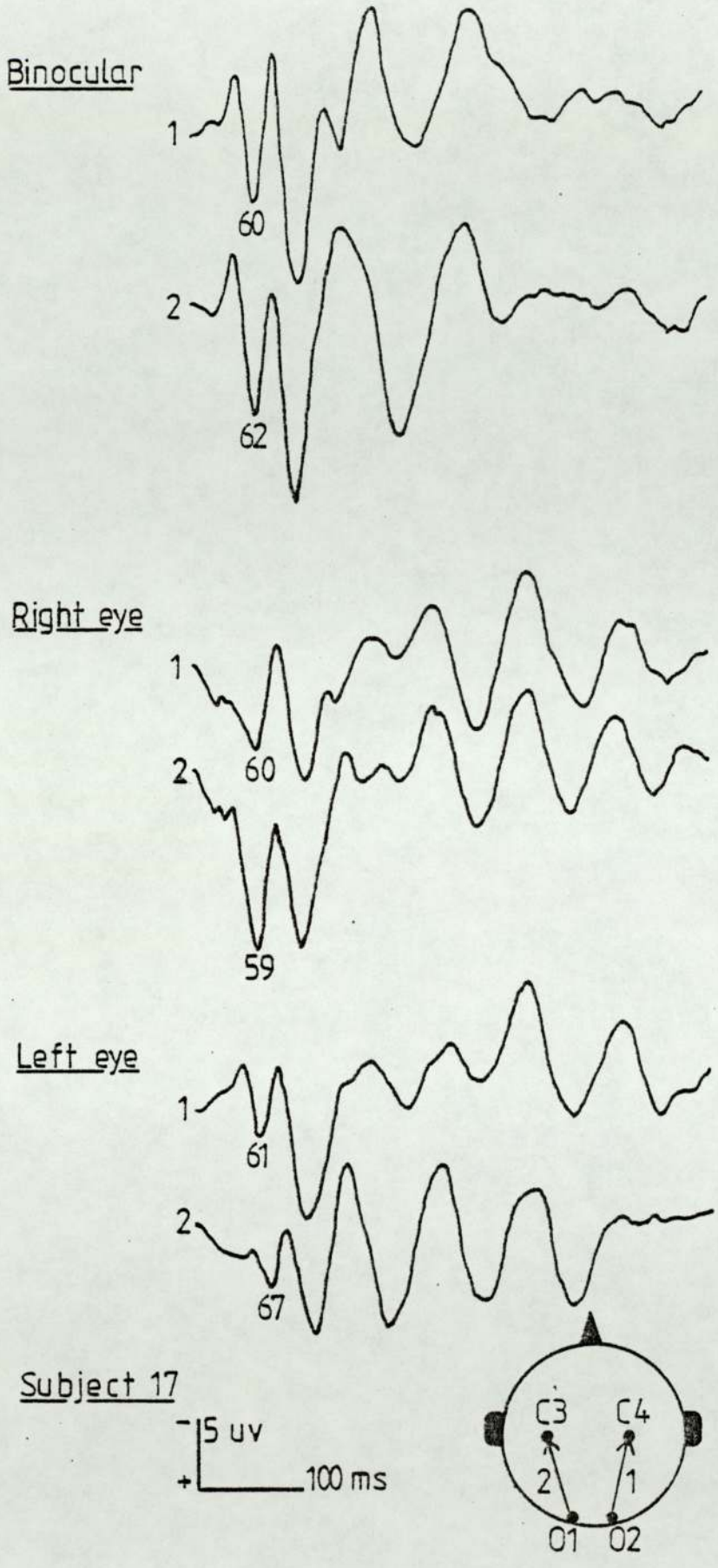

Binocular
1
30
2
33
Right eye
1
70
2
32
Left eye
1
32
2
60
Subject 8
5 uv
100 ms
C3
C4
2
1
O1
O2

Figure 6.6

The Flash VECPs of Albino Subject 17 with P1 Labelled

In this subject the resulting Cx value for latency of P1 is +3.5 ms indicating a moderate amount of contralateral lateralisation on monocular stimulation. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).


Binocular
1
60
2
62
Right eye
1
60
2
59
Left eye
1
61
2
67
Subject 17
5 uv
100 ms
C3
C4
2
1
O1
O2

lateralisation. Figure 6.7 illustrates the responses of subject 12; the flash VECP of this albino showed gross ipsilateral lateralisation (Cx = -17.5ms). However, more modest negative Cx values were the rule; Figure 6.7 also illustrates such a case (Subject 11; Cx = -3.5ms).

The mean Cx value within the albino group was +0.68ms (S.E. 2.83) and among the controls -0.12ms (S.E. 0.86). These mean values $\pm$ 1 S.E. are illustrated in Figure 6.8.

When ANOVA was performed on the raw data obtained from the control subjects and the albinos to whom they were matched, no significant interactions were found.

In both cases there was no significant interaction between the eye stimulated and the hemisphere showing the shortest P1 latency. These results are shown graphically in Figure 6.9.

6.2.2 N2 latency

An N2 component could be identified over both hemispheres on binocular and monocular stimulation in all albino and control subjects. The Cx values for this component are shown in Table 6.2.

Among the albino subjects Cx ranged from +50.0ms to -33.5ms and among the controls from +9.5ms to -9.0ms. A positive Cx value was found in 13 (59%) of albino subjects and negative in 9 (41%). Within the

Figure 6.7

The Flash VECPs of Albino Subjects 12 and 11 with P1 Labelled

The latency of the P1 component over each hemisphere on binocular and monocular stimulation is given. In (a) Cx = -17.5 ms. indicating an extreme amount of monocular ipsilateral lateralisation while in (b) Cx = -3.5 ms indicating a more moderate amount of hemispheric ipsilateral lateralisation. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).

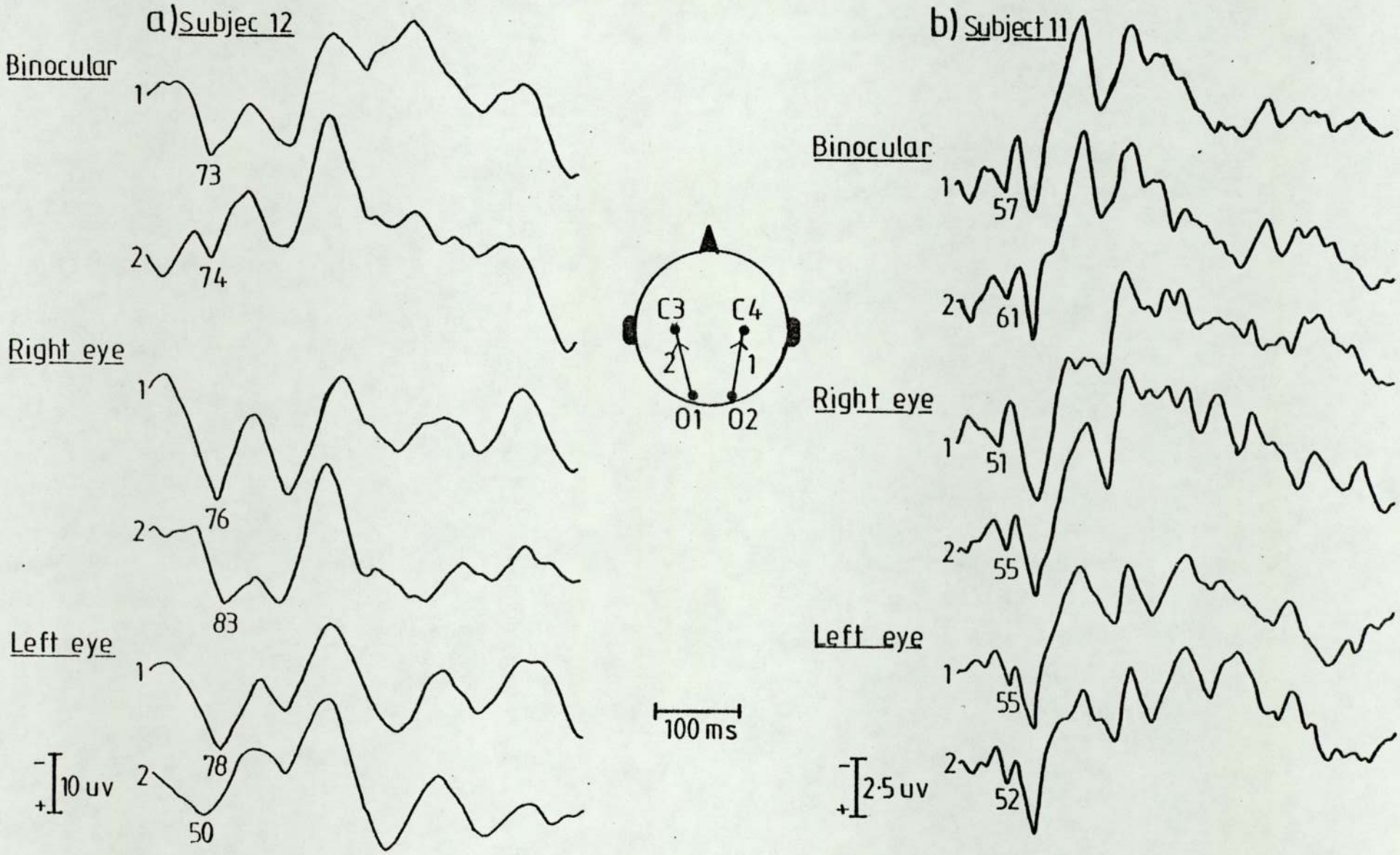

a) Subjec 12
Binocular
1
73
2
74
Right eye
1
76
2
83
Left eye
1
78
2
50
10 uv
C3
C4
2
1
O1
O2
100 ms
b) Subject 11
Binocular
1
57
2
61
Right eye
1
51
2
55
Left eye
1
55
2
52
2·5 uv

Figure 6.8

Graphical Illustration of the Mean Cx Values
$\pm$1 S.E. with Respect to the Latency of P1
in Both the Albino and Control Groups

The mean Cx values $\pm$ 1 S.E. are plotted for both groups.

(See text for further details)

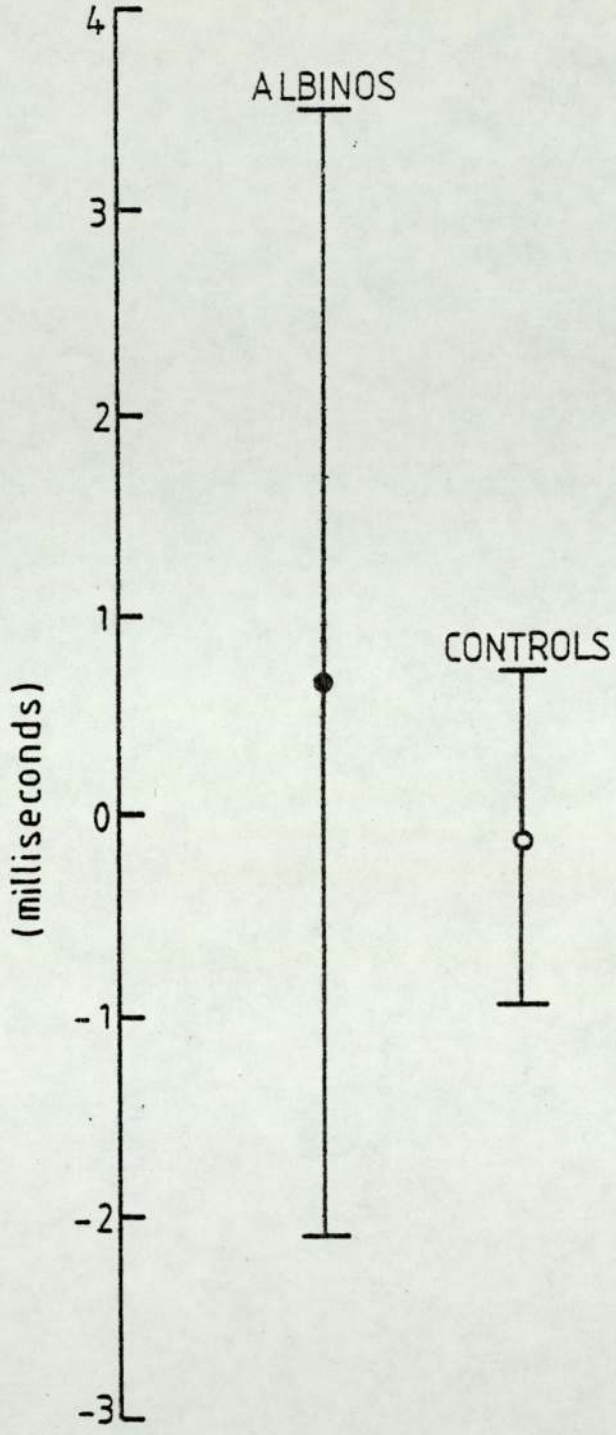

4
3
2
1
0
-1
-2
-3
(milliseconds)
ALBINOS
CONTROLS

Figure 6.9

Graphical Illustration of ANOVA Results Obtained Using the Raw P1 Latency Data from the Albino and Control Groups

The latency of the P1 component over each hemisphere on binocular and monocular stimulation for both groups is plotted. Neither the data from the albino or control group showed any interaction between the hemisphere over which the shorter P1 latency was recorded and the eye stimulated.

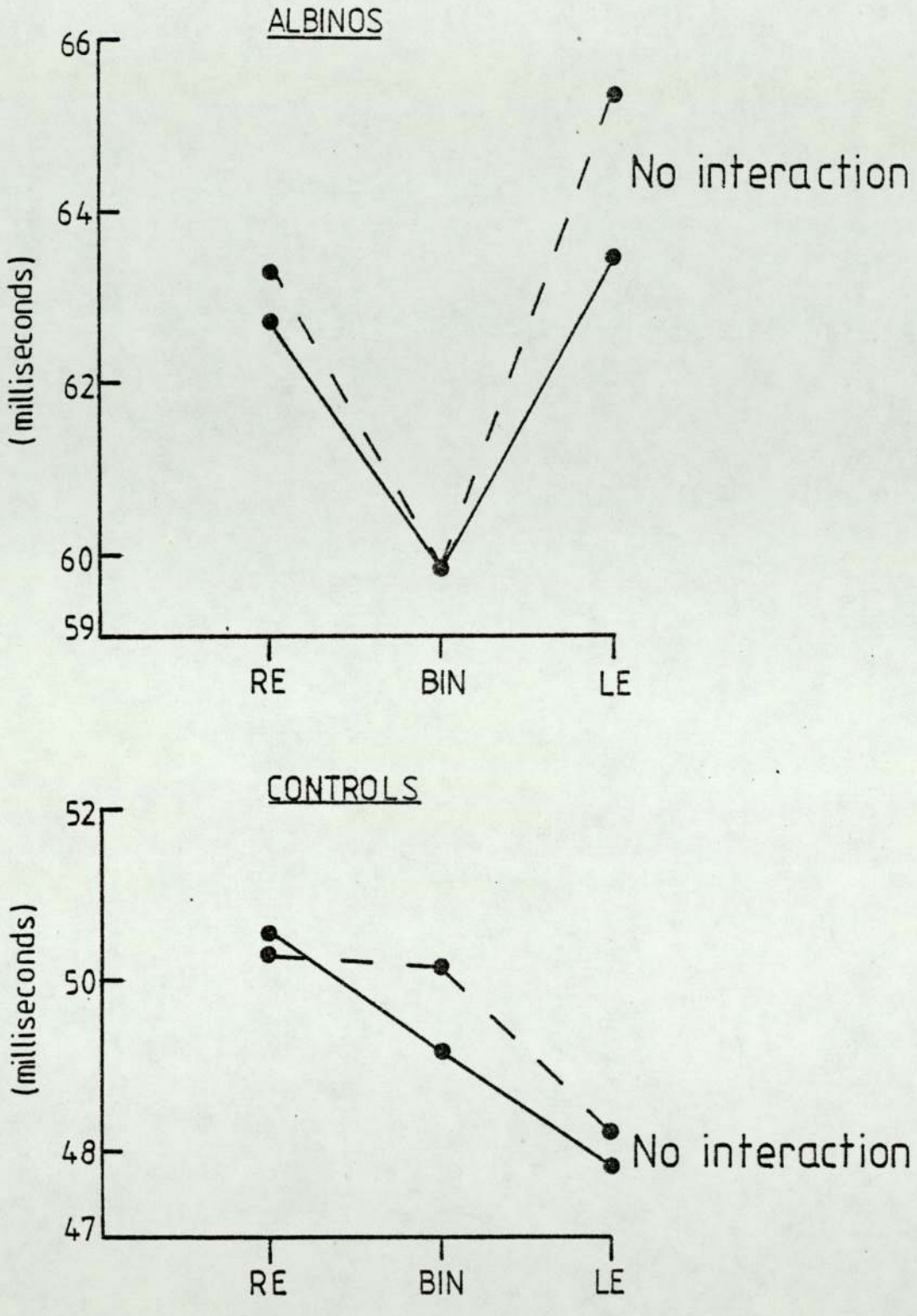

ALBINOS
66
64
62
60
59
(milliseconds)
No interaction
RE
BIN
LE
CONTROLS
52
50
48
47
(milliseconds)
No interaction
RE
BIN
LE
——— = Right hemisphere
— — = Left hemisphere
RE = Right eye
BIN = Binocular
LE = Left eye

Table 6.2

The Cx Values for N2 Latency

The calculated Cx values (in ms) for the latency of component N2 in the flash VECP are given for each albino and his matched control. (See text for further details).

SUBJECT	Cx (N2 LATENCY)	
	ALBINO	CONTROL
1	+8.0	+1.0
2	-3.0	0
3	-5.5	+3.0
4	-0.5	0
5	-2.0	+1.0
6	+2.5	0
7	+8.5	-1.0
8	+50.0	+0.5
9	+1.0	+0.5
10	+0.5	-1.5
11	-2.0	+4.0
12	-12.5	-9.0
13	-33.5	+1.5
14	+13.5	-4.0
15	+0.5	+2.5
16	-2.0	+2.0
17	+2.5	-5.0
18	-2.0	+9.5
19	+13.5	-0.5
21	+0.5	-2.5
22	+1.0	-0.5
23	+1.5	-5.0

control group 3 (14%) of the subjects showed a Cx of zero, 10 (45%) a positive Cx and 9 (41%) a negative value.

As found when considering component P1, among the control subjects N2 usually showed a certain amount of monocular lateralisation but not of a consistently contralateral or ipsilateral nature. Figure 6.10 shows 2 such contrasting responses; those of subject 3C (Cx = +3.0ms) and 12C (Cx = -9.0ms). In the former contralateral lateralisation is found but in the latter the hemispheric lateralisation is of the ipsilateral type.

Examination of Table 6.2 indicates that a similar diversity of Cx value were also found within the albino group.

As in the case of P1 latency, extreme ipsilateral and contralateral hemispheric monocular lateralisations were found but, typically, the lateralisations were of more modest amounts. Figures 6.11 and 6.12 illustrate two such cases. Figure 6.11 shows the response of subject 1 in whom Cx = +8.0ms indicating contralateral lateralisation on monocular stimulation while, in contrast, Figure 6.12 shows the ipsilateral lateralisation found in subject 12 (Cx = -12.5ms).

The mean Cx value for the albino group was +1.84ms (S.E. 3.04) and for the controls -0.16ms (S.E. 0.79). These mean values $\pm$ 1 S.E for both groups are shown in Figure 6.13.

FIGURE 6.10

The Flash VECPs of Control Subjects 3C and 12C with N2 Labelled

The latency of the N2 component over each hemisphere on binocular and monocular stimulation is given. In the case of (a) Cx = +3.0 ms this being typical of the small amount of monocular contralateral lateralisation seen within the control group. By contrast, in (b) Cx = -9.0 ms indicating ipsilateral monocular lateralisation. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).

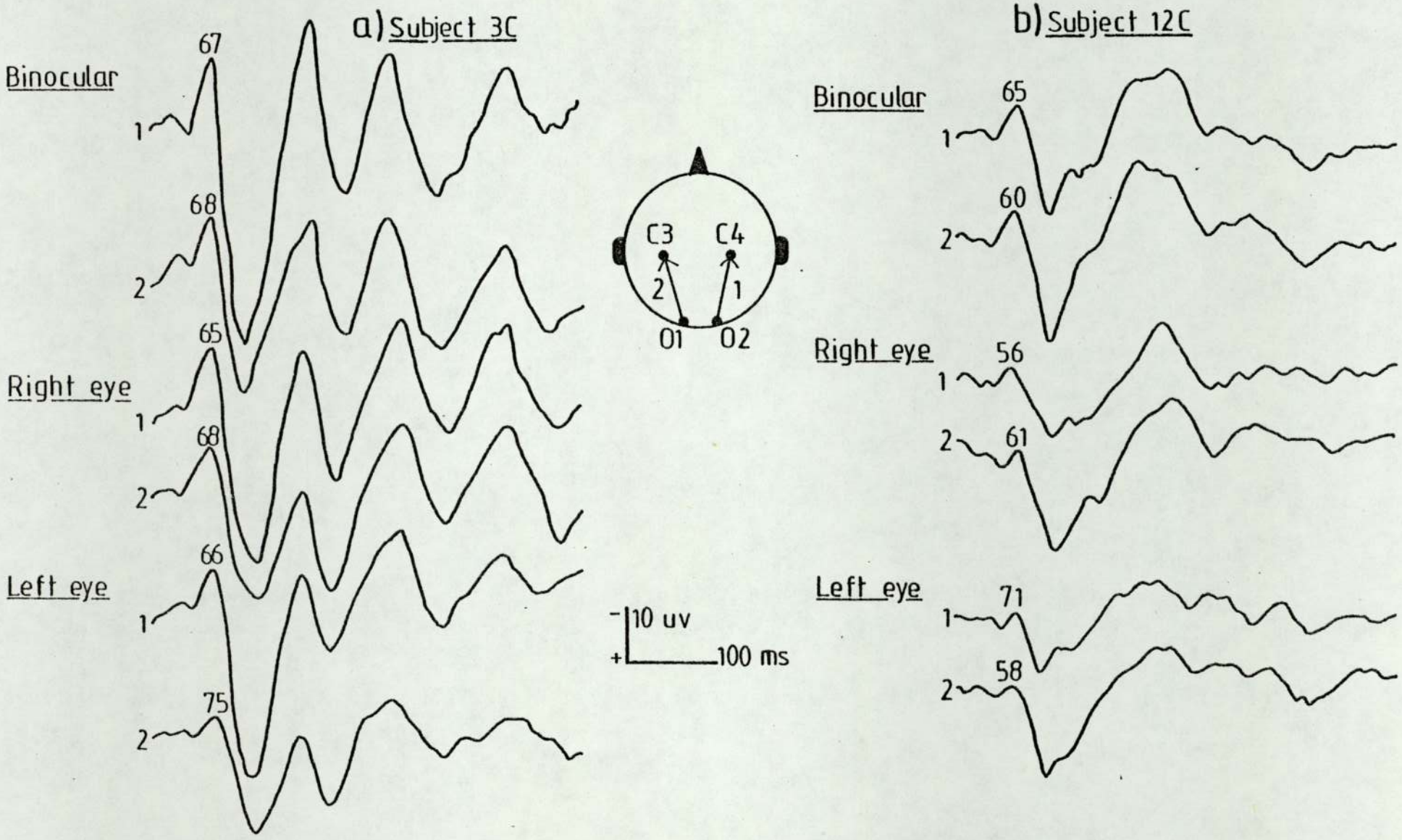

a) Subject 3C
b) Subject 12C
Binocular
Right eye
Left eye
67
68
65
68
66
75
65
60
56
61
71
58
1
2
C3
C4
O1
O2
10 uv
100 ms

Figure 6.11

The Flash VECPs of Albino Subject 1 with N2 Labelled

The latency of N2 over each hemisphere on binocular and monocular stimulation is shown. The resulting Cx value is + 8.0 ms. indicating a modest amount of contralateral lateralisation on monocular stimulation. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).

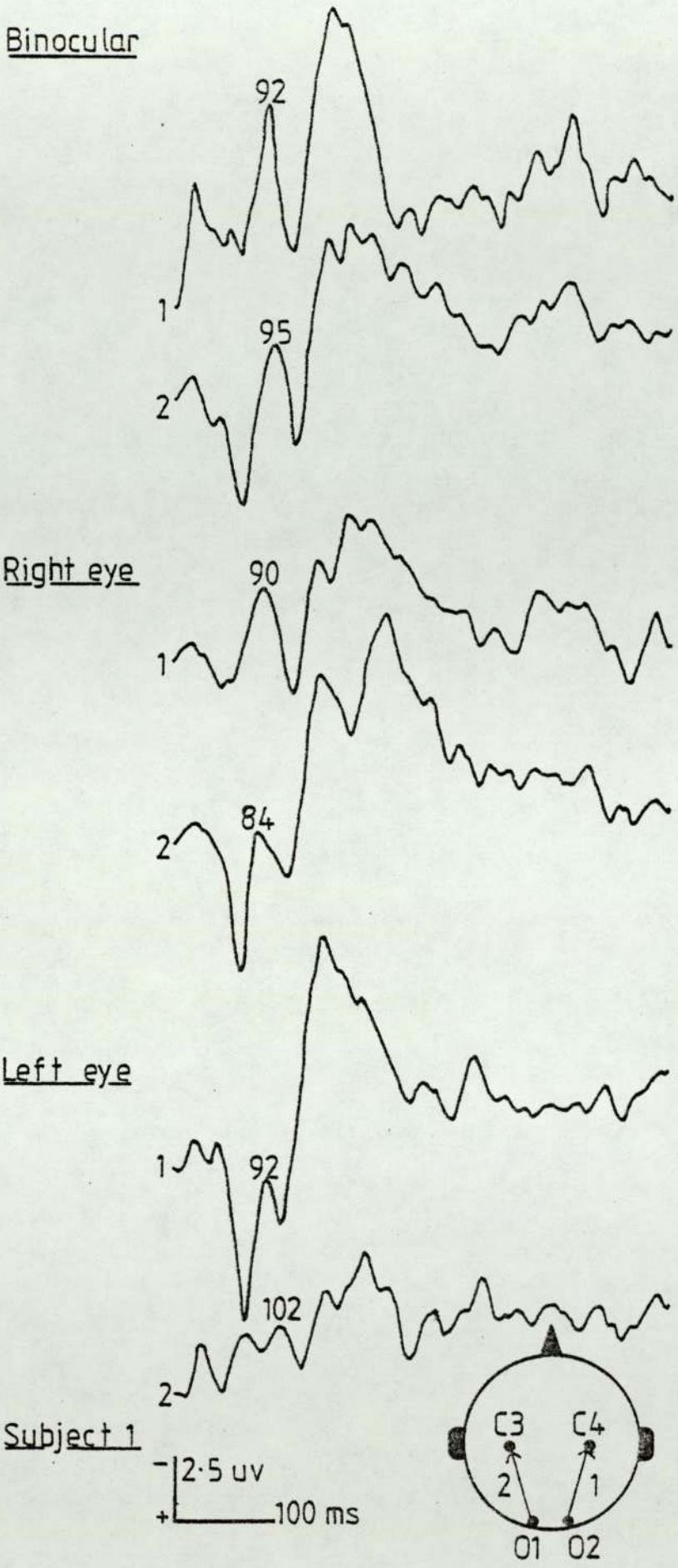

Binocular
92
1
95
2
Right eye
90
1
84
2
Left eye
1
92
102
2
Subject 1
2·5 uv
100 ms
C3
C4
2
1
O1
O2

Figure 6.12

The Flash VECPs of Albino Subject 12 with N2 Labelled

In this subject the resulting Cx values for the latency of the N2 component is -12.5 ms indicating ipsilateral lateralisation on monocular stimulation. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).

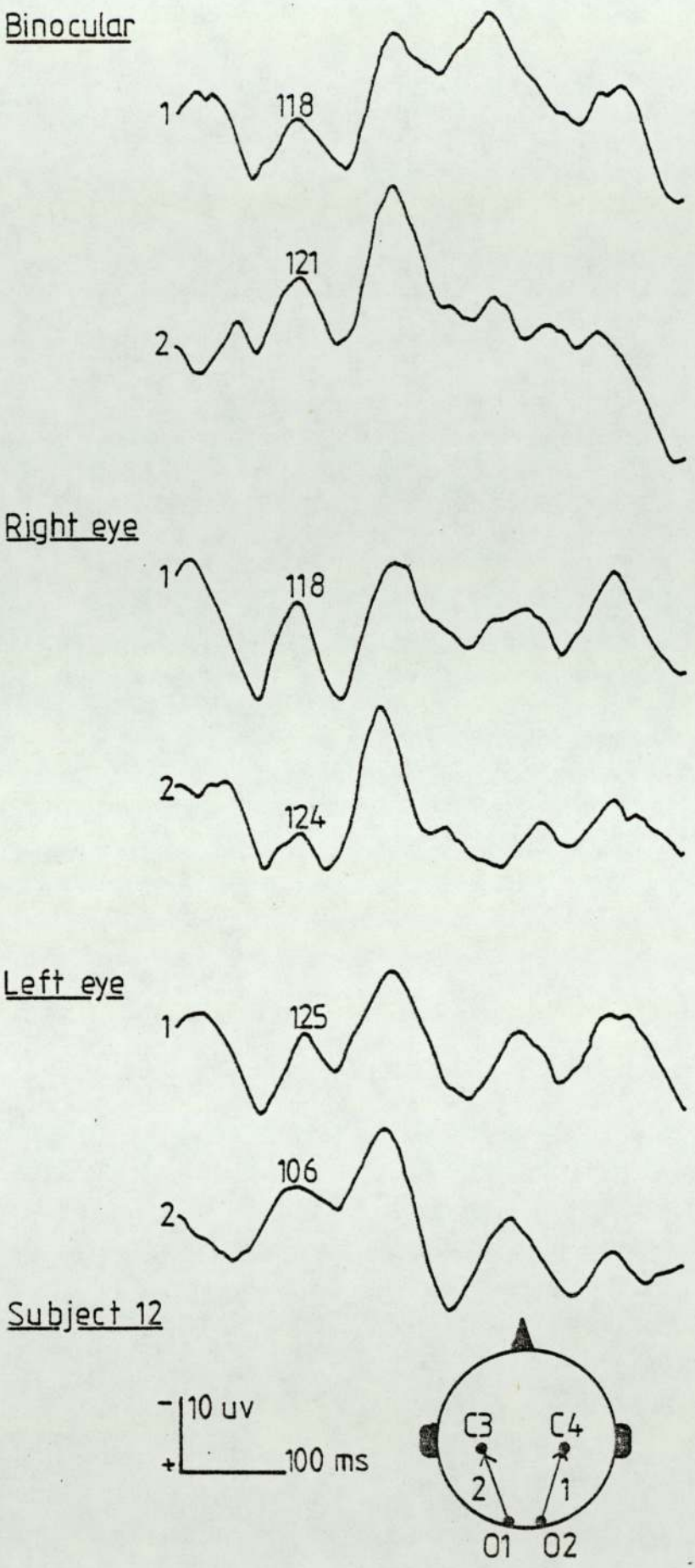
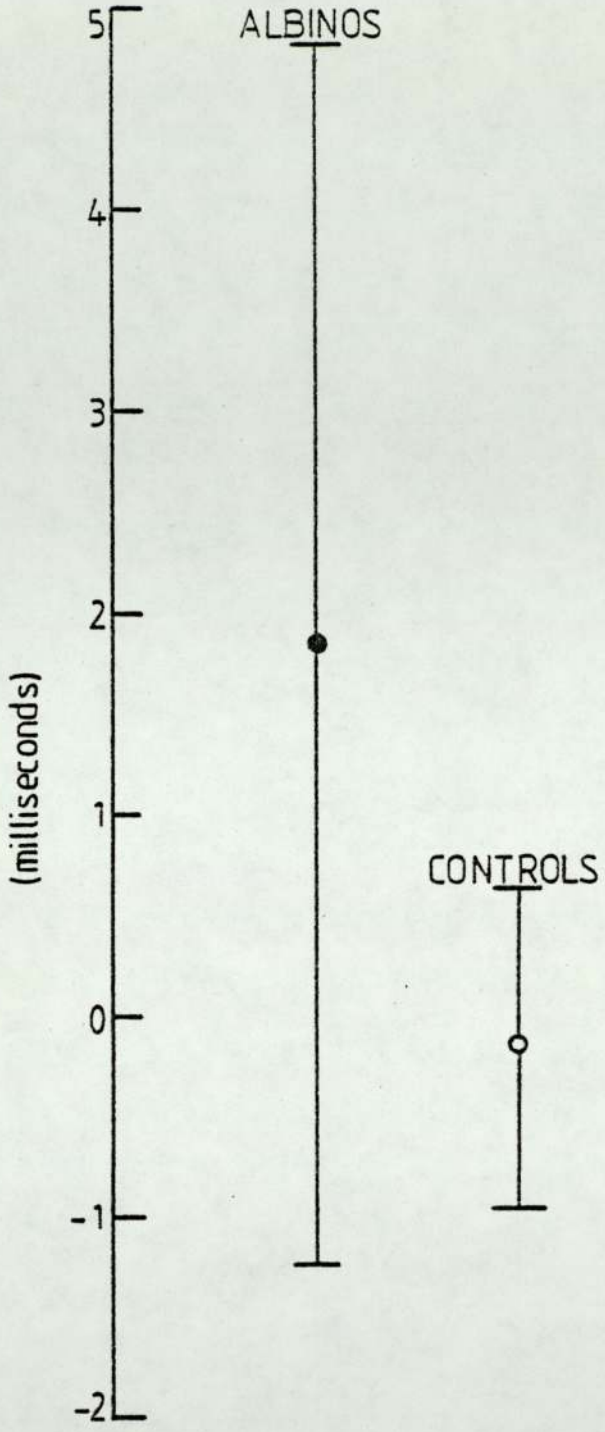

Binocular
1
118
121
2
Right eye
1
118
2
124
Left eye
1
125
106
2
Subject 12
10 uv
100 ms
C3
C4
2
1
O1
O2

Figure 6.13

Graphical Illustration of the Mean Cx Values
± 1 S.E. with Respect to the Latency of N2
in Both the Albino and Control Groups

The mean Cx values ± 1 S.E. are plotted for both groups.

(See text for further details)


ALBINOS
CONTROLS
5
4
3
2
1
0
-1
-2
(milliseconds)

Statistical analysis of the raw data using ANOVA produced similar results to that found when considering P1 latency. There was no significant interaction between the latency of the N2 component over the two hemispheres and the eye stimulated in both the albino and control groups. These results are illustrated graphically in Figure 6.14.

6.2.3 P2 latency

A P2 component was consistently present over both hemispheres on binocular and monocular stimulation in all albino and control subjects. The calculated Cx values for this component are shown in Table 6.3.

Among the albino subjects Cx ranged from +33.0ms to -16.0ms and among the control subjects from +6.0ms to -5.5ms. One major difference between the results obtained when considering this component measure rather than the latencies of P1 and N2 lies in the fact that 20 (91%) of the albino population showed a positive Cx value and only 2 (9%) a negative value. In contrast, the data from the control group showed a similar distribution to that found when considering P1 and N2; 2 (9%) showed a zero Cx, 13 (59%) a positive value and 7 (32%) a negative value.

Of the control subjects some showed little or no lateralisation on monocular stimulation although exceptions were found. Figure 6.15 illustrates two such cases; subject 15C (Cx = +6.0ms) and subject 4C (Cx = -2.0ms) indicating contralateral and ipsilateral lateralisation respectively.

Figure 6.14

Graphical Illustration of ANOVA Results Obtained Using the Raw N2 Latency Data from the Albino and Control Groups

The latency of the N2 component over both hemispheres on binocular and monocular stimulation is plotted for both the albinos and their controls. There was no interaction found between the hemisphere over which the shorter N2 latency was recorded and the eye stimulated in either group.

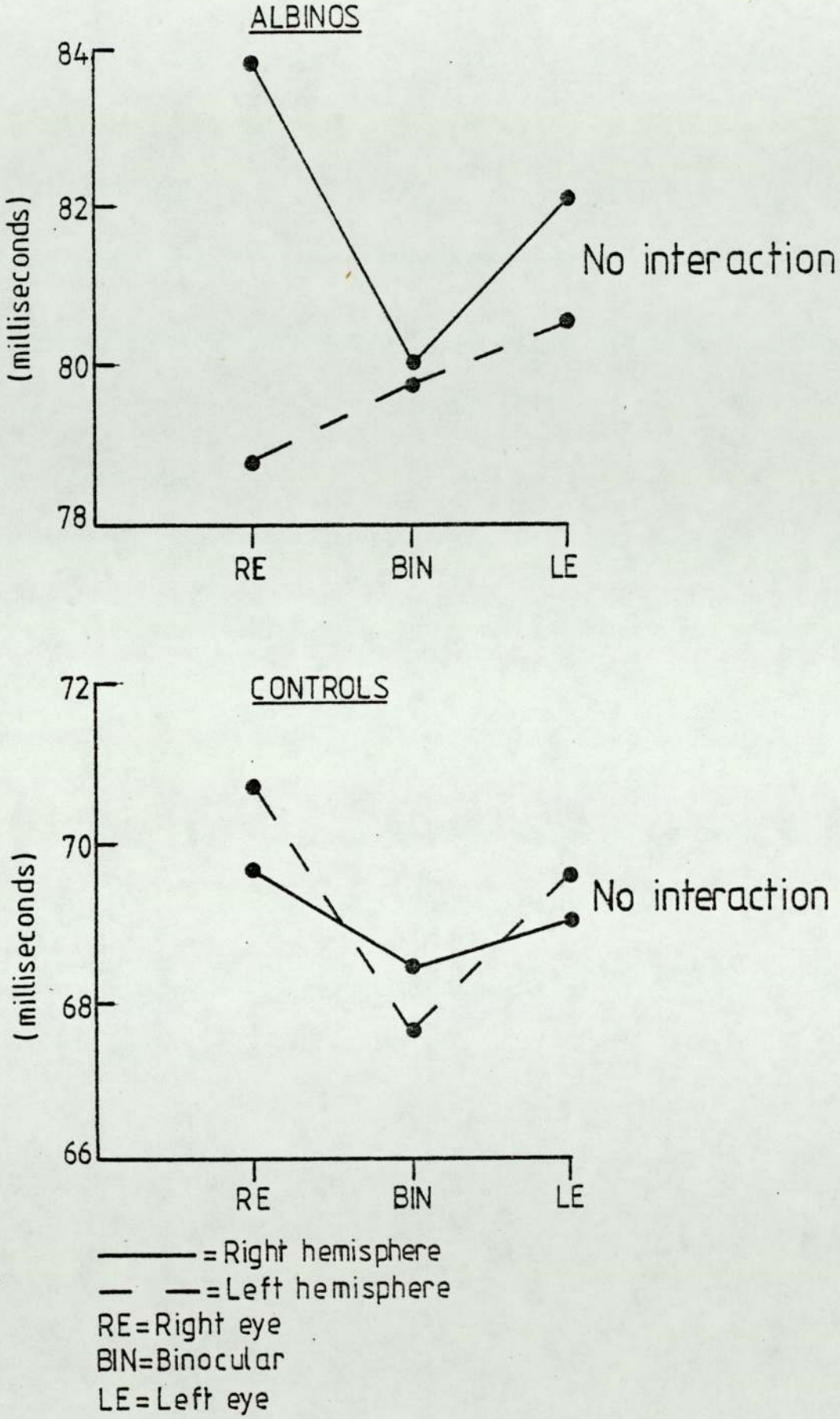

ALBINOS
84
82
80
78
(milliseconds)
RE
BIN
LE
No interaction
CONTROLS
72
70
68
66
(milliseconds)
RE
BIN
LE
No interaction
= Right hemisphere
= Left hemisphere
RE = Right eye
BIN = Binocular
LE = Left eye

Table 6.3

The Cx Values for P2 Latency

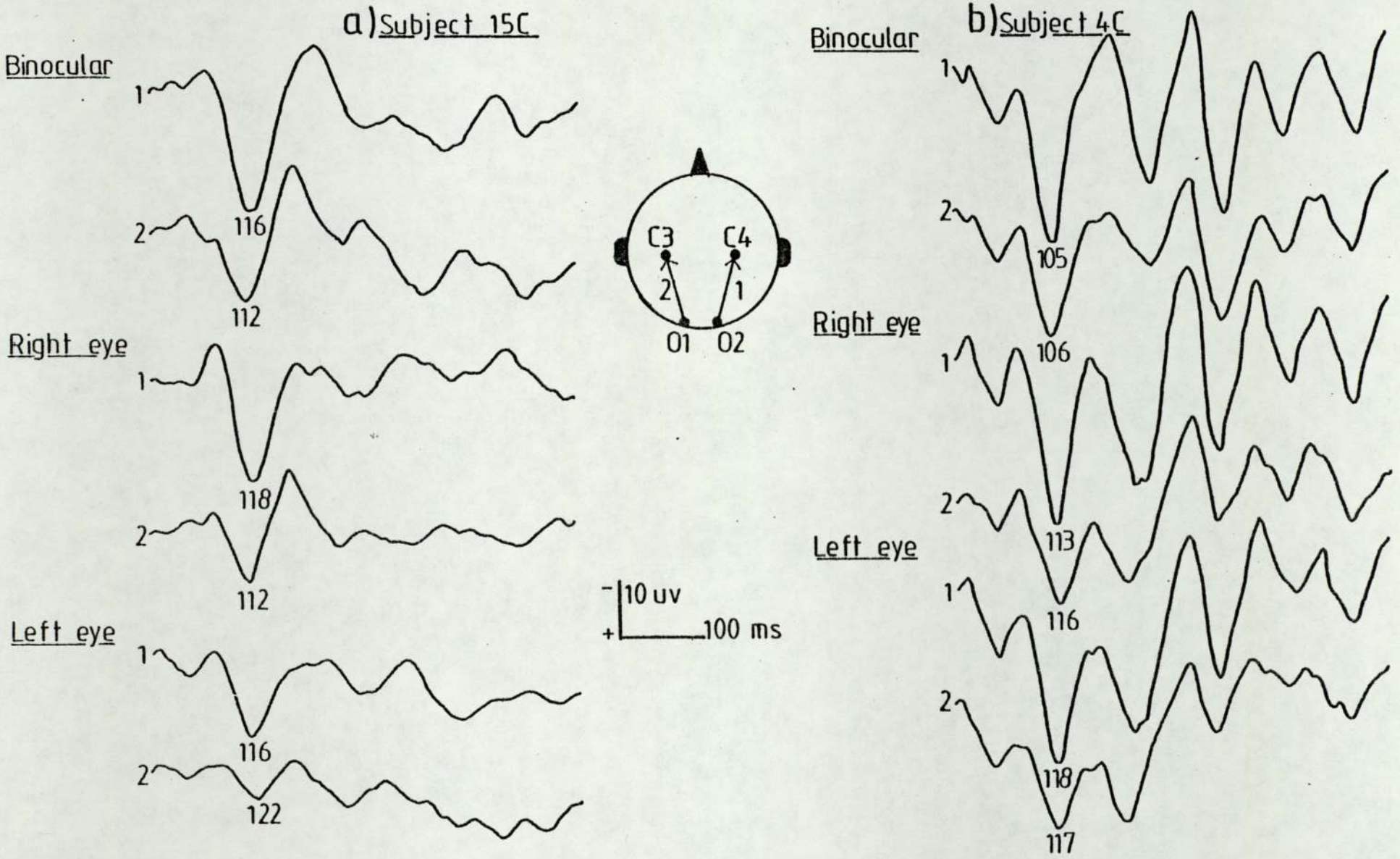
The calculated Cx values (in ms) for the latency of component P2 in the flash VECP are given for each albino and his matched control. (See text for further details).

SUBJECT	Cx (P2 LATENCY)	
	ALBINO	CONTROL
1	+11.0	-1.0
2	+4.5	+2.0
3	+6.5	0
4	+7.0	-2.0
5	-16.0	-0.5
6	+4.5	0
7	-0.5	+1.5
8	+33.0	-1.0
9	+3.5	+0.5
10	+5.0	+2.0
11	+3.5	+0.5
12	+8.5	+1.5
13	+12.5	-5.5
14	+5.5	+2.0
15	+3.0	+6.0
16	+2.5	+2.5
17	+4.0	-2.0
18	+6.5	+1.0
19	+26.5	+2.5
21	+1.5	+0.5
22	+3.0	+1.5
23	+1.0	-4.0

Figure 6.15

The Flash VECPs of Control Subjects 15C and 4C with P2 Labelled.

The latency of the P2 component over each hemisphere on binocular and monocular stimulation is given. (a) illustrates an unusual case within the control group. In this subject Cx =+6.0 ms. indicating a quite large amount of contralateral lateralisation on monocular stimulation. In contrast (b) shows the responses of a subject in whom Cx = - 2.0 ms indicating ipsilateral monocular lateralisation. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).


a) Subject 15C
Binocular
1
2
116
112
Right eye
1
2
118
112
Left eye
1
2
116
122
C3
C4
2
1
O1
O2
10 uv
100 ms
b) Subject 4C
Binocular
1
2
105
Right eye
1
2
106
113
Left eye
1
2
116
118
117

As described above, the majority of albino subjects showed contralateral lateralisation of P2 on monocular stimulation. An extreme example of this is shown in Figure 6.16. This illustrates the responses of subject 8 who displayed gross contralateral lateralisation resulting in a Cx of +33.0ms. However, this example is not typical of the general albino population. Figures 6.17 and 6.18 illustrate the results more usually seen within the group. These show the VECPs of subject 1 (Cx = +11.0ms) and 22 (Cx = +3.0ms) respectively, indicating more moderate contralateral lateralisations on monocular stimulation. Only 2 albinos showed ipsilateral lateralisation (see Table 6.3) and in only one of these was the lateralisation of a large amount. Figure 6.19 illustrates this case showing the responses of subject 5 (Cx = -16.0ms).

The mean Cx value of the albino group was +6.21ms (S.E. 2.00) and among the controls +0.36ms (S.E. 0.52). These mean values $\pm$ 1 S.E. for both groups are illustrated in Figure 6.20.

Statistical analysis using ANOVA on the raw data produced two significant results. Among the control group P2 was found to be of significantly shorter latency on binocular compared to monocular stimulation ($p < 0.01$; $F2, 42 = 7.70$). Such a result was not found within the albino group.

When considering the latency of the P2 component over the two hemispheres on monocular stimulation, among the albino group the latency was significantly shorter over the

FIGURE 6.16

The Flash VECPs of albino subject 8 with P2 labelled

The latency of P2 over each hemisphere on binocular and monocular stimulation is given. The resulting Cx value is +33.0ms. This example illustrates an extreme case within the albino group in that a very large amount of contralateral lateralisation on monocular stimulation is present. (Flash intensity 2, 1.8 flashes per second, 50 sweeps)

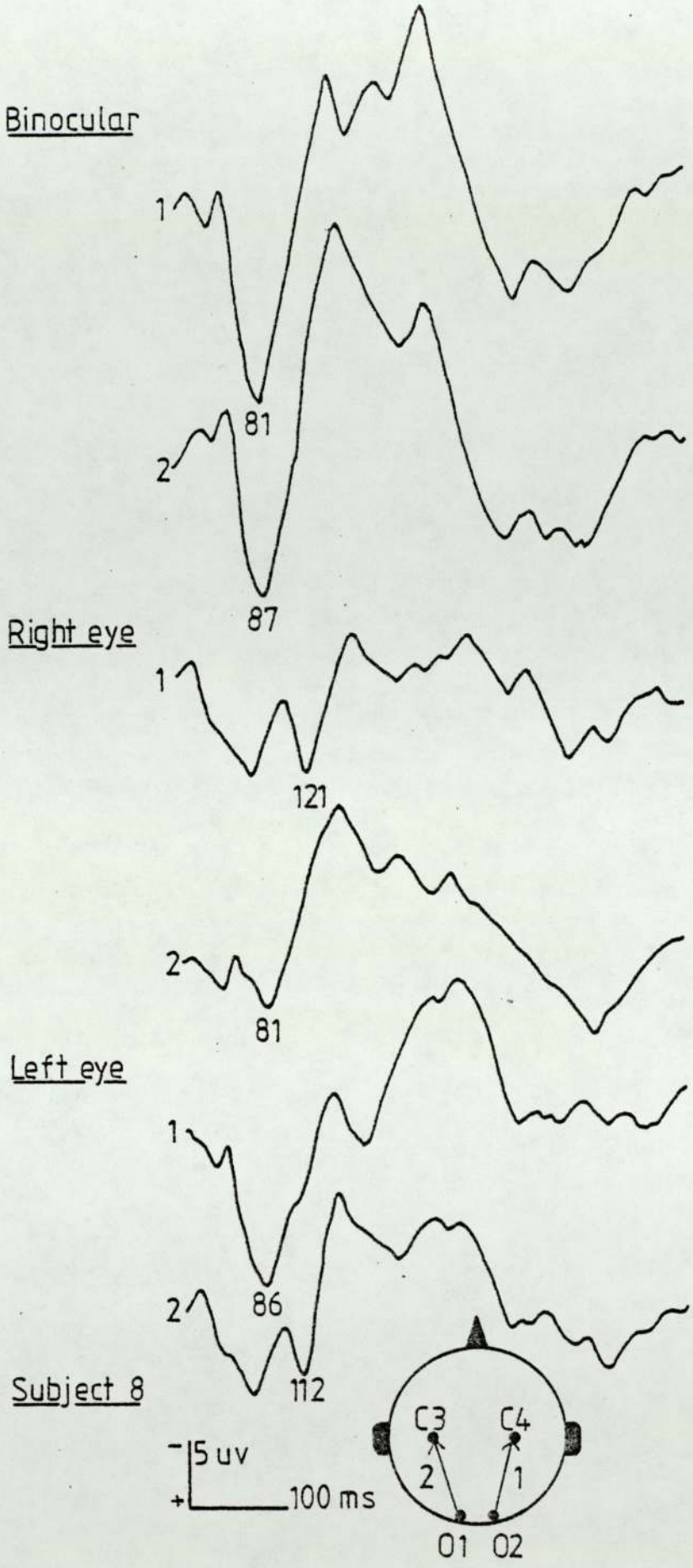

Binocular
1
2
81
87
Right eye
1
121
2
81
Left eye
1
2
86
112
Subject 8
5 uv
100 ms
C3
C4
2
1
O1
O2

FIGURE 6.17

The Flash VECPs of Albino Subject 1 with P2 Labelled

The recorded P2 latencies over the two hemispheres result in a Cx value of +11.0ms indicating a moderate amount of contralateral lateralisation on monocular stimulation. (Flash intensity 2, 1.8 flashes per second, 50 sweeps)

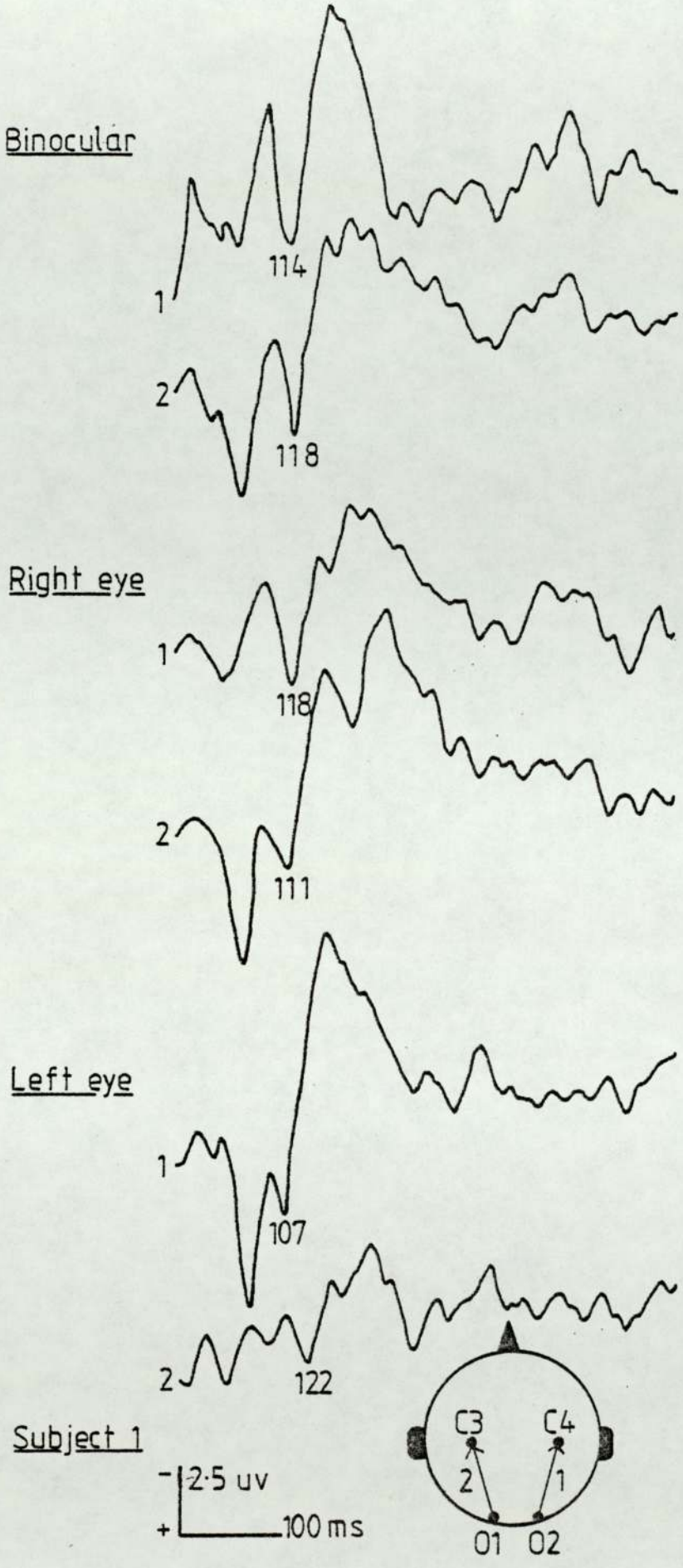

Binocular
1
114
2
118
Right eye
1
118
2
111
Left eye
1
107
2
122
Subject 1
2·5 uv
100 ms
C3
C4
2
1
O1
O2

FIGURE 6.18

The Flash VECPs of Albino Subject 22 with P2 Labelled

In this case a small amount of contralateral lateralisation of the P2 component was present on monocular stimulation; Cx = +3.0ms. (Flash intensity 2, 1.8 flashes per second, 50 sweeps)

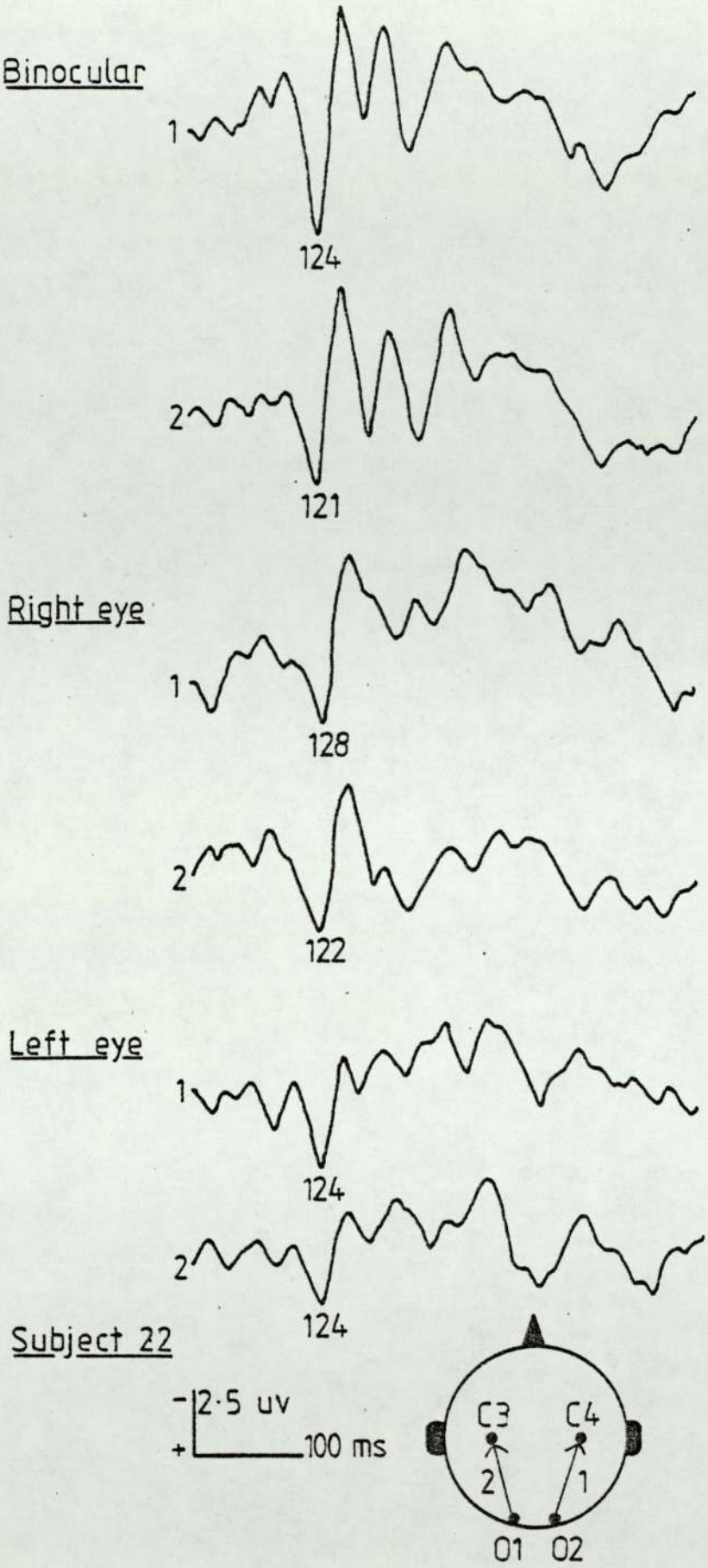

Binocular
1
124
2
121
Right eye
1
128
2
122
Left eye
1
124
2
124
Subject 22
-
2·5 uv
+
100 ms
C3
C4
2
1
O1
O2

Figure 6.19

The Flash VECPs of Albino Subject 5 with P2 Labelled

The latency of P2 over each hemisphere on binocular and monocular stimulation is shown. This albino was one of only two in whom ipsilateral lateralisation of the P2 component occurred on monocular stimulation. This albino showed the greater negative Cx value of -16.0 ms. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).

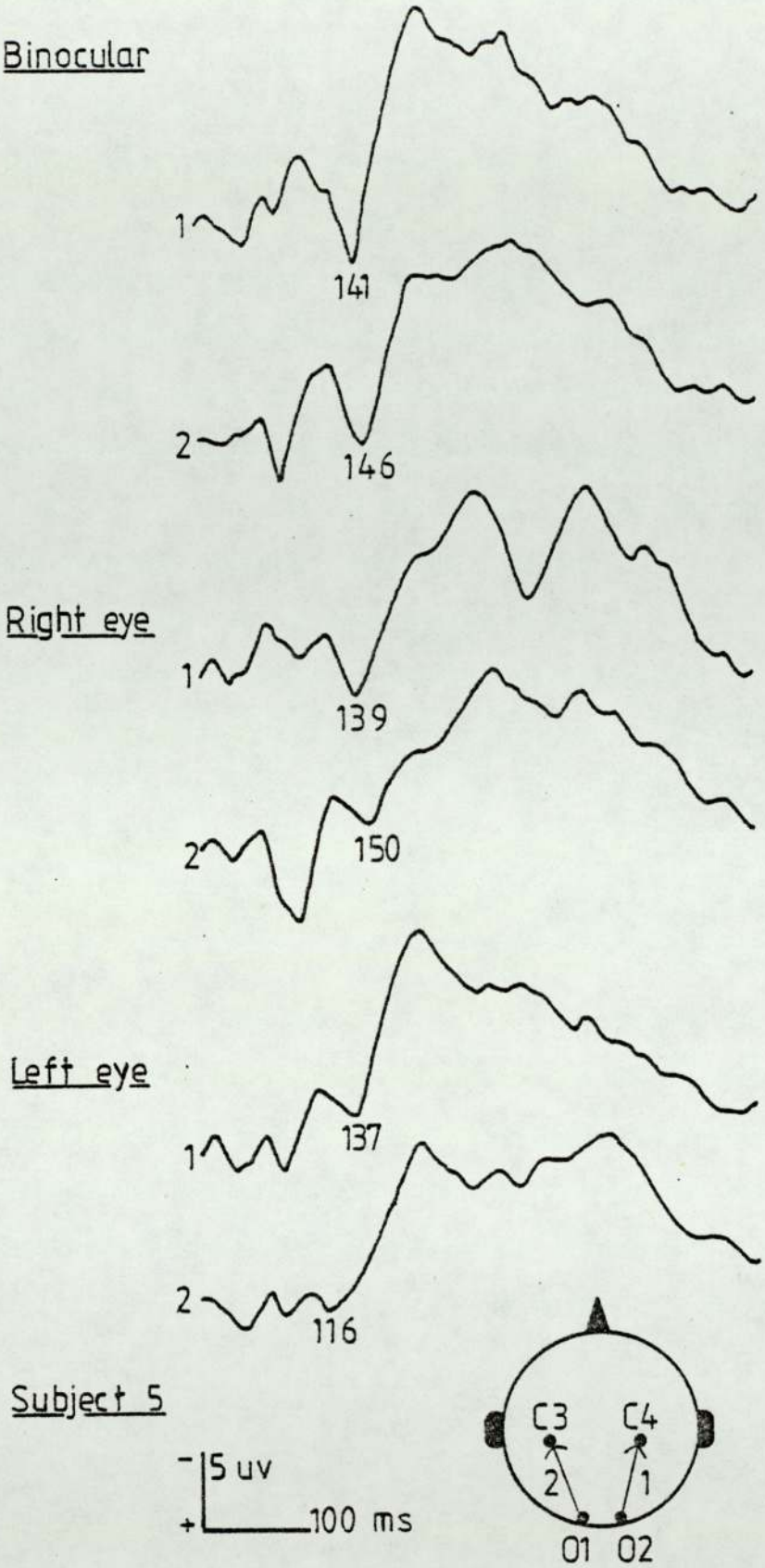
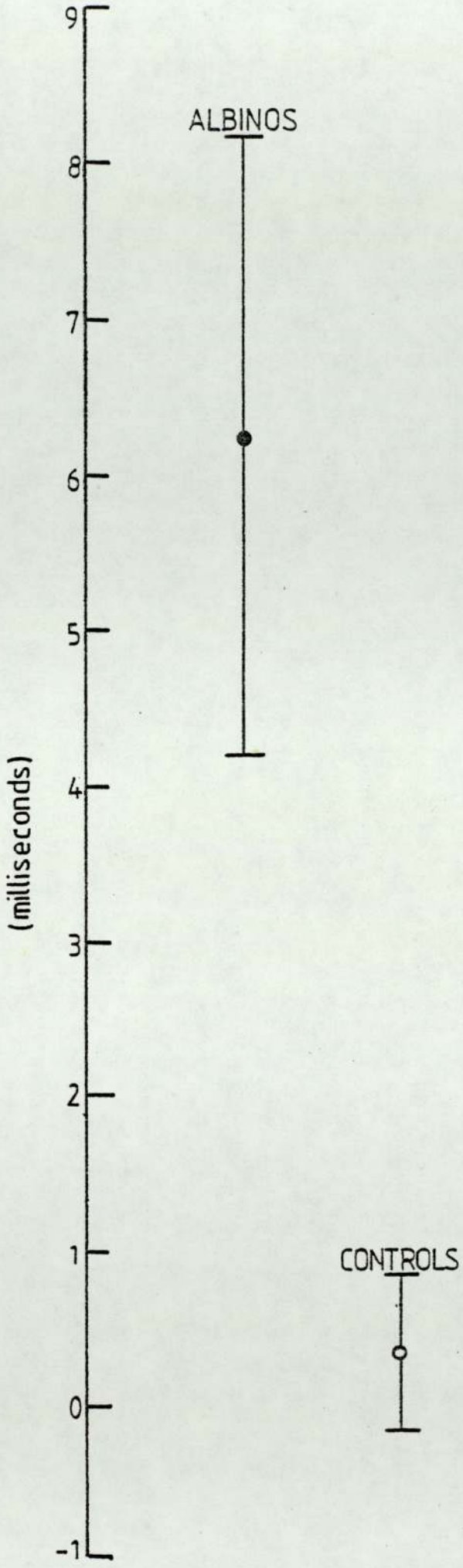

Binocular
1
141
2
146
Right eye
1
139
2
150
Left eye
1
137
2
116
Subject 5
5 uv
100 ms
C3
C4
2
1
O1
O2

FIGURE 6.20

Graphical illustration of the mean Cx values ± 1 S.E. with respect to the latency of P2 in both the Albino and Control Groups

The mean Cx values ± 1 S.E. are plotted for both groups

(see text for further details)


9
8
7
6
5
4
3
2
1
0
-1
(milliseconds)
ALBINOS
CONTROLS

hemisphere contralateral to the eye stimulation ($p < 0.001$; $F2, 42 = 9.71$). Among the control group such a result was not found and, therefore, there was no interaction between the latency of the P2 component over the two hemispheres and the eye stimulated. These results are illustrated graphically in Figure 6.21.

6.2.4 P1N2 amplitude

This could only be measured in those subjects in whom a P1 component could be clearly identified thus precluding the 23% of the albino subjects described in 6.2.1 in whom such a component was not consistently found. Table 6.4 shows the calculated Cx values for this measure in the remaining 17 albinos and their matched controls.

Among the albinos Cx ranged from +5.45uV to -5.55uV and in the controls from +2.85uV to -1.60uV. Eight (47%) of the albinos had a positive Cx and the remaining 9 (53%) a negative result. One of the control group (6%) showed a Cx of zero; of the remaining subjects, 13 (76%) showed a positive and 3 (18%) a negative value.

Within the control group the value of Cx was usually small. A typical example is shown in Figure 6.22 (subject 22C; Cx = +0.20uV). The range of Cx values was somewhat greater among the albino subjects; typical examples are shown in Figure 6.23. Here are illustrated the responses of subject 2 (Cx = +5.00uV) and subject 12

Figure 6.21

Graphical Illustration of ANOVA results Obtained Using the Raw P2 Latency Data from the Albino and Control Groups

The latency of P2 over each hemisphere on binocular and monocular stimulation is plotted. Within the control group P2 was significantly shorter in latency ($p < 0.01$) on binocular compared to monocular stimulation, such a result was not found within the albino group. However, within the latter group, but not the controls, there was a significant interaction ($p < 0.001$) between the latency of P2 over the two hemispheres and the eye stimulated; the latency was significantly shorter over the hemisphere contralateral to the eye stimulated.

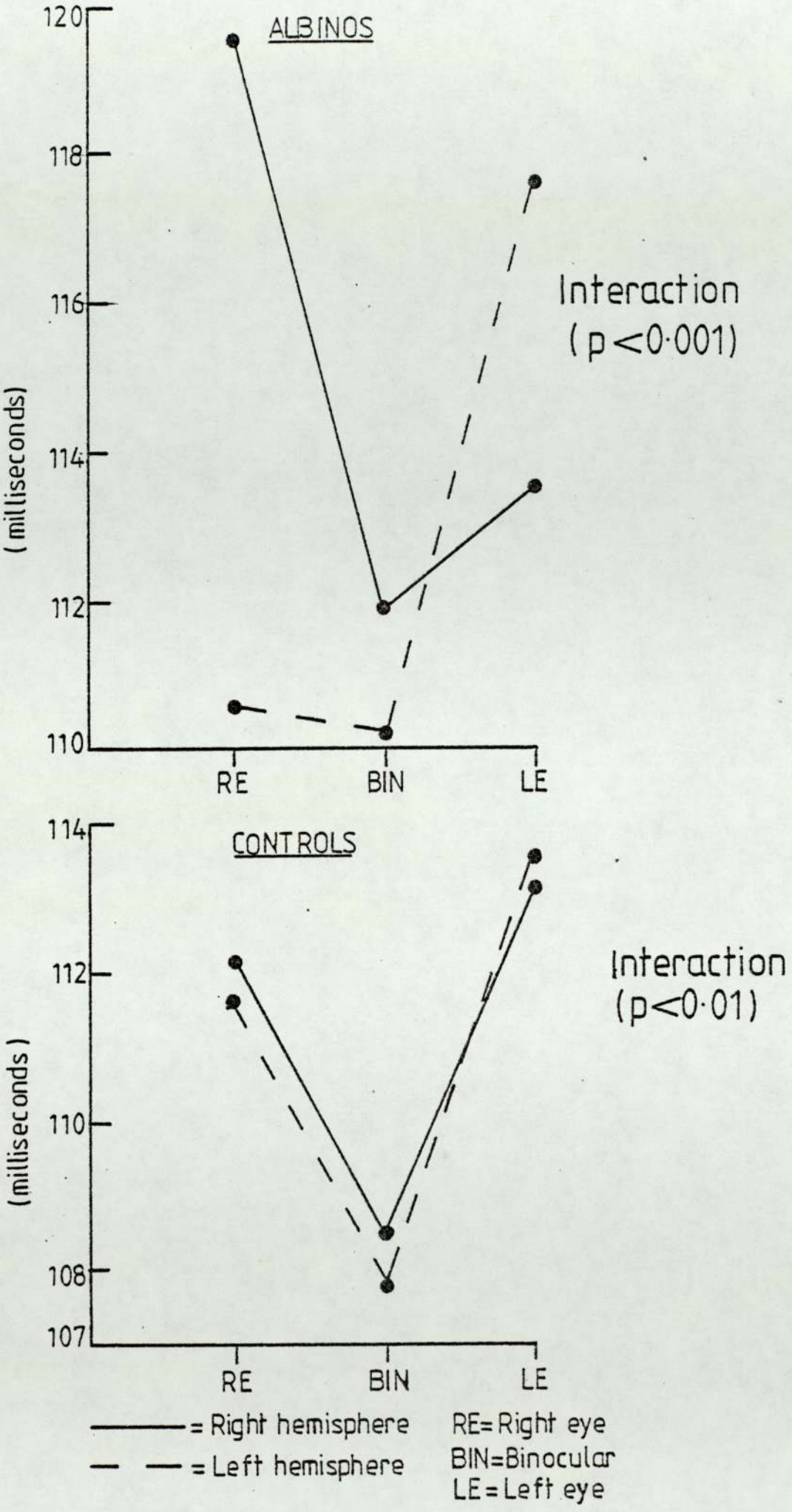

ALBINOS
120
118
116
114
112
110
(milliseconds)
RE
BIN
LE
Interaction
(p<0·001)
CONTROLS
114
112
110
108
107
(milliseconds)
RE
BIN
LE
Interaction
(p<0·01)
= Right hemisphere
= Left hemisphere
RE= Right eye
BIN=Binocular
LE = Left eye

Table 6.4

The Cx Values for P1N2 Amplitude

The calculated Cx values (in uV) for the amplitude of the P1N2 configuration in the flash VECP are given for each albino and his matched control. The values in five subjects are omitted because of the inconsistency of the P1 component in the VECPs of the albinos examined. (See text for further details).

SUBJECT	Cx (P1N2 AMPLITUDE)	
	ALBINO	CONTROL
1	+3.10	+0.15
2	+5.00	+0.80
3	-2.80	+0.80
4	-	-
5	+5.45	-0.10
6	+0.65	+1.10
7	-	-
8	-3.55	+1.60
9	-0.35	+0.45
10	-0.45	+0.30
11	-0.20	+0.65
12	-4.30	0
13	-5.55	-1.20
14	-	-
15	+0.50	-1.60
16	-	-
17	+1.40	+0.75
18	-0.20	+0.30
19	+1.80	+0.95
21	-	-
22	+0.65	+0.20
23	-2.00	+2.85

FIGURE 6.22

The Flash VECPs of Control Subject 22C with the P1N2 Amplitudes Labelled

The resulting Cx value is only +0.20uV. This is an example typical of the control group who tended to show only small amounts of lateralisation of the P1N2 amplitude on monocular stimulation. In the illustrated case a positive Cx is indicative of contralateral lateralisation. (Flash intensity 2, 1.8 flashes per second, 50 sweeps)

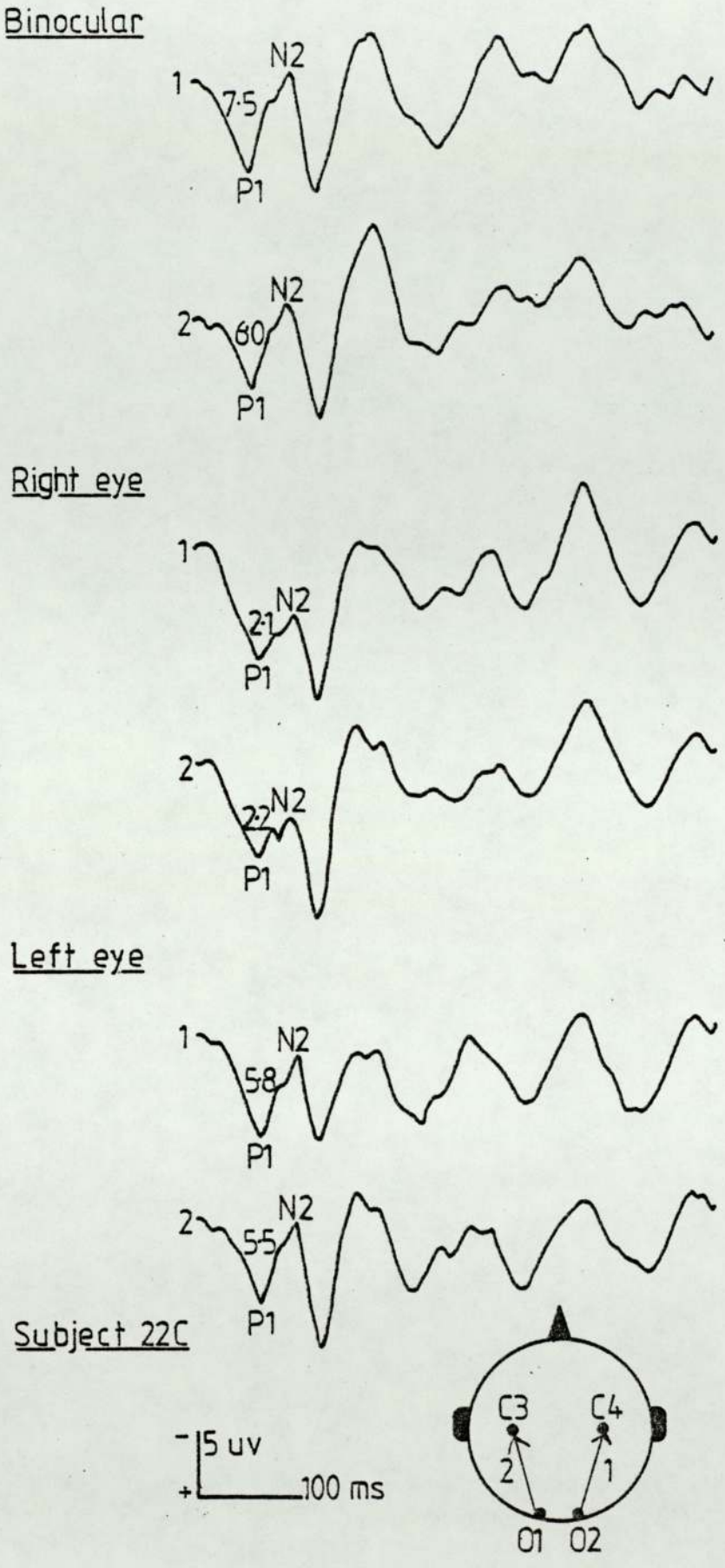
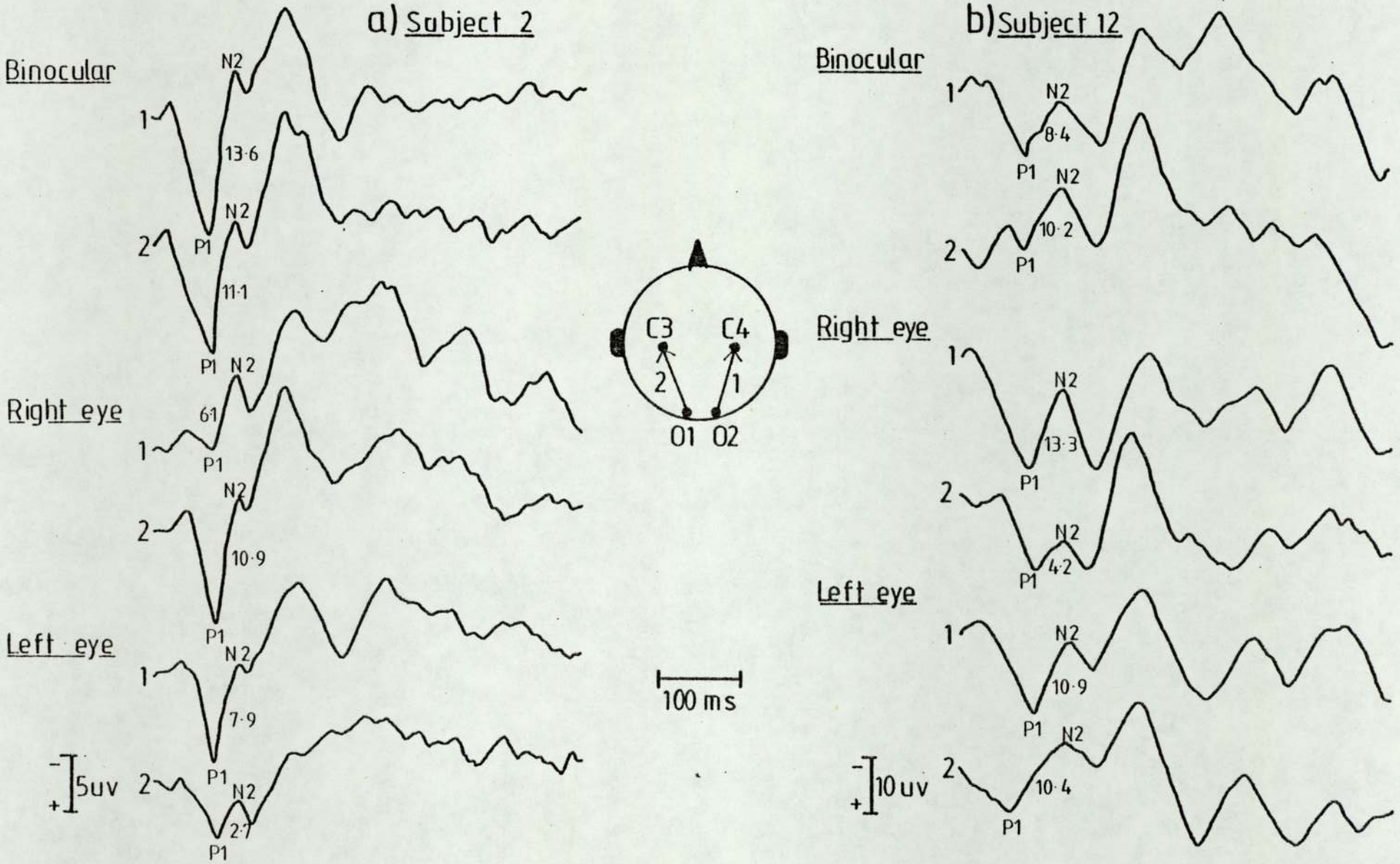

Binocular
1
N2
7·5
P1
2
N2
6·0
P1
Right eye
1
N2
2·1
P1
2
N2
2·2
P1
Left eye
1
N2
5·8
P1
2
N2
5·5
P1
Subject 22C
5 uv
100 ms
C3
C4
2
1
O1
O2

FIGURE 6.23

The Flash VECPs of Albino Subjects 2 and 12 with the P1N2 Amplitudes Labelled

In (a) Cx = +5.00uV indicating contralateral lateralisation on monocular stimulation while in (b) Cx = -4.30uV indicating ipsilateral lateralisation. (Flash intensity 2, 1.8 flashes per second, 50 sweeps)


a) Subject 2
b) Subject 12
Binocular
Right eye
Left eye
N2
P1
13·6
11·1
6·1
10·9
7·9
2·7
8·4
10·2
13·3
4·2
10·9
10·4
C3
C4
O1
O2
100 ms
5uv
10 uv

(Cx = -4.30uV) indicating contralateral and ipsilateral lateralisation respectively.

The mean Cx value within the albino group was -0.50uV (S.E. 0.73) and within the controls +0.47uV (S.E. 0.24). These means $\pm$ 1 S.E for both groups are illustrated in Figure 6.24.

Statistical analysis of the raw data using ANOVA showed that within both groups there was no significant interaction between the amplitude of P1N2 over the two hemispheres and the eye stimulated. These results are illustrated graphically in Figure 6.25.

6.2.5 N2P2 amplitude

This could be measured in all albino and control subjects. Table 6.5 shows the calculated Cx values for both groups.

Among the albinos Cx ranged from +3.20uV to -4.00uV; 9 (41%) showed a positive value and 13 (59%) a negative value. Within the control group Cx ranged from +3.10uV to -3.35uV. Two subjects (9%) showed no monocular lateralisation (Cx = 0); of the remaining 20 subjects an equal number, 10 (45.5%) showed positive and negative Cx values.

Both positive and negative Cx values were found among the control subjects. Figure 6.26 shows the responses of subject 3C (Cx = +3.10uV) and subject 7C (Cx = -3.35uV).

FIGURE 6.24

Graphical illustration of the mean Cx values ± 1 S.E. with respect to the amplitude of P1N2 in both the albino and control groups

The mean Cx values ± 1 S.E. are plotted for both groups

(see text for further details)

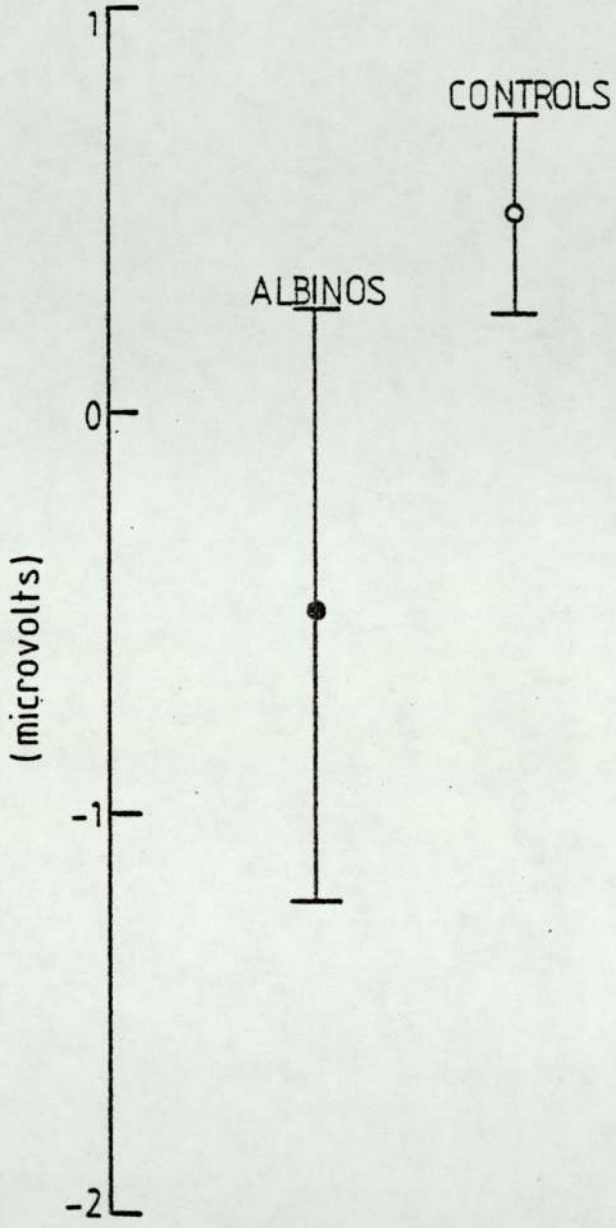

1
0
-1
-2
(microvolts)
ALBINOS
CONTROLS

Figure 6.25

Graphical Illustration of ANOVA Results Obtained Using the Raw P1N2 Amplitude Data from the Albino and Control Groups

The amplitude of P1N2 over each hemisphere on binocular and monocular stimulation are plotted. The data from both groups showed no interaction between the amplitudes over the two hemispheres and the eye stimulated.

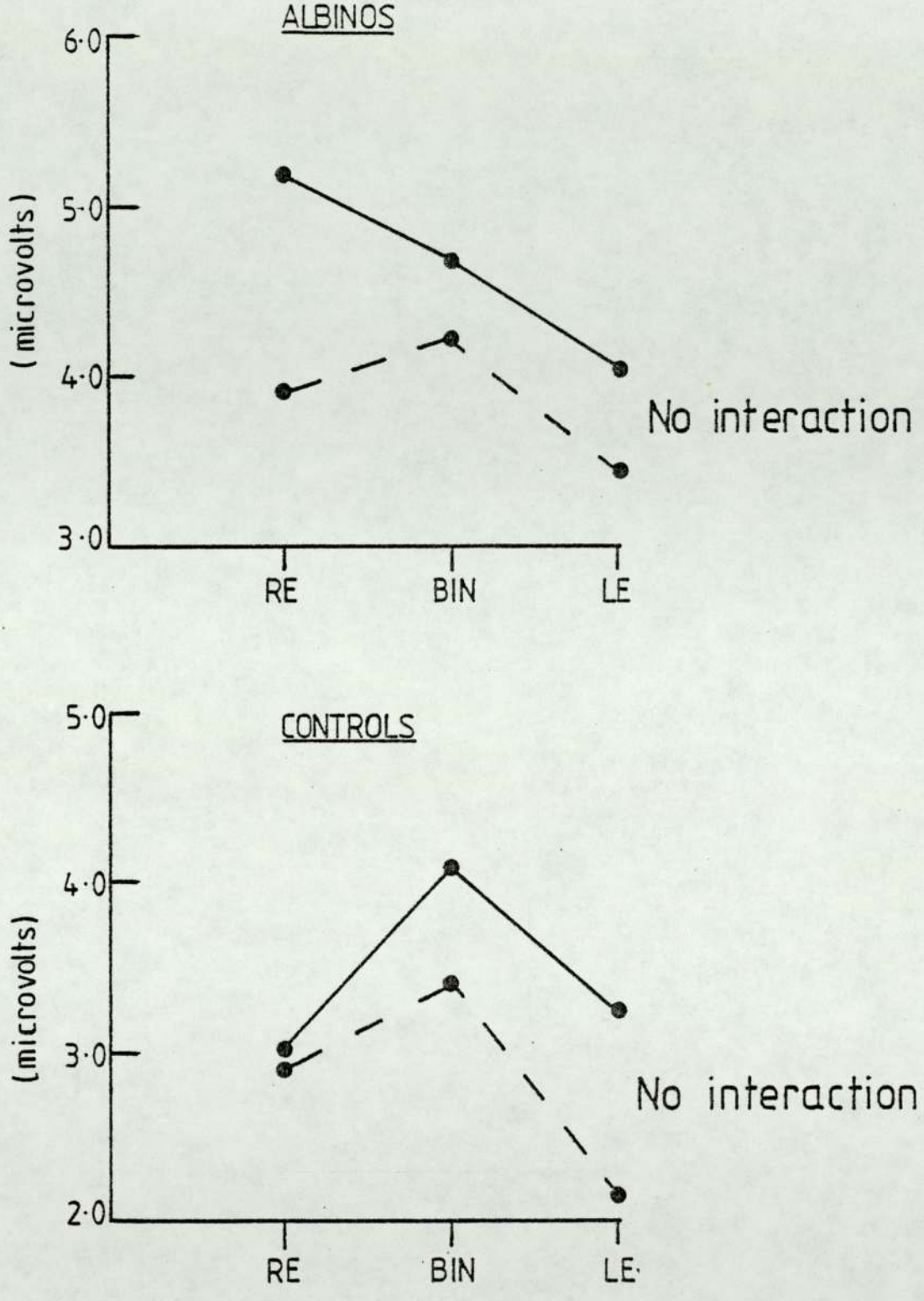

ALBINOS
6·0
5·0
4·0
3·0
(microvolts)
RE
BIN
LE
No interaction
CONTROLS
5·0
4·0
3·0
2·0
(microvolts)
RE
BIN
LE
No interaction
=Right hemisphere
=Left hemisphere
RE=Right eye
BIN=Binocular
LE=Left eye

Table 6.5

The Cx Values for N2P2 Amplitudes

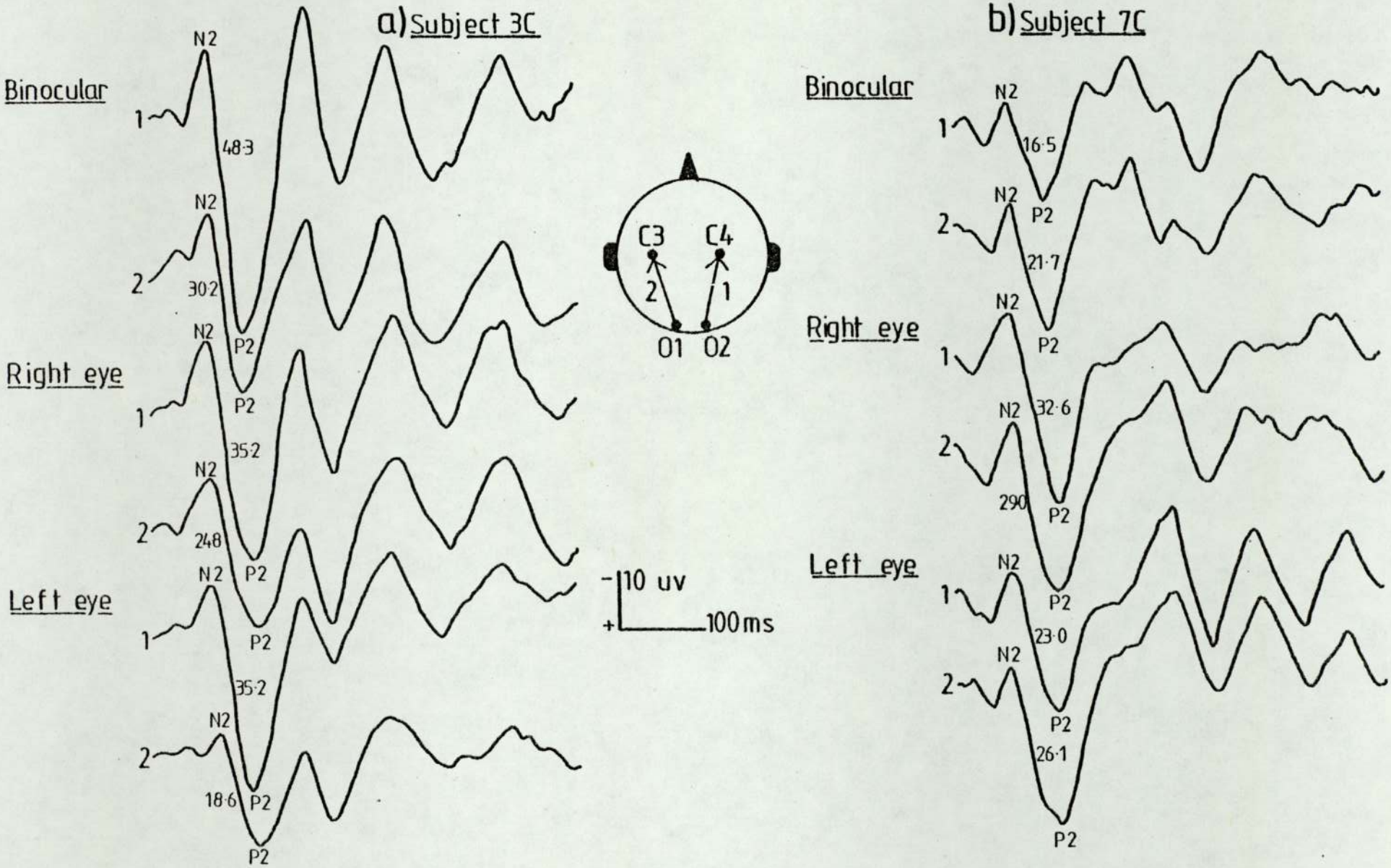
The calculcated Cx values (in uV) for the amplitude of the N2P2 configuration in the flash VECP are given for each albino and his matched control. (See text for further details).

SUBJECT	Cx (N2P2 AMPLITUDE)	
	ALBINO	CONTROL
1	-0.60	+0.50
2	-1.55	+1.00
3	-0.75	+3.10
4	-1.50	0
5	-0.65	-0.35
6	+0.15	+1.40
7	+3.20	-3.35
8	+2.35	-0.40
9	-1.00	-0.10
10	-1.45	+0.25
11	-0.60	+0.90
12	-4.00	+0.10
13	+0.50	+0.10
14	+2.90	-2.85
15	+3.10	-1.65
16	+1.75	-1.05
17	+1.35	-1.50
18	-2.80	+1.00
19	-0.15	+1.65
21	-2.45	-1.25
22	+0.85	0
23	-0.05	-3.15

Figure 6.26

The Flash VECPs of Control Subjects 3C and 7C with the N2P2 Amplitudes Labelled

In (a) Cx = +3.10uV where in (b) Cx = -3.35uV indicating contralateral and ipsilateral lateralisation on monocular stimulation respectively. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).


a) Subject 3C
b) Subject 7C
Binocular
Right eye
Left eye
N2
P2
1
2
48·3
30·2
35·2
24·8
35·2
18·6
16·5
21·7
32·6
29·0
23·0
26·1
C3
C4
O1
O2
10 uv
100 ms

A similar diversity of Cx values was also found within the albino group. Figure 6.27 shows two typical examples, one showing contralateral lateralisation (subject 17; Cx +1.35uV) and the other ipsilateral lateralision (subject 21; Cx = -2.45uV).

The mean Cx value within the albino group was -0.06uV (S.E. 0.41) and among the controls -0.26uV (S.E. 0.34). These means $\pm$ 1 S.E. in both groups are illustrated in Figure 6.28.

Statistical analysis of the raw data using ANOVA showed that among the control group the amplitude was significantly greater on binocular compared to monocular stimulation ($p < 0.01$; $F_{2, 42} = 6.23$). Such a result was not present among the albinos. Within both groups there was no significant interaction between the N2P2 amplitude over the two hemispheres and the eye stimulated. These results are illustrated graphically in Figure 6.29.

6.2.6 The flash VECPs of albino 20

As reported in Section 5.5 and illustrated in Figure 5.1, albino 20 was the only subject whose visual fields were measured and found to show a gross defect in the form of a nasal hemianopia with central sparing and some temporal field constriction of the right eye. For this reason the VECPs of this subject are considered separately. The existence of such a field defect should alone affect the

Figure 6.27

The Flash VECPs of Albino Subjects 17 and 21 with the N2P2 Amplitudes Labelled

In (a) Cx = +1.35uV and in (b) Cx =-2.45uV. These illustrate two contrasting responses showing contralateral and ipsilateral lateralisation on monocular stimulation respectively. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).

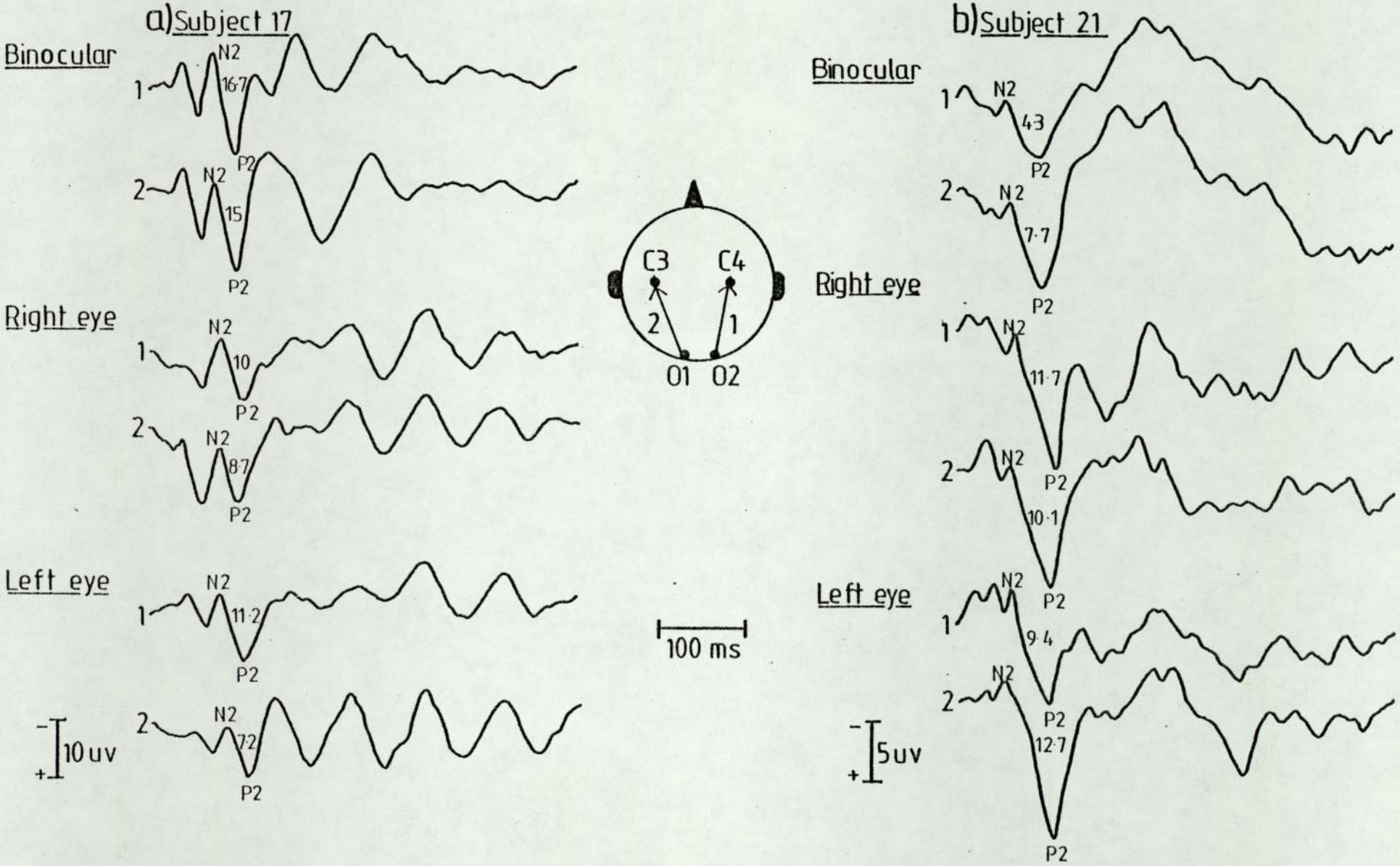

a) Subject 17
Binocular
1
N2
16·7
P2
2
N2
15
P2
Right eye
1
N2
10
P2
2
N2
8·7
P2
Left eye
1
N2
11·2
P2
2
N2
7·2
P2
10 uv
C3
C4
2
1
O1
O2
100 ms
b) Subject 21
Binocular
1
N2
4·3
P2
2
N2
7·7
P2
Right eye
1
N2
11·7
P2
2
N2
10·1
P2
Left eye
1
N2
9·4
P2
2
N2
12·7
P2
5uv

Figure 6.28

Graphical Illustration of the Mean Cx Values ± 1 S.E. With Respect to the Amplitude of N2P2 in both the Albino and Control Groups

The mean Cx values ± 1 S.E. are plotted for both groups.

(See text for further details)

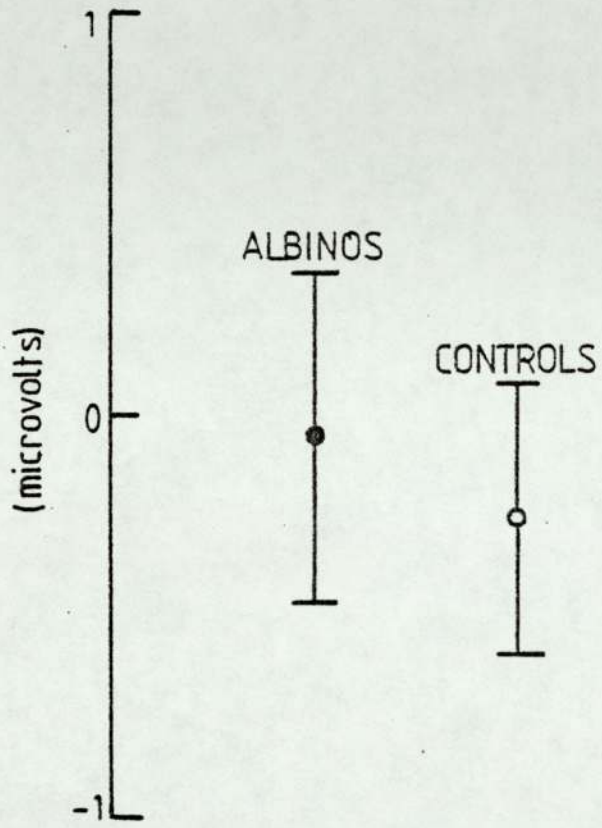
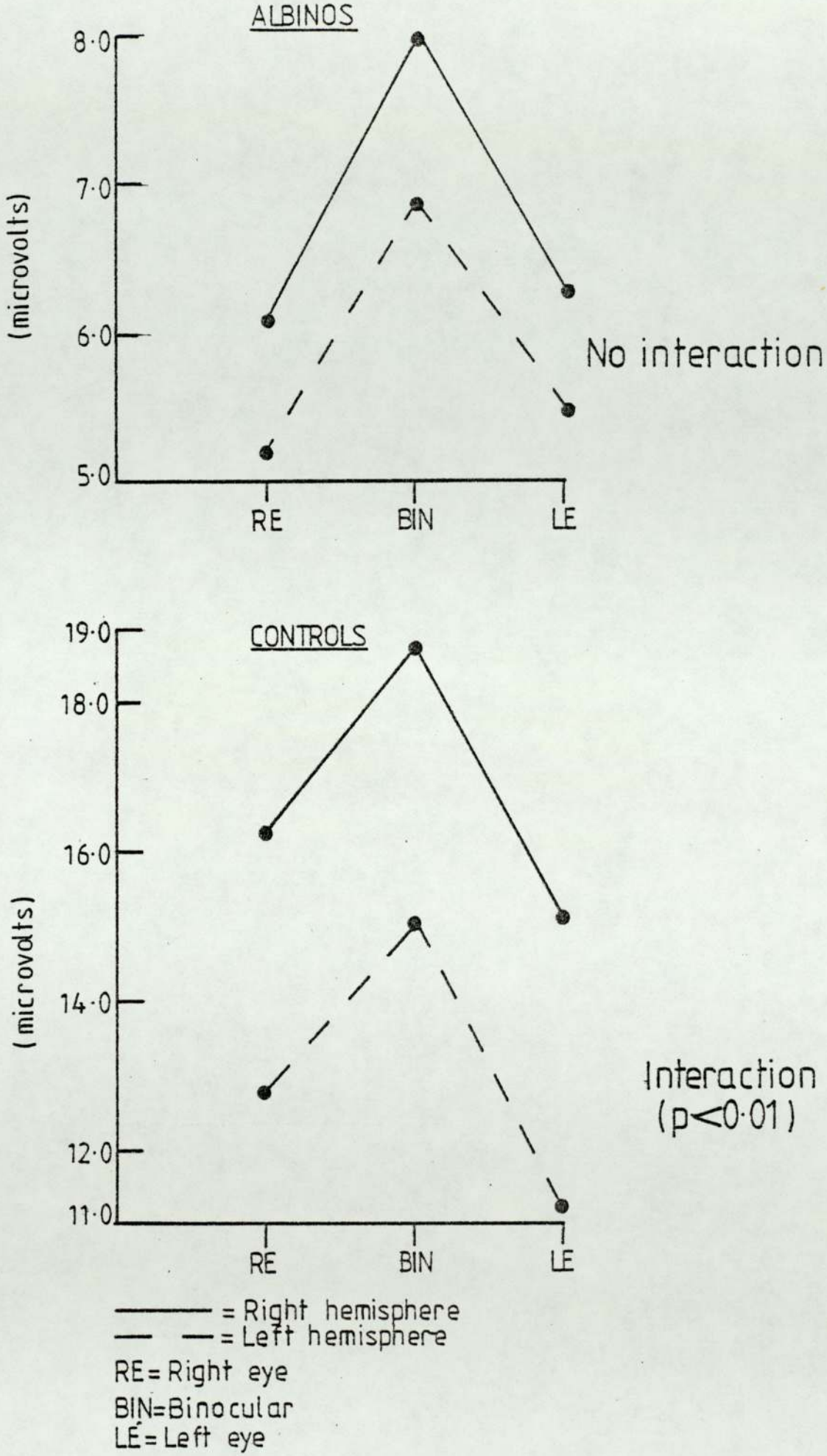

1
0
-1
(microvolts)
ALBINOS
CONTROLS

Figure 6.29

Graphical Illustration of ANOVA Results Obtained Using the Raw N2P2 Amplitude Data from the Albino and Control Groups

The amplitudes of N2P2 over the two hemispheres on binocular and monocular stimulation are plotted. Within the control group this measure was significantly greater ($p < 0.01$) over the two hemispheres on binocular compared to monocular stimulation; such a result was not found within the albino group. In neither group was there any significant interaction between the amplitude of N2P2 over the two hemispheres and the eye stimulated.


ALBINOS
8·0
7·0
6·0
5·0
(microvolts)
RE
BIN
LE
No interaction
CONTROLS
19·0
18·0
16·0
14·0
12·0
11·0
(microvolts)
RE
BIN
LE
Interaction
(p<0·01)
= Right hemisphere
= Left hemisphere
RE = Right eye
BIN = Binocular
LE = Left eye

response irrespective of the presence of albinism; the flash VECPs of this subject are illustrated in Figure 6.30.

The binocular responses appear normal in configuration. A P1 component is present over both hemispheres although the P1N2 amplitude is of greater amplitude over the right hemisphere. A clear P2 component is also seen over both hemispheres with a shorter latency over the right hemisphere (90ms) compared to the left (98ms). The N2P2 amplitude is, however, of greater amplitude over the left (9.0uV) compared to the right (7.9uV).

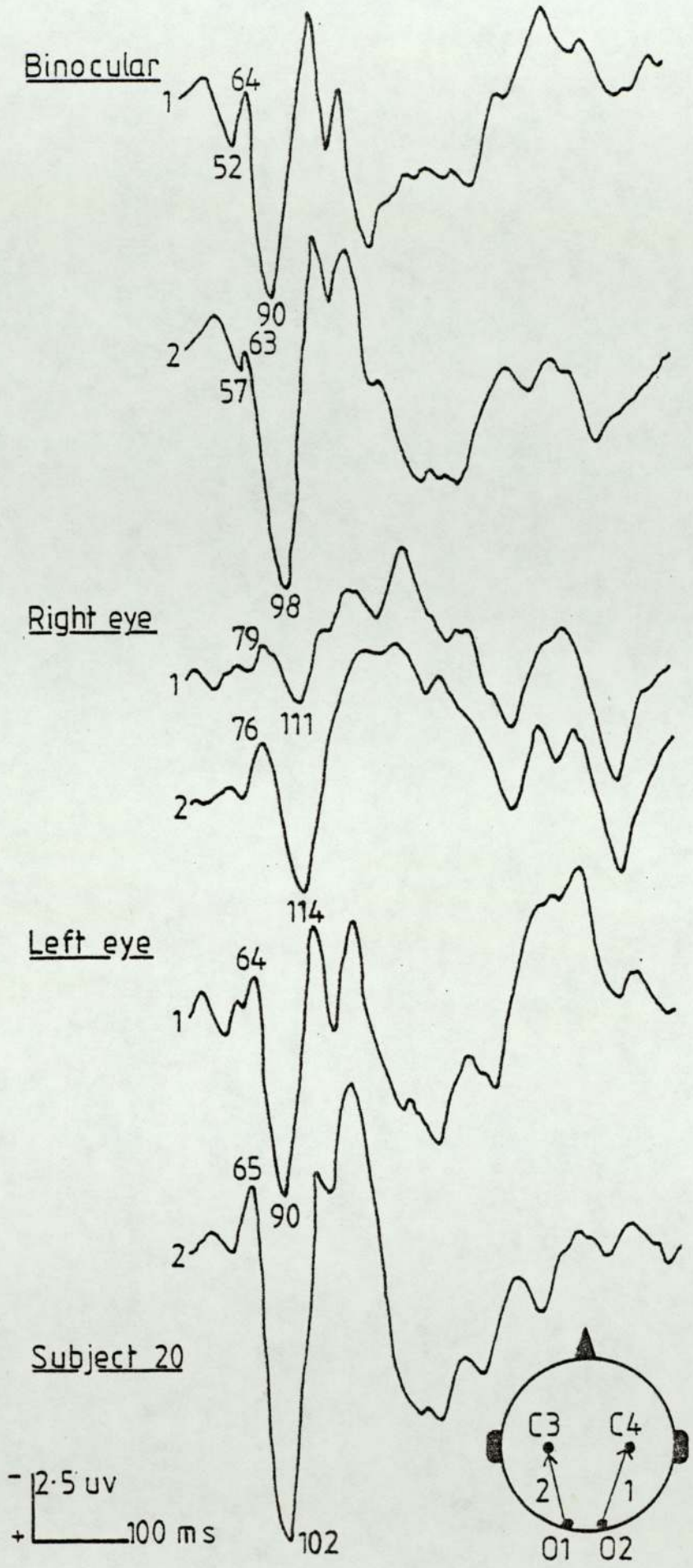
Monocular stimulation of the left eye also produced clear responses over both hemispheres with again N2P2 of greater amplitude over the left hemisphere (13.5uV) compared to the right (8.4uV). P2 has a shorter latency over the right hemispheres (90ms) compared to the left (102ms). This slight increase in latency over the left hemispheres when compared to the binocular measure may be due to the presence of misrouting in the subject.

Responses from the right eye were, however, somewhat different from the binocular or left eye responses. As can be see in Figure 6.35, P2 has a longer latency over both hemispheres; 111ms over the right and 114ms over the left. In addition, N2P2 is also reduced over both hemispheres. The amplitude over the left measuring 5.7uV but that over the right, as would be expected, is even more reduced at only 2.3uV. The results from this right

Figure 6.30

The Flash VECPs of Albino Subject 20

The binocular, right and left eye responses of Subject 20, the only albino to display a gross field defect are illustrated. See text for further details. (Flash intensity 2, 1.8 flashes per second, 50 sweeps).


Binocular
1
64
52
90
2
63
57
98
Right eye
1
79
111
2
76
114
Left eye
1
64
90
2
65
102
Subject 20
2·5 uv
100 ms
C3
C4
2
1
O1
O2

eye are consistent with the existence of the field defect found in this subject. The amplitude of the response is particularly reduced over the hemisphere contralateral to the field defect; the lesser reduction over the left may be due to the constriction of the temporal field also found in this eye. This form of lateralisation is consistent with previous reports of the flash VECP being reduced over the contralateral hemisphere in hemianopic field defects (Harding, Thompson and Panayiotopoulos, 1970; Harding 1977).

6.2.7 Repeatability studies

During the recording of the flash VECPs in the albino subjects the repeatability of the responses was usually checked at the time of examination. However, it was considered necessary to also examine the stability of the responses of a longer period of time in order to ensure that any lateralisations found were consistent in nature. Consequently, albino subjects 11, 12, 17 and 18 were further examined under identical conditions after a period of time between 2 - 9 months following the initial visit. The responses were again measured and the Cx values calculated for the P1, N2, P2 latencies and the P1N2, N2P2 amplitudes. Table 6.6 list these subjects with the Cx values for each component measure on the two occasions.

From this table it can be seen that the lateralisations obtained were very repeatable particularly when considering

Table 6.6

The Repeatability of the Flash VECP
in 4 Albino Subjects

The calculated Cx values for each component measure (P1, N2 and P2 latencies, P1N2 and N2P2 amplitudes) are given for the 4 albinos who underwent repeated investigations. Each column shows the values for the responses recorded on the 1st and 2nd visits. (See text for further details).

	Cx VALUES									
	P1		N2		P2		P1N2		N2P2	
SUBJECT	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
11	-3.5	-3.0	-2.0	-1.5	+3.5	+2.0	-0.20	-0.95	-0.60	-0.20
12	-17.5	-11.5	-12.5	-9.5	+8.5	+14.0	-4.30	+1.15	-4.00	-3.70
17	+3.5	+3.5	+2.5	+5.5	+4.0	+3.0	+1.40	+2.15	+1.35	+0.80
18	-8.5	-1.5	-2.0	-3.0	+6.5	+4.5	-0.20	-0.20	-2.80	+0.05

Key: 1st = 1st Visit
2nd = 2nd Visit

the Cx values pertaining to the latency measures. In all subjects the Cx values for the P1, N2 and P2 latencies remained of the same sign (positive or negative) as on the initial visit and were of similar magnitudes. With regard to the amplitude measures, this was also true for subjects 11 and 17. However, in subjects 12 and 18 the P1N2 and N2P2 Cx values respectively underwent a change in sign and hence lateralisation on the second visit. This is probably due to the fact that amplitude is a more variable measure than latency (Schreinmachers and Henkes, 1968; Vaughan 1966, 1969; Lewis et al. 1972; Aunon and Cantor 1977).

6.2.8 The P1 quotient

When the albino flash responses were being examined it became evident that some of the responses were untypical of the waveform usually seen in subjects of such a young age group.

By examining Figures 6.4, 6.7, 6.11 and 6.19 it can be seen that in some albinos the amplitude of P1N2 was large often being equal to or greater than N2P2. This large P1 component was usually present bilaterally on binocular stimulation and lateralised over the contralateral hemisphere on monocular stimulation. Such a flash VECP waveform with an enlarged P1 is usually associated with the responses of elderly subjects (Dustman and Beck 1966, 1969; Harding 1974; Cosi et al. 1982; Harding 1982) but not with subjects falling within the age range of the albinos

examined; the oldest was only 35 years old.

In order to quantify this increase in P1N2 amplitude of some subjects a P1 quotient (P1q) was calculated for each eye of every albino subject. The P1q was calculated to show the relationship between the size of P1N2 compared to N2P2. The two amplitudes were measured from the contralateral hemisphere of each eye and the P1q calculated using the formula P1q = P1N2/N2P2 x 100%. In the cases where no P1 was found over the contralateral hemisphere, and hence no P1N2 measurable, the P1q was recorded as zero.

Certain albinos in particular showed a VECP waveform with an enlarged P1 component; these were subjects 1,2,3, 5,9,12,17,18 and 19. The presence of this waveform configuration did not seem to be connected with the presence or absence of nystagmus; all but one albino showed this defect. It also did not appear to be related to the presence of strabismus. By examining Table 5.3, of the above mentioned albinos, only one, number 12, showed a squint. However, comparison with Table 5.2 reveals that those albinos with a large P1 were also those with VA's at the lower end of the range measured; those of subjects 1,2,5,17,18 and 19 measuring 6/60 or less and those of subjects 3,9 and 12 slightly better at the 6/36 or 6/24 level. Therefore, there seemed to exist a possible link between the existence of an enlarged P1 and hence large P1q and poor V.A. For this reason the V.As of the two

eyes of each albino were converted to decimal values using the table formulated by Drasdo and Haggerty (1981); this table only converts V.As. down to the Snellen level of 6/60 so the values were extrapolated to enable conversion of the lower V.As recorded in some albinos.

The Plq and V.A. for each eye of the albinos are shown in Table 6.7. The values of subject 16 are omitted because the V.As of this subject could not be measured and again subject 20, displaying the gross field defect, is excluded. To determine if a relationship is present between the Plq and V.A., (i.e. the larger the Plq, the lower the V.A.), Spearmans rank-correlation test was employed. The resulting correlation coefficient of -0.395 ($p < 0.01$; Witte 1980), shows that such a relationship is present.

6.2.9 Summary

Table 6.8 shows the calculated Cx values for each component measure for the flash VECPs of the albinos examined and as such summarises the results shown in Tables 6.1, 6.2, 6.3, 6.4 and 6.5. Clearly, the greater number of positive Cx values, indicating contralateral lateralisation on monocular stimulation, fall within the P2 latency column. This finding is further illustrated in Figure 6.31 and Table 6.9 which summarises in graphical and tabular form the mean Cx values $\pm$ 1S.E for each component measure in the albino and control groups. The mean Cx value of the P2 latency (+6.21; S.E. 2.00) is set apart from the mean

Table 6.7

The P1 Quotients (P1q) and Visual Acuities (V.As) of the Albino Subjects

The calculated P1q values and V.As represented decimally (see text) are shown for the right and left eyes of each albino.

Subjects 16 and 20 are omitted; in the former case because the VAs could not be measured and in the latter case because of the presence of a gross field defect of the right eye. Subjects 1, 2, 3, 5, 9, 12, 17, 18 and 19 in particular show large P1q values compared to the other albinos.

SUBJECT	RIGHT EYE		LEFT EYE	
	Pl_q	V.A.	Pl_q	V.A.
1	289	0.10	279	0.10
2	727	0.10	988	0.10
3	190	0.17	33	0.17
4	8	0.08	0	0.08
5	790	0.10	289	0.10
6	40	0.17	17	0.33
7	0	0.33	0	0.33
8	51	0.33	13	0.33
9	138	0.17	173	0.25
10	44	0.10	52	0.10
11	45	0.10	23	0.17
12	100	0.17	206	0.17
13	6	0.25	17	0.17
14	0	0.10	10	0.17
15	10	0.25	21	0.10
17	102	0.10	48	0.10
18	321	0.08	70	0.07
19	124	0.03	198	0.03
21	3	0.33	6	0.33
22	26	0.25	52	0.33
23	93	0.10	73	0.17

Key: Pl_q = Pl quotient
V.A. = Visual Acuity.

TABLE 6.8

Summary Table of Albino Flash VECP Results

The calculated Cx values for each component measure (P1, N2 and P2 latencies, P1N2 and N2P2 amplitudes) are shown for each albino subject. (see text for further details)

SUBJECT	Cx VALUES				
	P1	N2	P2	P1N2	N2P2
1	+5.5	+8.0	+11.0	+3.10	-0.60
2	0	-3.0	+4.5	+5.00	-1.55
3	-14.5	-5.5	+6.5	-2.80	-0.75
4	-	-0.5	+7.0	-	-1.50
5	+1.5	-2.0	-16.0	+5.45	-0.65
6	+2.5	+2.5	+4.5	+0.65	+0.15
7	-	+8.5	-0.5	-	+3.20
8	+33.0	+50.0	+33.0	-3.55	+2.35
9	-2.0	+1.0	+3.5	-0.35	-1.00
10	+2.5	+0.5	+5.0	-0.45	-1.45
11	-3.5	-2.0	+3.5	-0.20	-0.60
12	-17.5	-12.5	+8.5	-4.30	-4.00
13	-14.5	-33.5	+12.5	-5.55	+0.50
14	-	+13.5	+5.5	-	+2.90
15	+4.0	+0.5	+3.0	+0.50	+3.10
16	-	-2.0	+2.5	-	+1.75
17	+3.5	+2.5	+4.0	+1.40	+1.35
18	-8.5	-2.0	+6.5	-0.20	-2.80
19	+13.5	+13.5	+26.5	+1.80	-0.15
21	-	-0.50	+1.5	-	-2.45
22	+1.5	+1.0	+3.0	+0.65	+0.85
23	+4.5	+1.5	+1.0	-2.00	-0.05

Figure 6.31

Summary Diagram Showing the Mean Cx Values ± 1 S.E. For Each Component Measure of the Flash VECPs Recorded in both the Albinos and their Controls

(See text for further details)

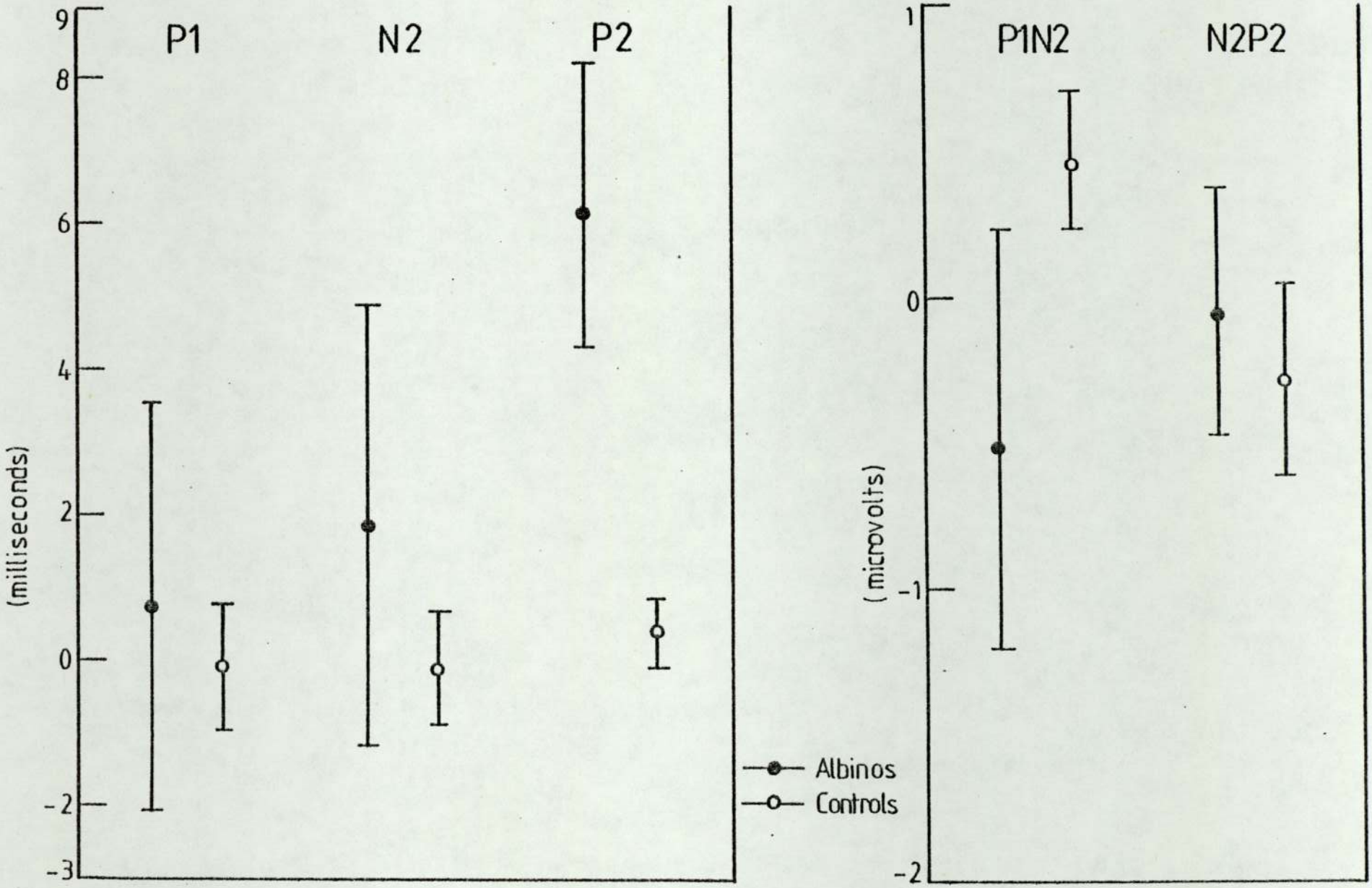

P1
N2
P2
9
8
6
4
2
0
-2
-3
(milliseconds)
P1N2
N2P2
1
0
-1
-2
(microvolts)
Albinos
Controls

Table 6.9

Summary Table of the Flash Components' mean Cx Values ± 1 S.E.

For each component measure of the flash VECP, the mean Cx value ± 1 S.E. is given for the albino group and their controls. This forms a tabulation of the results illustrated graphically in Figure 6.31. (See text for further details).

Component Measure	Mean Cx Value ± 1 S.E.	
	Albinos	Controls
P1 latency	+0.68 ± 2.83	-0.12 ± 0.86
N2 latency	+1.84 ± 3.04	+0.16 ± 0.79
P2 latency	+6.21 ± 2.00	-0.36 ± 0.52
P1N2 amplitude	-0.50 ± 0.73	+0.47 ± 0.24
N2P2 amplitude	-0.06 ± 0.41	-0.26 ± 0.34

Cx values for the other measures in the albino group and all of the measures in the control group.

Statistical analysis of the flash VECP results showed that:

1) Contralateral lateralisation of the flash VECP in albino subjects is present at a statistically significant level ($p < 0.001$) only with regard to the latency of the P2 component. Although contralateral lateralisation of other component measures is found these do not reach a statistically significant level when compared to the control group.

2) Within the control group P2 had a significantly shorter latency ($p < 0.01$) and N2P2 a significantly greater amplitude ($p < 0.01$) under binocular conditions when compared to stimulation of one eye alone. These effects were not apparent within the albino group.

3) In some albinos the flash VECP shows an unusually large P1 component which lateralises contralaterally on monocular stimulation. The relative size of P1N2 compared to N2P2 when calculated as the P1 quotient shows an inverse relationship to the level of the V.A. recorded. This relationship is not a strong one ($r = -0.395$) but is, nevertheless, present.

6.3 The pattern reversal VECP

During the initial part of the study pattern reversal VECPs were recorded in two albinos; subject 11, a 27 year old male, oculocutaneous albino and subject 22 a 35 year old, male ocular albino. The binocular and left eye responses of subject 11 are shown in Figure 6.32. As illustrated, using 50' checks, no prominent P100 component was present in either response. Repeated recordings using larger, 2 degree, checks also proved unsuccessful in evoking a reliable response.

These results show marked contrast to the responses recorded from this albino's matched control; Figure 6.33 illustrates the prominent P100 component found using 50' checks on both binocular and monocular stimulation in this subject.

It was considered a possibility that the poor P100 response recorded in subject 11 could be a result of his low VA, that of the left eye being 6/36. In an attempt to eliminate this, responses were then recorded in subject 22 whose VAs were somewhat better. Figure 6.34 illustrates the response of the left eye of this subject (VA 6/18). However, again no prominent P100 component was found.

From the pattern reversal responses recorded in these two subjects, it proved impossible to measure the latency or amplitude of any P100 component and, therefore, not

Figure 6.32

The Pattern Reversal Responses of Albino Subject 11

The binocular and left eye responses to 50' checks are shown. A dotted vertical line is drawn at 100 ms illustrating the absence of a clear P100 component in either response. Increasing the check size to 2 degrees also fails to elicit a clear P100. All the responses are recorded from a transverse row of occipital electrodes, all referred to FZ. (2 reversals per second, 50 sweeps).

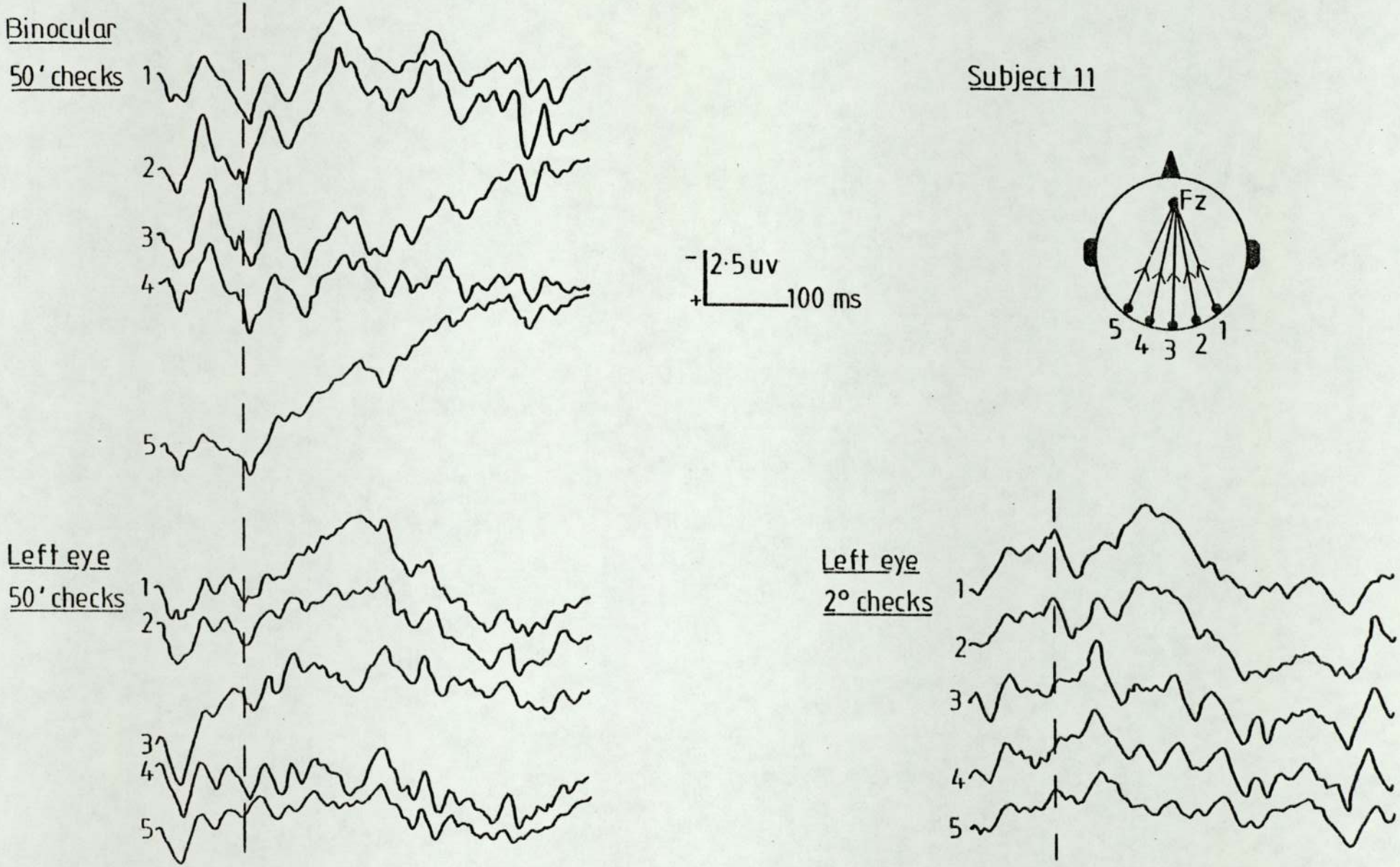

Binocular
50' checks
1
2
3
4
5
2·5 uv
100 ms
Subject 11
Fz
5 4 3 2 1
Left eye
50' checks
1
2
3
4
5
Left eye
2° checks
1
2
3
4
5

FIGURE 6.33

The Binocular and Left Eye Pattern Reversal Responses of Control Subject 11C

The responses of subject 11C, the control matched to the albino whose VECPs are shown in Figure 6.32 are illustrated. A clear P100 component is recorded at each occipital electrode. Note the difference in amplitude scale when comparing the two figures. (Check size 50', 2 reversals per second, 50 sweeps)

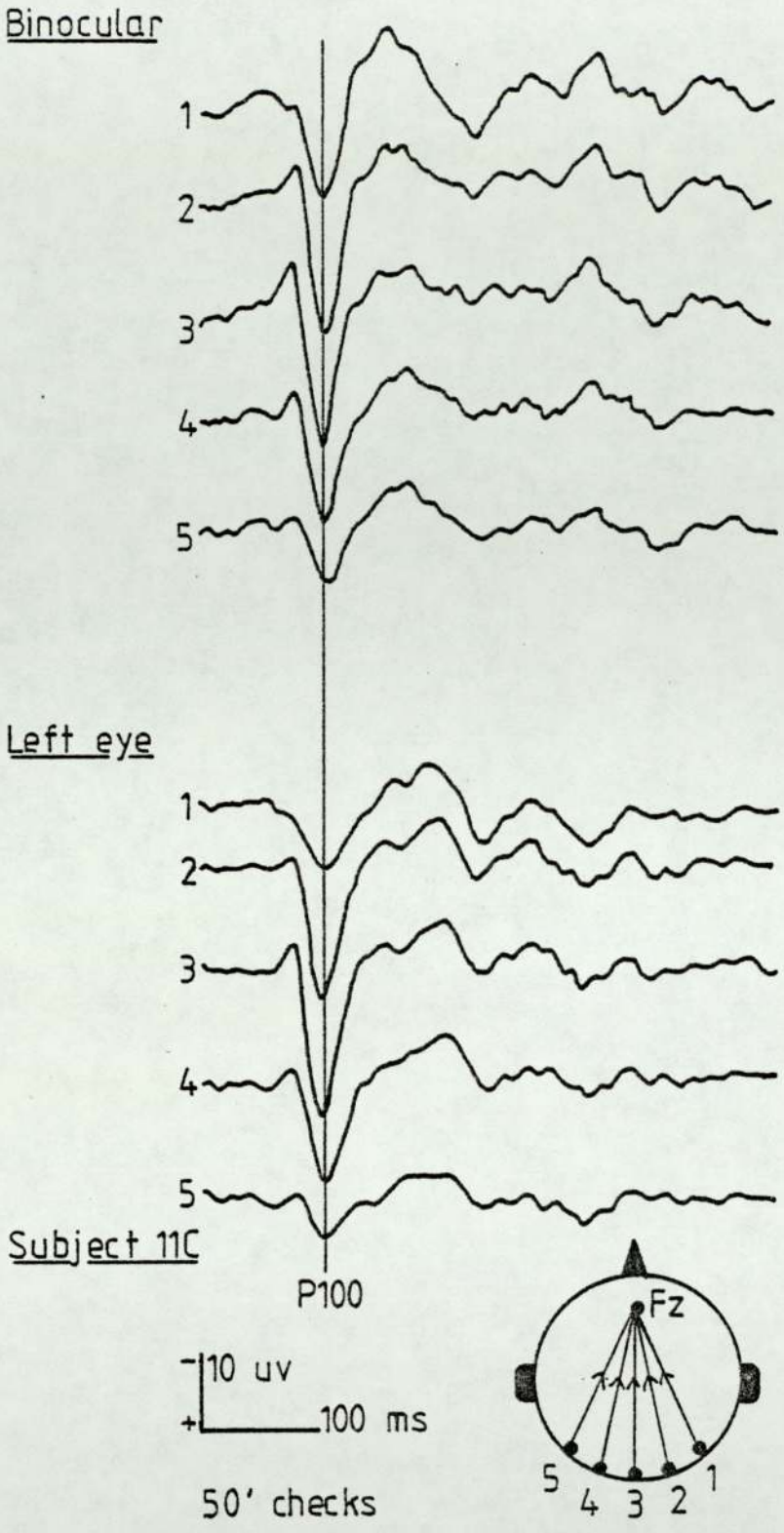
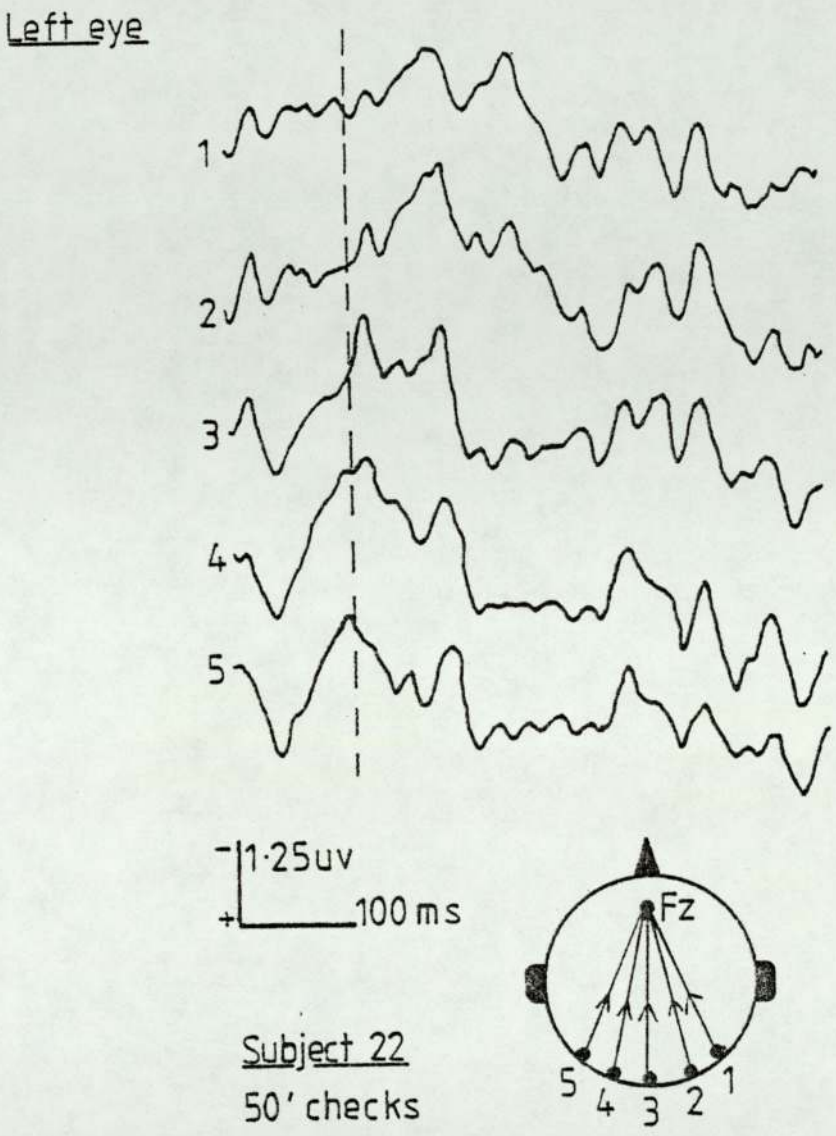

Binocular
1
2
3
4
5
Left eye
1
2
3
4
5
Subject 11C
P100
10 uv
100 ms
50' checks
Fz
5
4
3
2
1

FIGURE 6.34

The Left Eye Pattern Reversal Response of Albino Subject 22

It was postulated that the poor responses recorded in Albino 11 (illustrated in Figure 6.32) could be due to the low V.A. found in this subject (left eye 6/36). Therefore, responses were recorded from albino 22 whose left eye had the somewhat better acuity of 6/18. A dotted vertical line is drawn at 100 ms and again no prominant P100 was found. (Check size 50', 2 reversals per second, 50 sweeps)


Left eye
1
2
3
4
5
1·25uv
100 ms
Fz
5
4
3
2
1
Subject 22
50' checks

possible to calculate any Cx values in order to determine if lateralisation on monocular stimulation did indeed occur. Visual inspection of the responses also failed to identify any such lateralisation. Consequently, this line of investigation was abandoned and pattern reversal replaced by pattern appearance-disappearance stimulation.

6.4 The pattern appearance-disappearance VECP

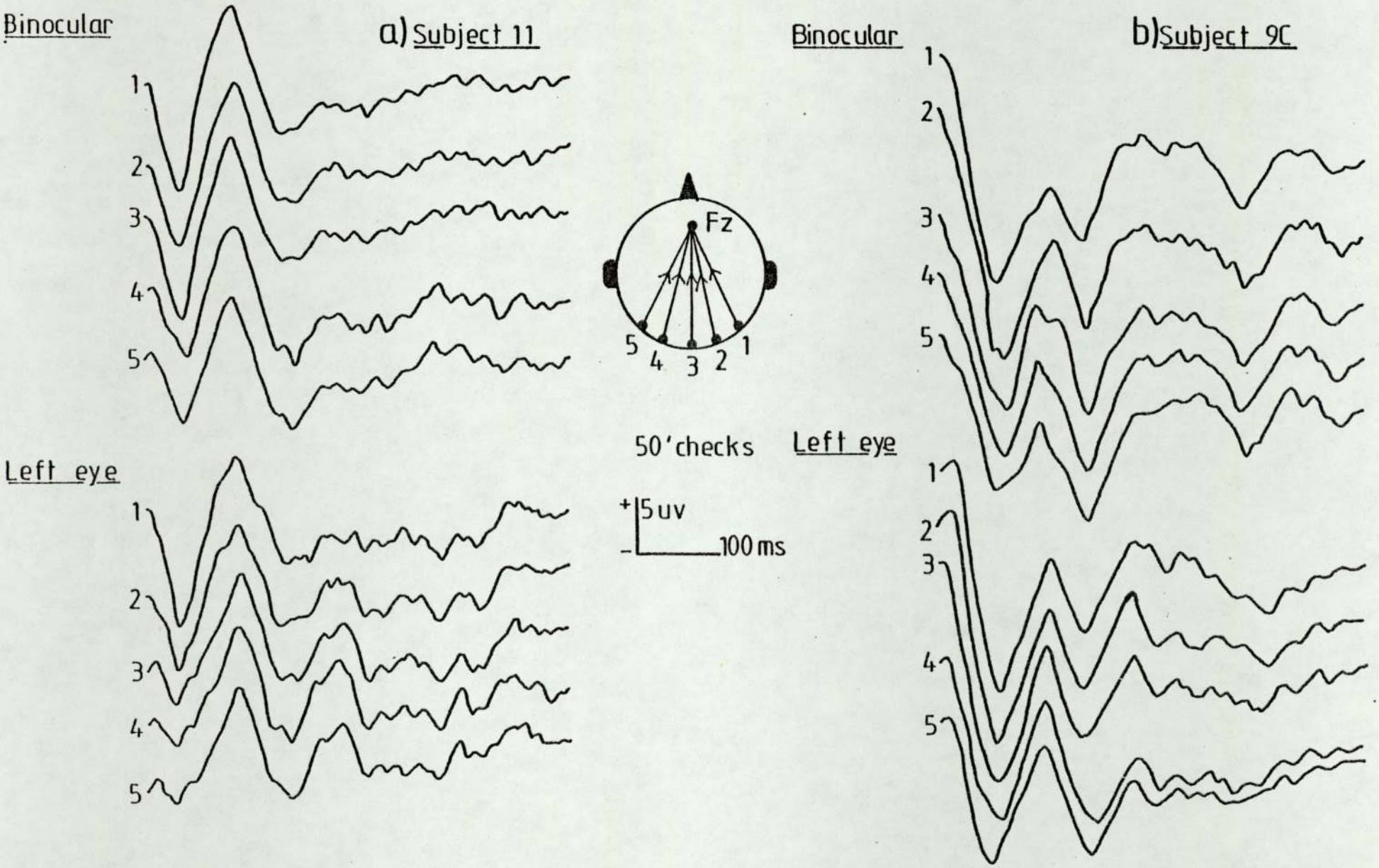
These responses were recorded in 13 albino subjects, including subject 20 who showed the hemianopic field defect; again the results from this subject will be described separately. Table 6.10 shows the remaining 12 subjects who were investigated.

This method of stimulation proved superior to pattern reversal in eliciting a response in albinos and usually produced a simple type of response waveform consisting primarily of a positive component which will be called CI; a negative CII; a positive CIII and the 'OFF' response were usually absent or poorly defined. Figure 6.35 shows the binocular and left eye pattern appearance-disappearance responses to 50' checks of subject 11. By comparing Figure 6.35 with 6.32 it can be seen that pattern appearance-disappearance stimulation produced a much more easily identifiable response. (Note that the pattern appearance-disappearance responses are illustrated with an upward deflection indicating positivity in contrast to the flash and pattern reversal in which an upward

Figure 6.35

The Pattern Appearance-Disappearance Responses of Albino Subject 11 and Control Subject 9C

The responses illustrated in (a) are in marked contrast to the pattern reversal responses recorded in this subject (See Figure 6.32). The waveform is dominated by a positive component (CI) at about 100 ms. This response type was also found in some of the younger control subjects; such a case is illustrated in (b). Here again the response is dominated by a positive component. Note that these responses are drawn with the opposite polarity to those shown in Figure 6.32. (Check size 50', 50 sweeps).


Binocular
a) Subject 11
1
2
3
4
5
Left eye
1
2
3
4
5
Fz
5 4 3 2 1
50'checks
+ 5uv
- 100 ms
Binocular
b) Subject 9C
1
2
3
4
5
Left eye
1
2
3
4
5

deflection indicates negativity). However, this type of response consisting mainly of a large positive component was not limited to the albinos; in the younger control subjects a similar waveform was also often seen; a typical example is also shown in Figure 6.35 illustrating the binocular and left eye responses of subject 9C, aged 16 years.

For analysis of the results the latency and amplitude (measured from the trough of the preceding negative component) of the CI component were measured at each electrode position in both the albinos and their controls. Initially, the full field responses will be considered. These responses were treated in a similar fashion to those obtained by flash stimulation. The electrodes were divided into pairs, O1, O2 and O3, O4. Each pair thus consisting of an electrode over each hemisphere and symmetrically placed about the midline. The Cx values for the CI component latencies and amplitudes with their means and standard errors were calculated for each pair of electrodes and the raw data subjected to ANOVA.

6.4.1 Electrodes O1 and O2-CI latency

A CI component was present at both these electrodes and hence over both hemispheres in all albino and control subjects. The calculated Cx values for the CI component latencies are shown in Table 6.10.

Table 6.10

The Cx Values for the Latency of the CI Component at Electrodes O1 and O2.

The calculated Cx Values (in ms) for the latency of CI at O1 and O2 in the pattern appearance-disappearance VECP are given for each albino and his matched control. (See text for further details).

Subject	Cx (CI Latency) Electrodes 01 and 02	
	Albino	Control
3	-3.5	-0.5
5	+4.5	-0.5
7	0	+7.0
8	+9.5	-0.5
9	+2.0	+3.0
11	+4.0	-2.0
12	-1.0	+3.5
14	+1.5	+2.5
17	-6.0	-0.5
18	-2.0	+2.5
21	+2.0	+1.5
22	-0.5	-1.0

Among the albino subjects Cx ranged from +9.5ms to -6.0ms and among the controls from +7.0ms to -2.0ms. Six albinos (50%) showed a positive Cx, 5 (42%) a negative value and only one subject (8%) a Cx of zero. Six controls (50%) showed a positive Cx and 6 (50%) a negative value.

Thus both contralateral and ipsilateral lateralisation on monocular stimulation was present among both the albinos and controls. Figure 6.36 illustrates the responses recorded from electrodes O1 and O2 under binocular and monocular conditions in albino subjects 11 and 18. The former showed a Cx value of +4.0ms indicating contralateral lateralisation while in the latter Cx = -2.0ms indicating ipsilateral lateralisation. Among the controls a similar diversity of Cx values was found; Figure 6.37 illustrates the responses of subject 9C (Cx = +3.0ms) and subject 11C (Cx = -2.0ms).

The mean Cx value among the albino group was +0.88ms (S.E. 1.17) and among the controls +1.25ms (S.E. 0.74). The mean values $\pm$ 1 S.E. are shown in Figure 6.38.

ANOVA on the raw CI latency data revealed no interaction between the latency of the component over each hemisphere at sites O1 and O2 and the eye stimulated in both the albino and control groups leading to a statistically insignificant result in both cases. This is illustrated graphically in Figure 6.39.

FIGURE 6.36

The Pattern Appearance-Disappearance Responses of Albino Subjects 11 and 18

The binocular and monocular responses recorded from electrodes O1 and O2 are shown; the latency of the CI component over each hemisphere is labelled. In (a) Cx = +4.0ms indicating contralateral lateralisation on monocular stimulation. In contrast, the responses shown in (b) result in a Cx of -2.0ms indicating ipsilateral lateralisation. (Check size 50', 50 sweeps)

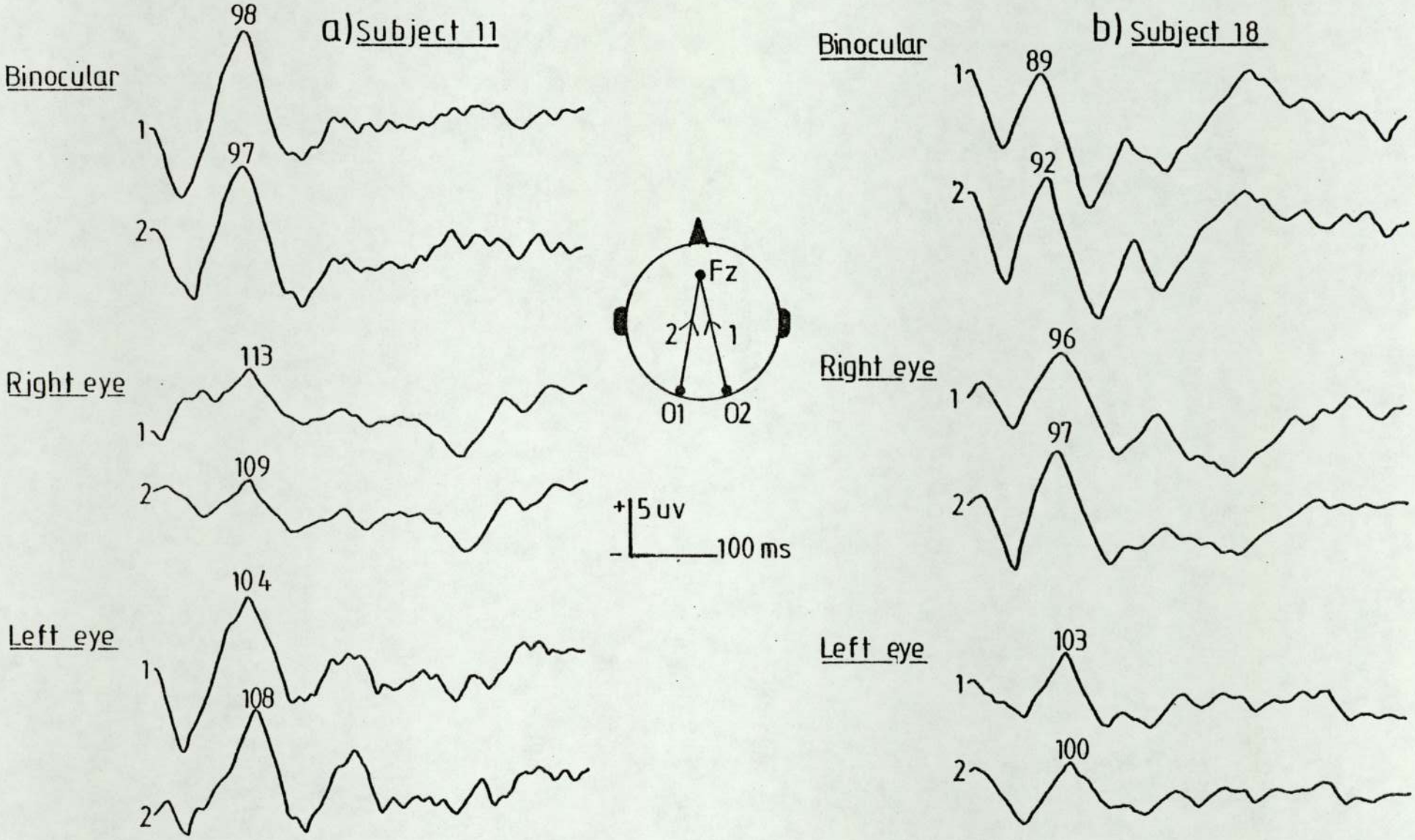

a) Subject 11
Binocular
98
1
97
2
Right eye
113
1
109
2
Left eye
104
1
108
2
Fz
2
1
01
02
+
5 uv
-
100 ms
b) Subject 18
Binocular
89
1
92
2
Right eye
96
1
97
2
Left eye
103
1
100
2

Figure 6.37

The Pattern Appearance-Disappearance Responses of Control Subjects 9C and 11C

The binocular and monocular responses recorded from electrodes O1 and O2 are shown; the latency of the CI component over each hemisphere is labelled. In (a) Cx = +3.0 ms and in (b) Cx = - 2.0 ms indicating contralateral and ipsilateral lateralisation on monocular stimulation respectively. (Check size 50', 50 sweeps).

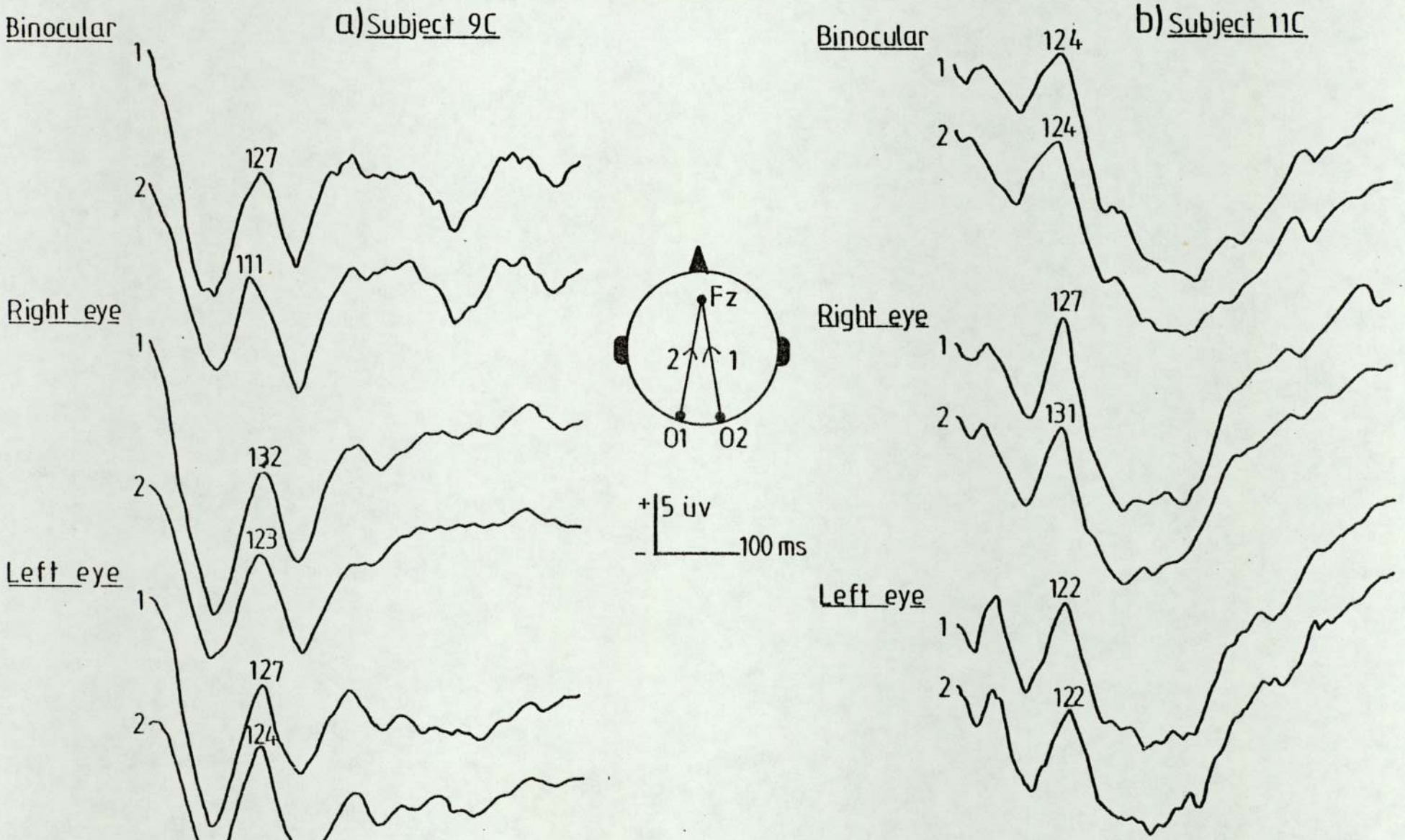

a) Subject 9C
Binocular
1
127
2
111
Right eye
1
132
2
123
Left eye
1
127
2
124
Fz
2
1
01
02
+ 5 uv
- 100 ms
b) Subject 11C
Binocular
124
1
2
124
Right eye
127
1
131
2
Left eye
122
1
122
2

FIGURE 6.38

Graphical illustration of the mean Cx values ± 1 S.E. with respect to the latency of the CI component recorded at electrodes O1 and O2 in both the albino and control groups

The mean Cx values ± 1 S.E. are plotted for both groups

(see text for further details)

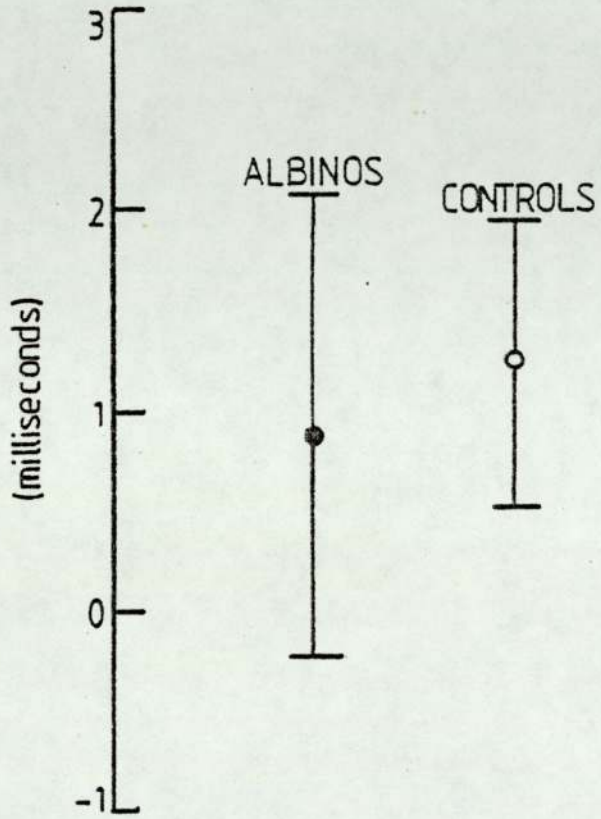
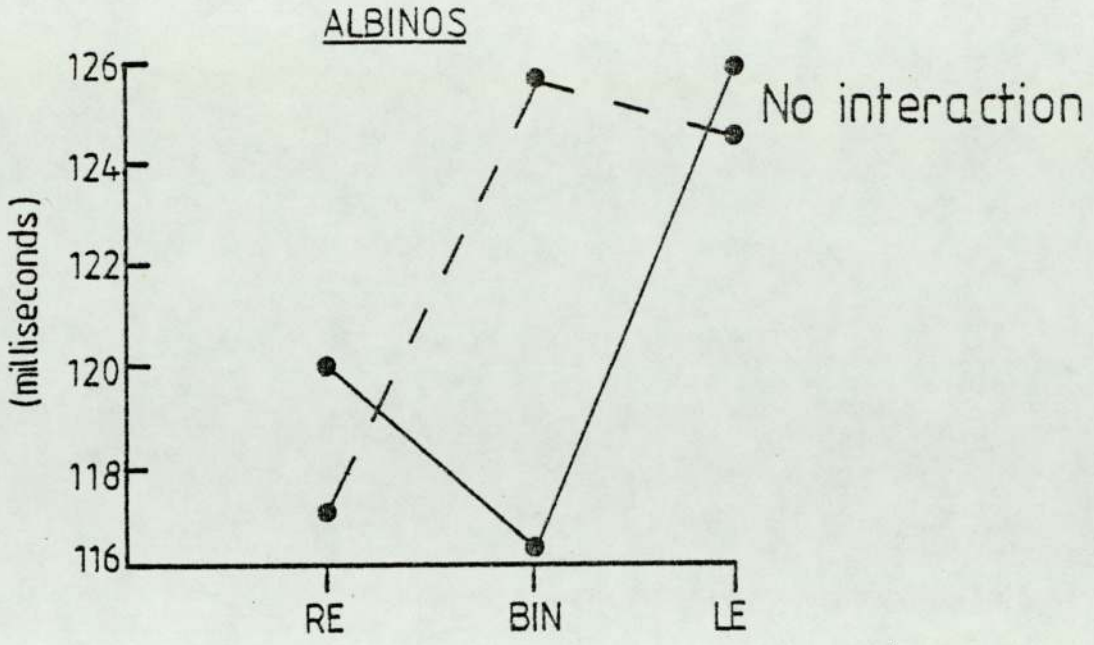
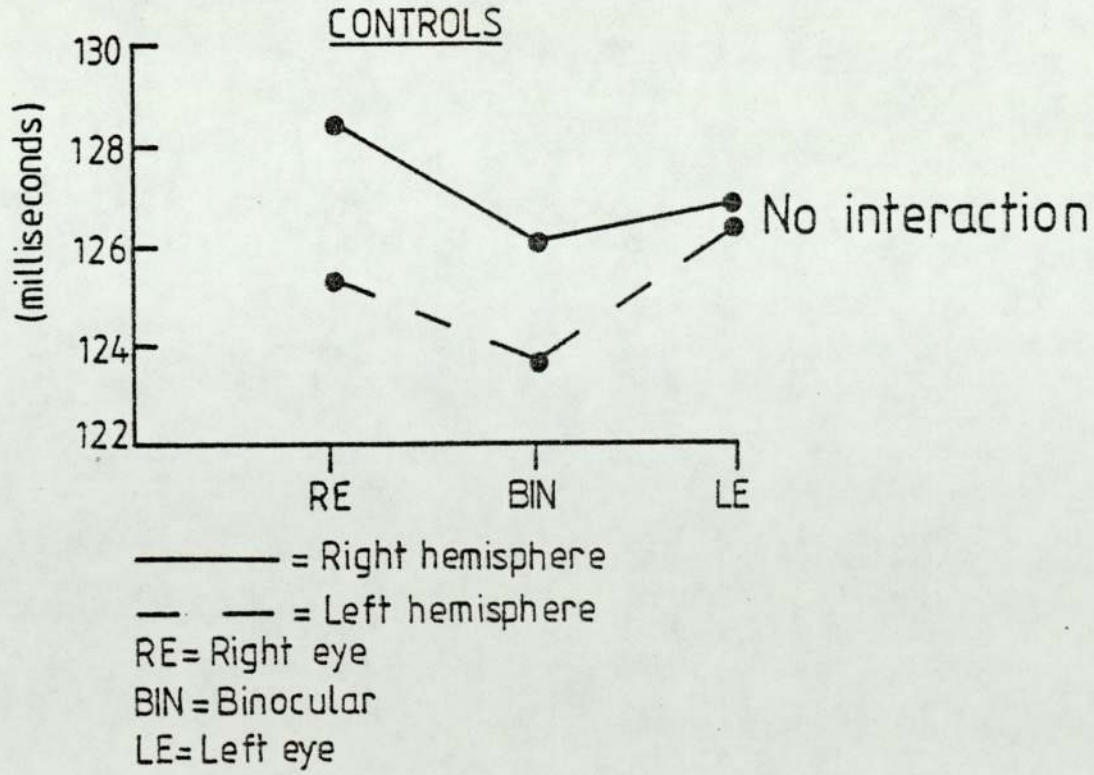

3
2
1
0
-1
(milliseconds)
ALBINOS
CONTROLS

Figure 6.39

Graphical Illustration of ANOVA Results Obtained Using the Raw CI Latency Data from Recordings at O1 and O2 in both the Albino and Control Groups

The latency of the CI recorded over the right and left hemispheres on binocular and monocular stimulation for both groups is plotted. There was no interaction found between the hemisphere over which the shorter CI latency was recorded and the eye stimulated in either group.


ALBINOS
126
124
122
120
118
116
(milliseconds)
RE
BIN
LE
No interaction


CONTROLS
130
128
126
124
122
(milliseconds)
RE
BIN
LE
No interaction
= Right hemisphere
= Left hemisphere
RE = Right eye
BIN = Binocular
LE = Left eye

6.4.2 Electrodes O3 and O4-CI latency

A CI component could be measured at these electrodes in all of the control subjects but in only 9 of the albinos (see Table 6.11). In subjects 3, 7 and 14 a reliable component was absent in one or more of the responses at these extreme electrode positions. The calculated Cx values for the CI latency at electrodes O3 and O4 for the 9 albinos and their controls are shown in Table 6.11.

Among the albino subjects Cx ranged from +13.5ms to -5.0ms and among the controls from +9.0ms to -5.0ms. Five (56%) of the albinos showed a positive Cx and 4 (44%) a negative value. Similarly, 5 (56%) of the controls showed a Cx of a positive value and 4 (44%) a negative value.

Hence, as when considering electrodes O1 and O2, the responses recorded at O3 and O4 showed both contralateral and ipsilateral lateralisation on monocular stimulation in both albino and control groups.

In some albinos, the amount of contralateral lateralisation was large; Figure 6.40 illustrates such a case. This shows the binocular and monocular responses of subject 9 in whom Cx = +11.0ms. In contrast Figure 6.40 also shows the responses of subject 8 in whom Cx = -5.0ms.

Considering the control subjects, Figure 6.41 illustrates

Table 6.11

The Cx Values for the Latency of the CI Component At Electrodes O3 and O4

The calculated Cx values (in ms) for the latency of CI at O3 and O4 in the pattern appearance-disappearance VECP are given for each albino and his matched control (See text for further details).

Subject	Cx (CI Latency) Electrodes 03 and 04	
	Albino	Control
5	+11.0	-5.0
8	-5.0	+9.0
9	+11.0	+3.0
11	+7.5	-3.0
12	+13.5	+2.5
17	-0.5	-1.5
18	-1.5	+2.5
21	+1.0	-3.0
22	-3.5	+0.5

Figure 6.40

The Pattern Appearance-Disappearance Responses of Albino Subjects 9 and 8

The binocular and monocular responses recorded from electrodes O3 and O4 are shown; the latency of the CI components over the two hemispheres are labelled. In (a) Cx =+11.0 ms indicating contralateral lateralisation on monocular stimulation while in (b) Cx = -5.0 ms indicating ipsilateral lateralisation. (Check size 50', 50 sweeps).

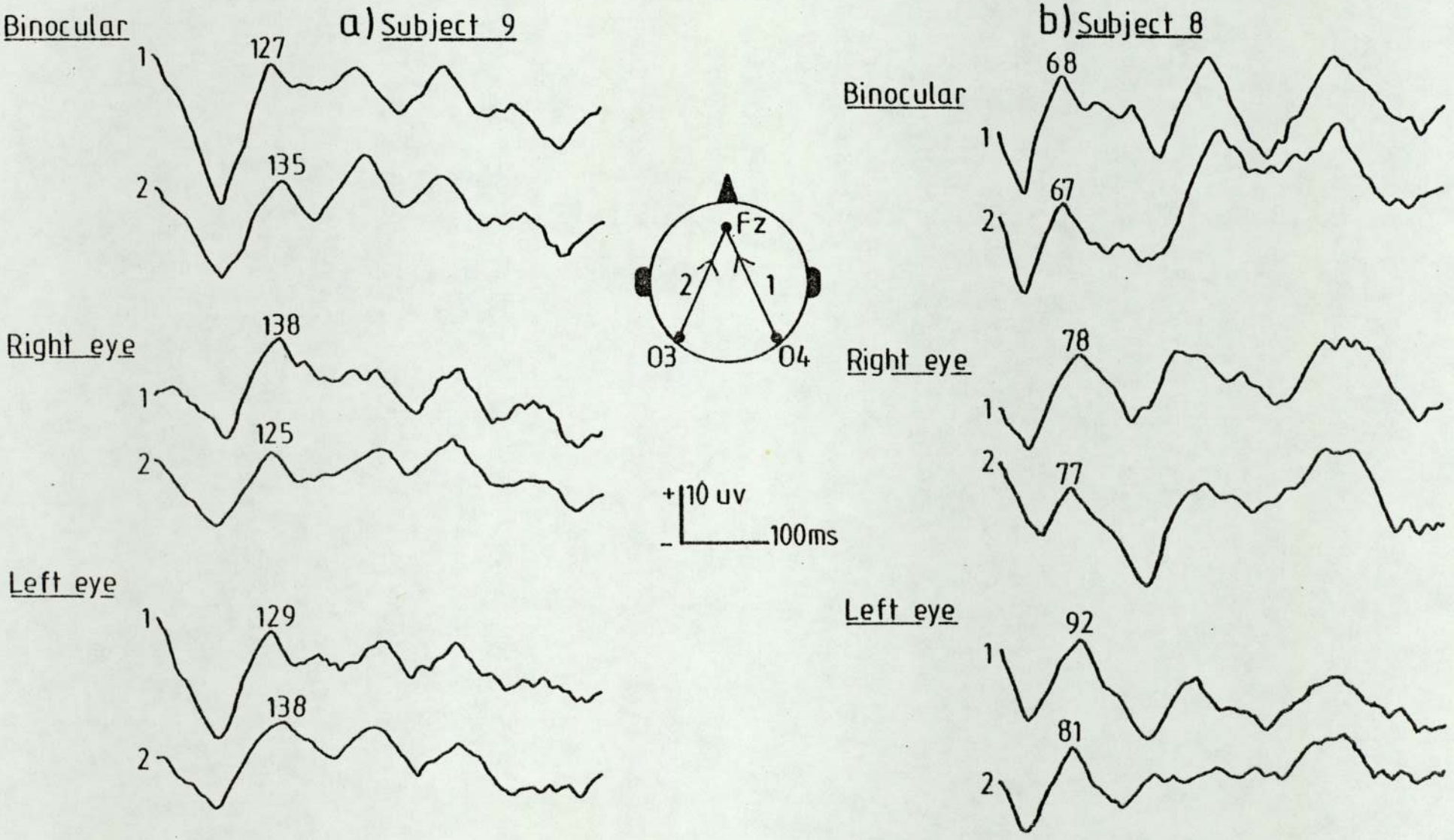
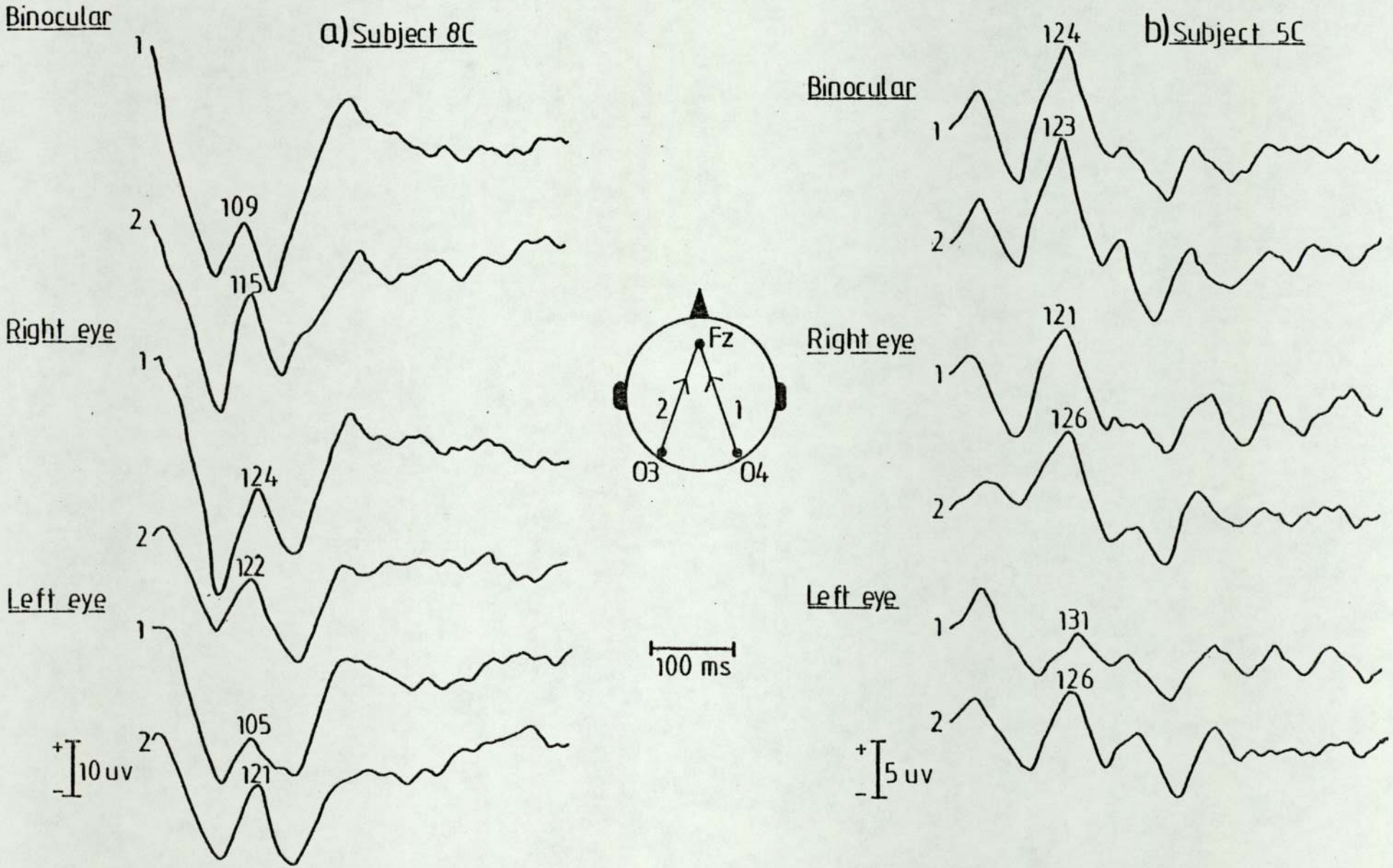

a) Subject 9
Binocular
1
127
2
135
Right eye
1
138
2
125
Left eye
1
129
2
138
Fz
2
1
O3
O4
+ 10 uv
100ms
b) Subject 8
Binocular
1
68
2
67
Right eye
1
78
2
77
Left eye
1
92
2
81

Figure 6.41

The Pattern Appearance-Disappearance Responses of Control Subjects 8C and 5C

The binocular and monocular responses recorded from electrodes O3 and O4 are shown; the latency of the CI component over each hemisphere is labelled. In (a) Cx = +9.0 ms while in (b) Cx = -5.0 ms indicating monocular contralateral and ipsilateral lateralisation respectively. (Check size 50', 50 sweeps).


Binocular
a) Subject 8C
1
109
2
115
Right eye
1
124
2
122
Left eye
1
105
2
121
+
10 uv
-
Fz
2
1
O3
O4
100 ms
b) Subject 5C
Binocular
124
1
123
2
Right eye
121
1
126
2
Left eye
1
131
126
2
+
5 uv
-

the responses of subject 8C who shows monocular contralateral lateralisation (Cx = +9.0ms) and subject 5C who, in contrast, showed ipsilateral lateralisation resulting in a Cx value of -5.0ms.

The mean Cx value among the albino group was +3.70ms (S.E. 2.35) and among the controls +0.56ms (S.E. 1.42). These values are illustrated graphically in Figure 6.42.

ANOVA on the raw data produced one significant result within the control group. Under binocular conditions the latency of the CI component was significantly shorter ($p < 0.05$; $F_{2, 16} = 3.89$) than on stimulation of each eye alone. Such a result was not found within the albino group. However, in neither group was there any significant interaction between the latency of CI over the two hemispheres and the eye stimulated. This is illustrated in Figure 6.43.

6.4.3 Electrodes O1 and O2-CI amplitude

The amplitude of the CI component at these electrode sites was measured in all albino and control subjects. The calculated Cx values are shown in Table 6.12.

Positive and negative Cx values were found in both groups. Among the albinos Cx ranged from + 2.30uV to -4.10uV and among the controls from +2.55uV to -3.80uV. In 4 (33%) of the albinos Cx was positive and in 7 (58%) negative;

Figure 6.42

Graphical Illustration of the Mean Cx Values ± 1 S.E. with Respect to the Latency of CI recorded at Electrodes O3 and O4 in both the Albino and Control Groups.

The mean Cx values ± 1 S.E. are plotted for both groups. (See text for details).

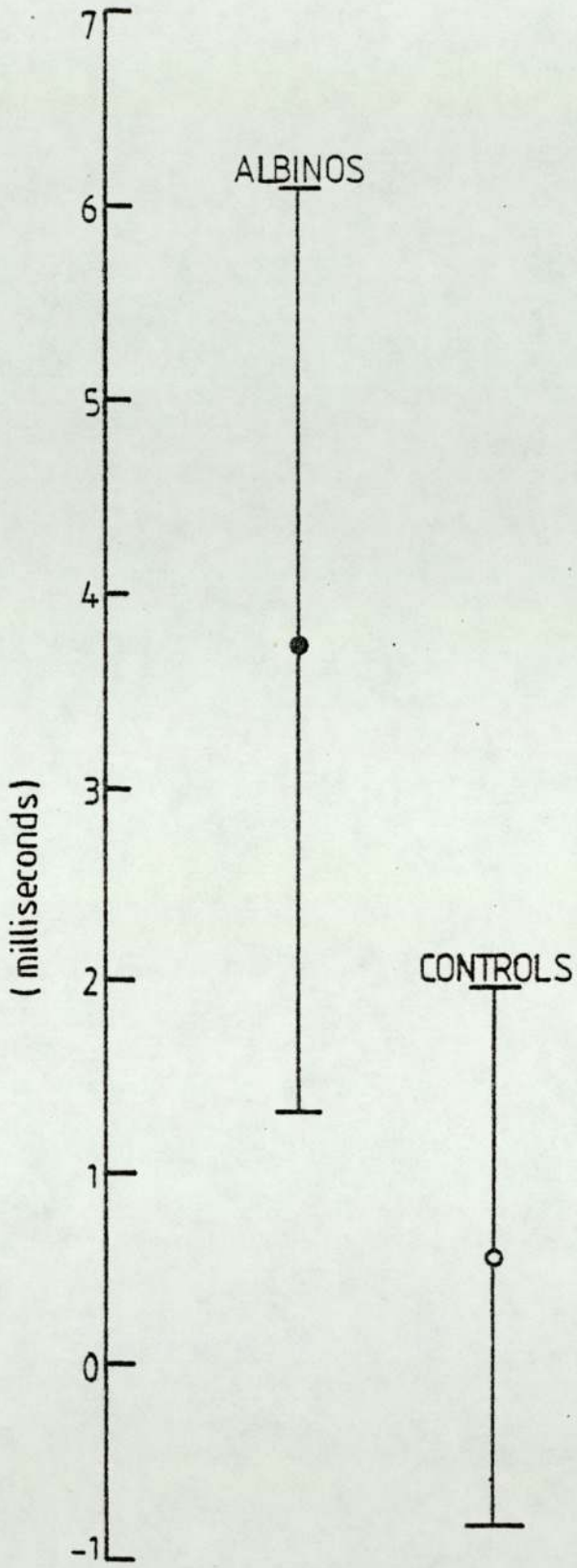

7
6
5
4
3
2
1
0
-1
(milliseconds)
ALBINOS
CONTROLS

Figure 6.43

Graphical Illustration of ANOVA Results Obtained Using the Raw CI Latency Data from Recordings at O3 and O4 in both the Albino and Control Groups

The latency of the CI component recorded over the right and left hemispheres on binocular and monocular stimulation for both groups are plotted. In neither group was there any interaction between the hemisphere over which the short CI latency was recorded and the eye stimulated. However, within the control group the latency of CI was found to be significantly shorter ($p<0.05$) over the hemispheres on binocular compared to monocular stimulation. This effect was not seen within the albino group.

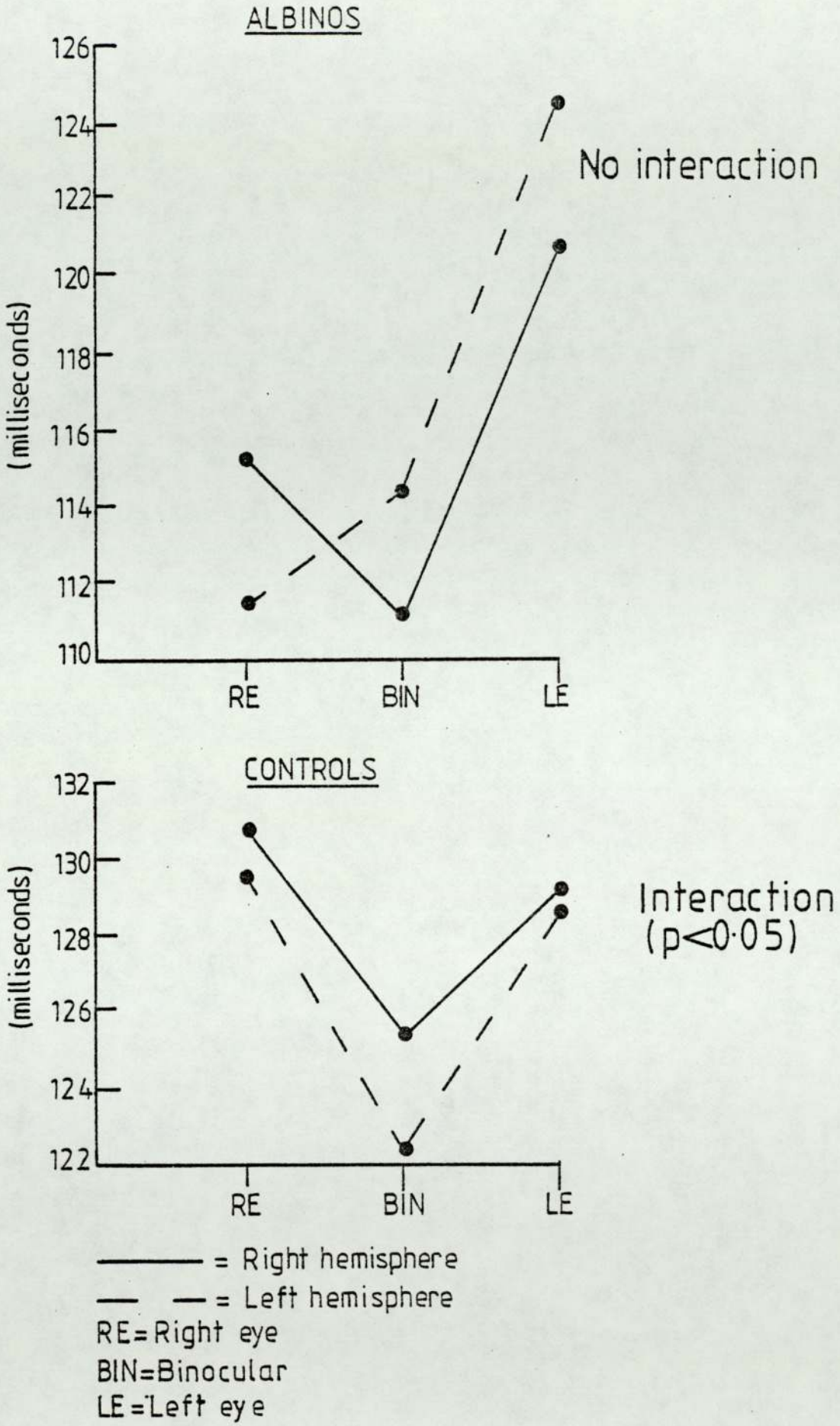

ALBINOS
126
124
122
120
118
116
114
112
110
(milliseconds)
No interaction
RE
BIN
LE
CONTROLS
132
130
128
126
124
122
(milliseconds)
Interaction
(p<0·05)
RE
BIN
LE
= Right hemisphere
= Left hemisphere
RE=Right eye
BIN=Binocular
LE=Left eye

Table 6.12

The Cx Values for the Amplitude of the CI Component at Electrodes O1 and O2

The calculated Cx values (in uV) for the amplitude of CI at O1 and O2 in the pattern appearance-disappearance VECP are given for each albino and his matched control. (See text for further details).

Subject	Cx (CI Amplitude) Electrodes O1 and O2	
	Albino	Control
3	-1.05	-0.80
5	0	-1.95
7	+1.55	-1.90
8	-2.45	-3.30
9	-0.60	-0.70
11	+1.60	-1.25
12	-4.10	+0.50
14	-1.40	-2.45
17	-0.65	-3.80
18	+2.30	-1.50
21	-0.85	+2.55
22	+1.50	+0.35

only one subject showed a Cx of zero. In the control group 3 (25%) showed a positive Cx and 9 (75%) a negative value.

Therefore, as in the case of the CI latency values, both contralateral and ipsilateral lateralisation on monocular stimulation were present in the albinos and controls when considering the amplitude of the CI component. Figure 6.44 illustrates the responses of subject 18 who showed contralateral lateralisation (Cx = +2.30uV) and, in contrast, the respones of subject 12 who showed a Cx of -4.10uV indicating ipsilateral lateralisation. Among the controls a similar range of positive and negative Cx values was found. Figure 6.45 illustrates the responses of subject 21C in whom Cx = +2.55uV and subject 8C in whom Cx = -3.30uV.

The mean Cx value among the albinos was -0.35uV (S.E. 0.54) and among the controls -1.19uV (S.E. 0.51). These means $\pm$ 1 S.E. are shown in Figure 6.46.

ANOVA on the raw CI amplitude data revealed that within the control group the amplitude of CI was significantly greater on binocular stimulation ($p < 0.025$; $F_{2,22} = 4.64$) compared to monocular stimulation. This was not found within the albino group. However, in neither group was there any significant interaction between the amplitude of CI over the two hemispheres and the eye stimulated. This result is illustrated graphically in Figure 6.47.

Figure 6.44

The Pattern Appearance-Disappearance Responses of Albino Subjects 18 and 12

The binocular and monocular responses recorded from electrodes O1 and O2 are shown; the amplitude of the CI component over each hemisphere is labelled. In (a) Cx = +2.30 uV indicating contralateral lateralisation on monocular stimulation, while in (b) Cx = -4.10 uV indicating ipsilateral lateralisation. (Check Size 50', 50 sweeps).

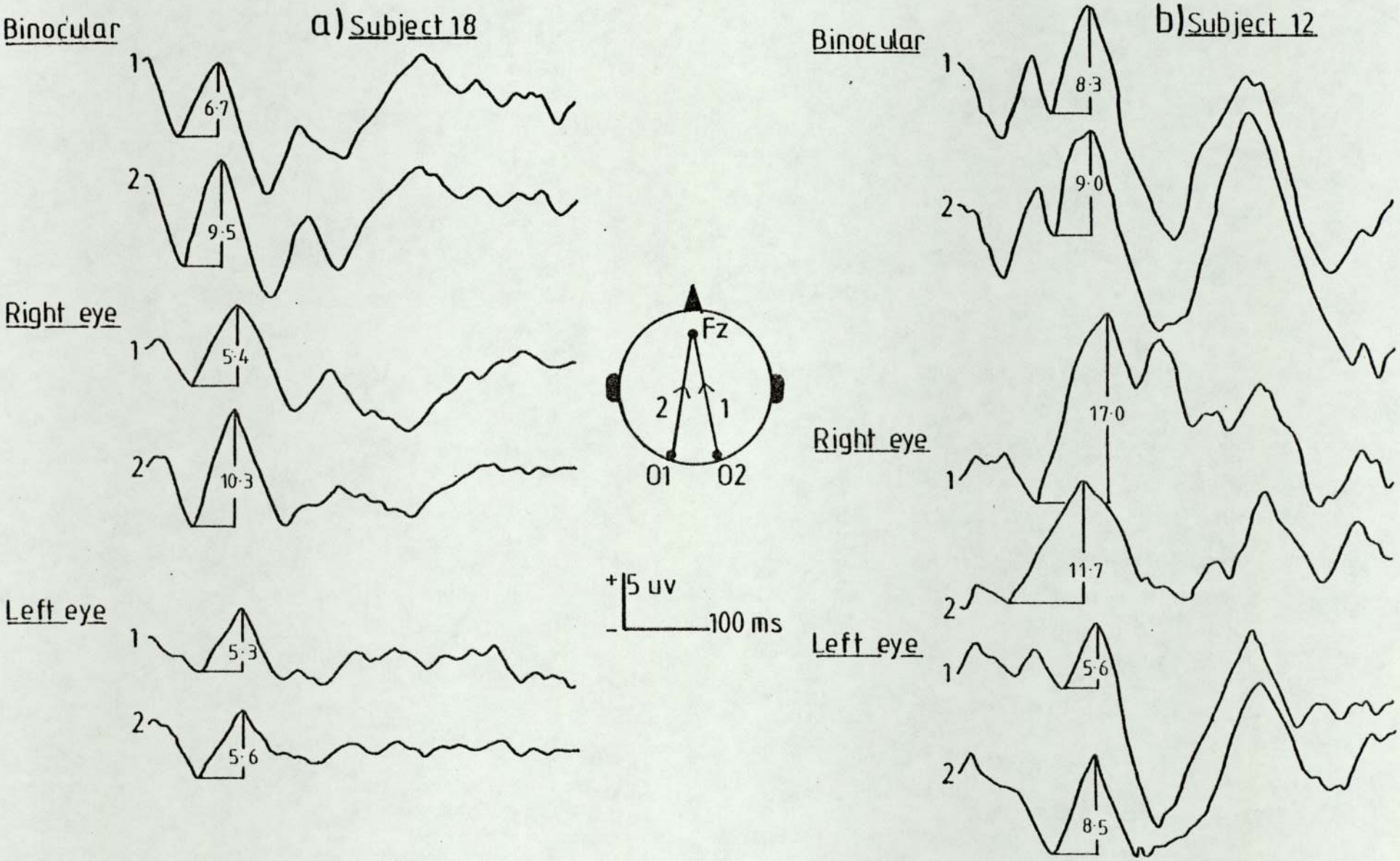

a) Subject 18
Binocular
1
6·7
2
9·5
Right eye
1
5·4
2
10·3
Left eye
1
5·3
2
5·6
Fz
2
1
O1
O2
+ 5 uv
- 100 ms
b) Subject 12
Binocular
1
8·3
2
9·0
Right eye
1
17·0
2
11·7
Left eye
1
5·6
2
8·5

Figure 6.45

The Pattern Appearance-Disappearance Responses of Control Subjects 21C and 8C

The binocular and monocular responses recorded from electrodes O1 and O2 are shown; the amplitude of CI over each hemisphere is given. In (a) Cx = +2.55 uV and in (b) Cx = -3.00 uV. These indicate contralateral and ipsilateral lateralisation on monocular stimulation respectively. (Check size 50', 50 sweeps).

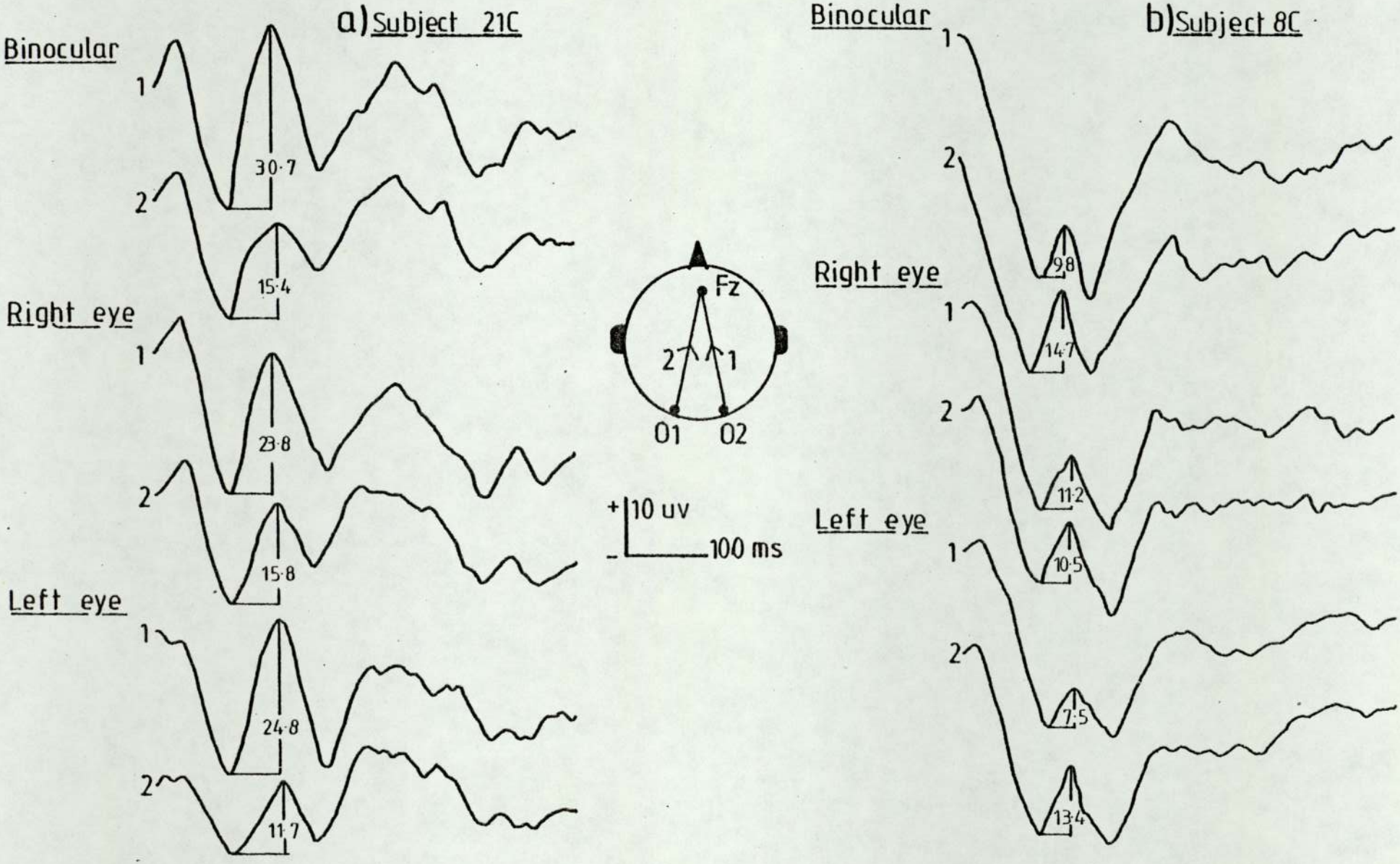

a) Subject 21C
Binocular
1
30·7
2
15·4
Right eye
1
23·8
2
15·8
Left eye
1
24·8
2
11·7
Fz
2
1
O1
O2
+ 10 uv
- 100 ms
Binocular
b) Subject 8C
1
9·8
2
Right eye
1
14·7
2
11·2
Left eye
1
10·5
2
7·5
13·4

Figure 6.46

Graphical Illustration of the Mean Cx Values ± 1 S.E. With Respect to the Amplitude of CI Recorded at Electrodes O1 and O2 in both the Albino and Control Groups

The mean Cx values ± 1 S.E. are plotted for both groups. (See text for further details).

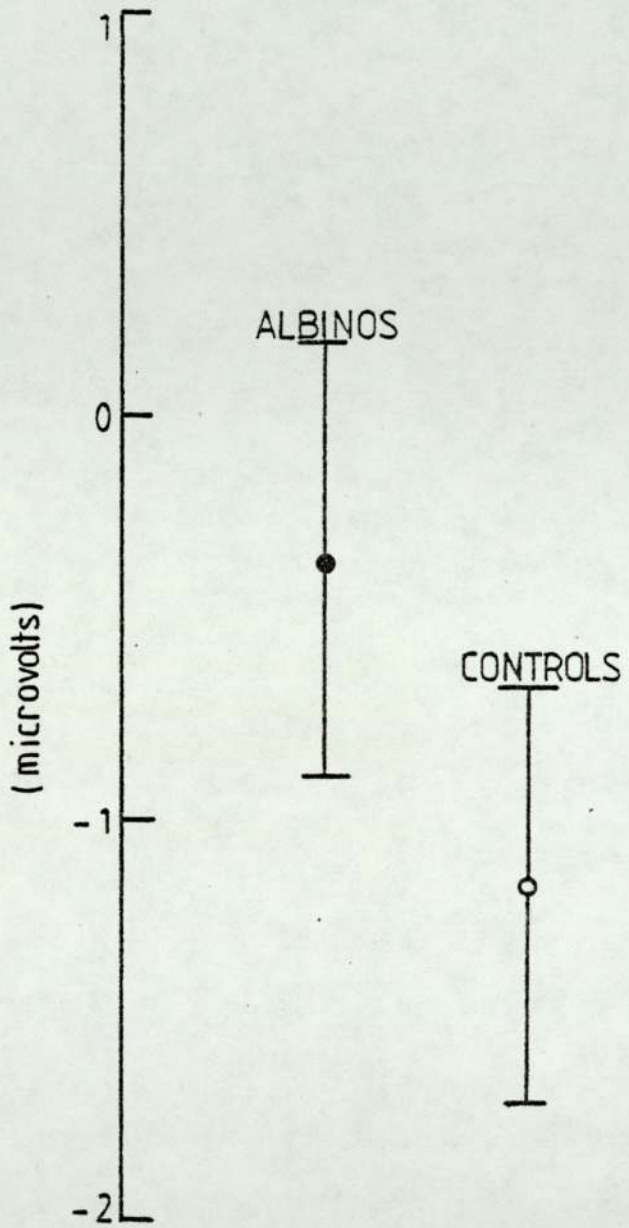
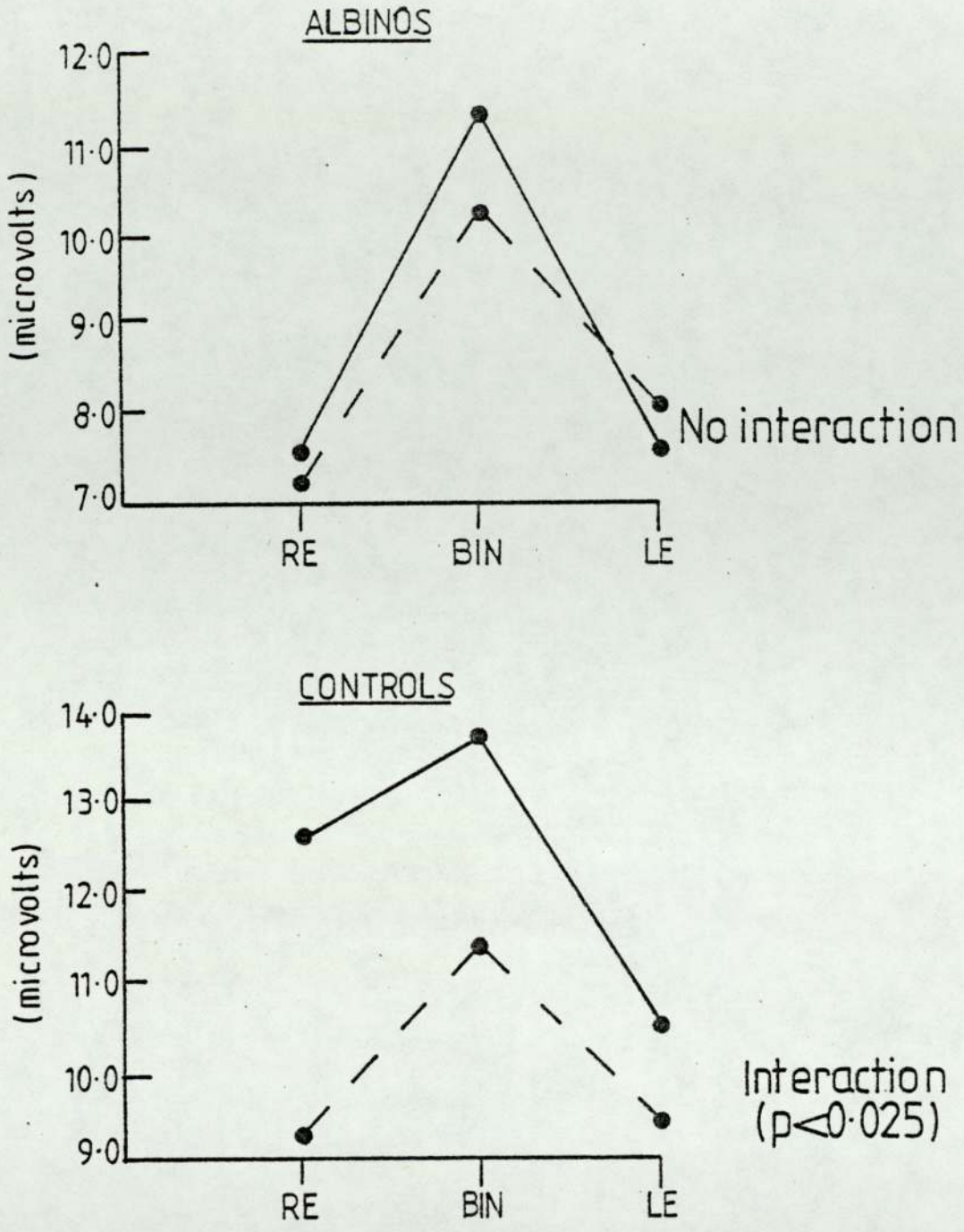

1
0
-1
-2
(microvolts)
ALBINOS
CONTROLS

Figure 6.47

Graphical Illustration of ANOVA Results Obtained Using the Raw CI Amplitude Data from Recordings at O1 and O2 in both the Albino and Control Groups

The amplitude of CI recorded over the right and left hemispheres on binocular and monocular stimulation for both groups are plotted. In neither group was there any interaction between the hemisphere over which the larger CI was recorded and the eye stimulated. However, within the control group the amplitude was significantly greater ($p < 0.025$) on binocular compared to monocular stimulation. Such an effect was not seen within the albino group.


ALBINOS
12·0
11·0
10·0
9·0
8·0
7·0
(microvolts)
RE
BIN
LE
No interaction
CONTROLS
14·0
13·0
12·0
11·0
10·0
9·0
(microvolts)
RE
BIN
LE
Interaction
(p<0·025)
= Right hemisphere
= Left hemisphere
RE = Right eye
BIN = Binocular
LE = Left eye

6.4.4 Electrodes O3 and O4-CI amplitude

As in the case of the CI latency measure, due to the absence of a reliable component in three albinos at these electrode sites, the amplitude of the CI component could only be measured in 9 albinos. The calculated Cx values for these albinos and their controls are shown in Table 6.13.

Again both positive and negative Cx values were found among the albinos and controls. In the former group Cx ranged from +4.25uV to -7.30uV and among the latter from +5.65uV to -7.00uV. Four (44%) of the albinos showed a positive Cx value and 5 (56%) a negative value. In three (33%) of the controls Cx was positive and in 6 (66%) negative.

Therefore, again both contralateral and ipsilateral lateralisation on monocular stimulation was present among the albinos and the controls. Considering the albino subjects, Figure 6.48 illustrates the responses of subject 18 in whom Cx = +2.80uV and those of subject 8 in whom Cx = -7.30uV indicating contralateral and ipsilateralisation respectively.

In contrast, Figure 6.49, illustrates the responses of two control subjects, 22C and 8C who showed contralateral (Cx = +1.05uV) and ipsilateral (Cx = -7.00uV) lateralisation respectively.

Table 6.13

The Cx Values for the Amplitude of the CI Component at Electrodes O3 and O4.

The calculated Cx values (in uV) for the amplitude of CI at O3 and O4 in the pattern appearance-disappearance VECP are given for each albino and his matched control.(See text for further details).

Subject	Cx (CI Amplitude) Electrodes 03 and 04	
	Albino	Control
5	+0.15	-3.15
8	-7.30	-7.00
9	-0.35	-1.00
11	+2.65	-1.05
12	-3.65	+5.65
17	-0.25	-0.40
18	+2.80	-2.20
21	-1.25	+0.70
22	+4.25	+1.05

Figure 6.48

The Pattern Appearance-Disappearance Responses of Albino Subjects 18 and 8

The binocular and monocular responses recorded from electrodes O3 and O4 are shown; the amplitude of CI over each hemisphere is labelled. In (a) Cx = +2.80 uV indicating contralateral lateralisation on monocular stimulation while in (b) Cx = -7.30uV indicating monocular ipsilateral lateralisation. (Check size 50', 50 sweeps).

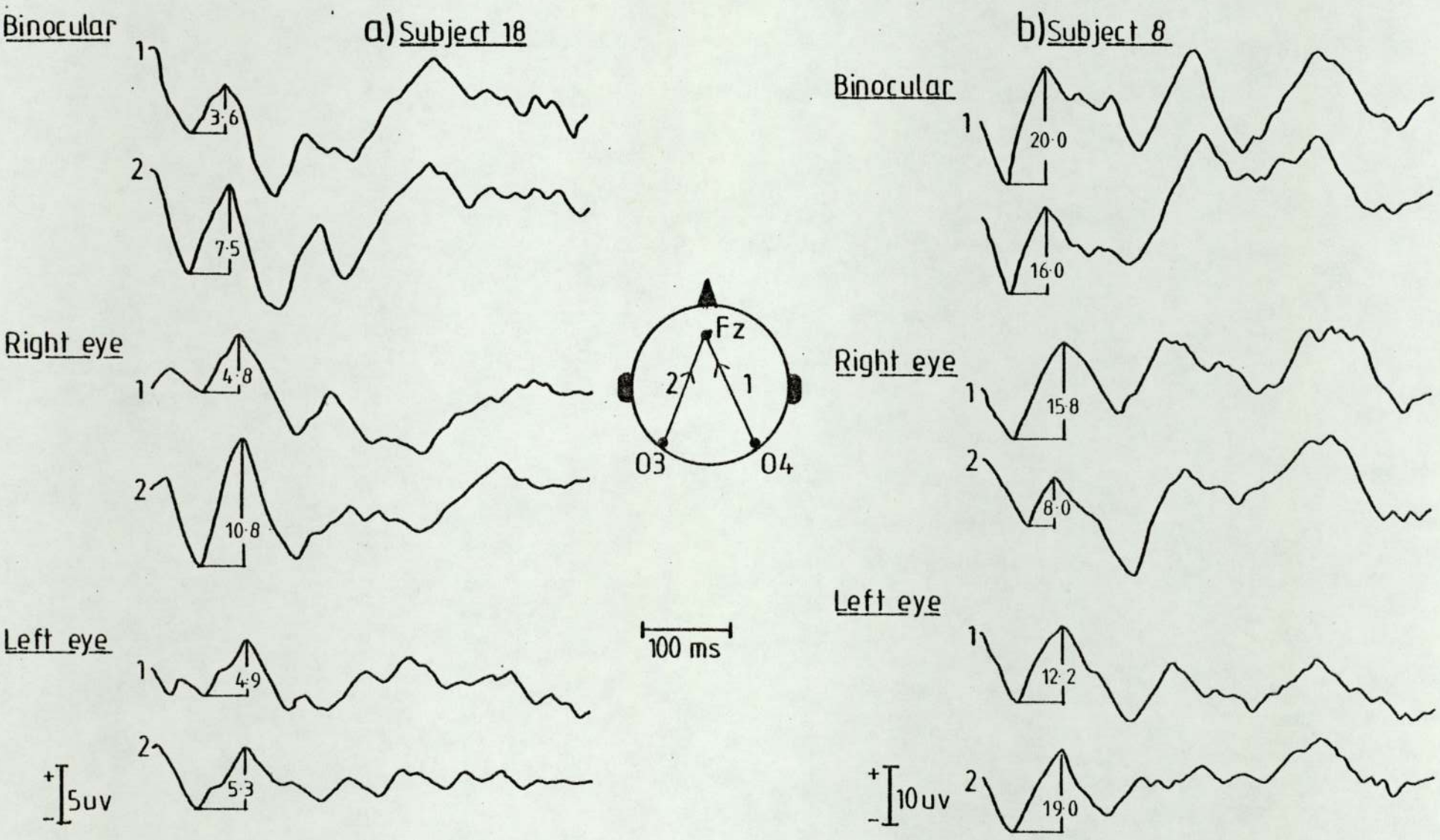
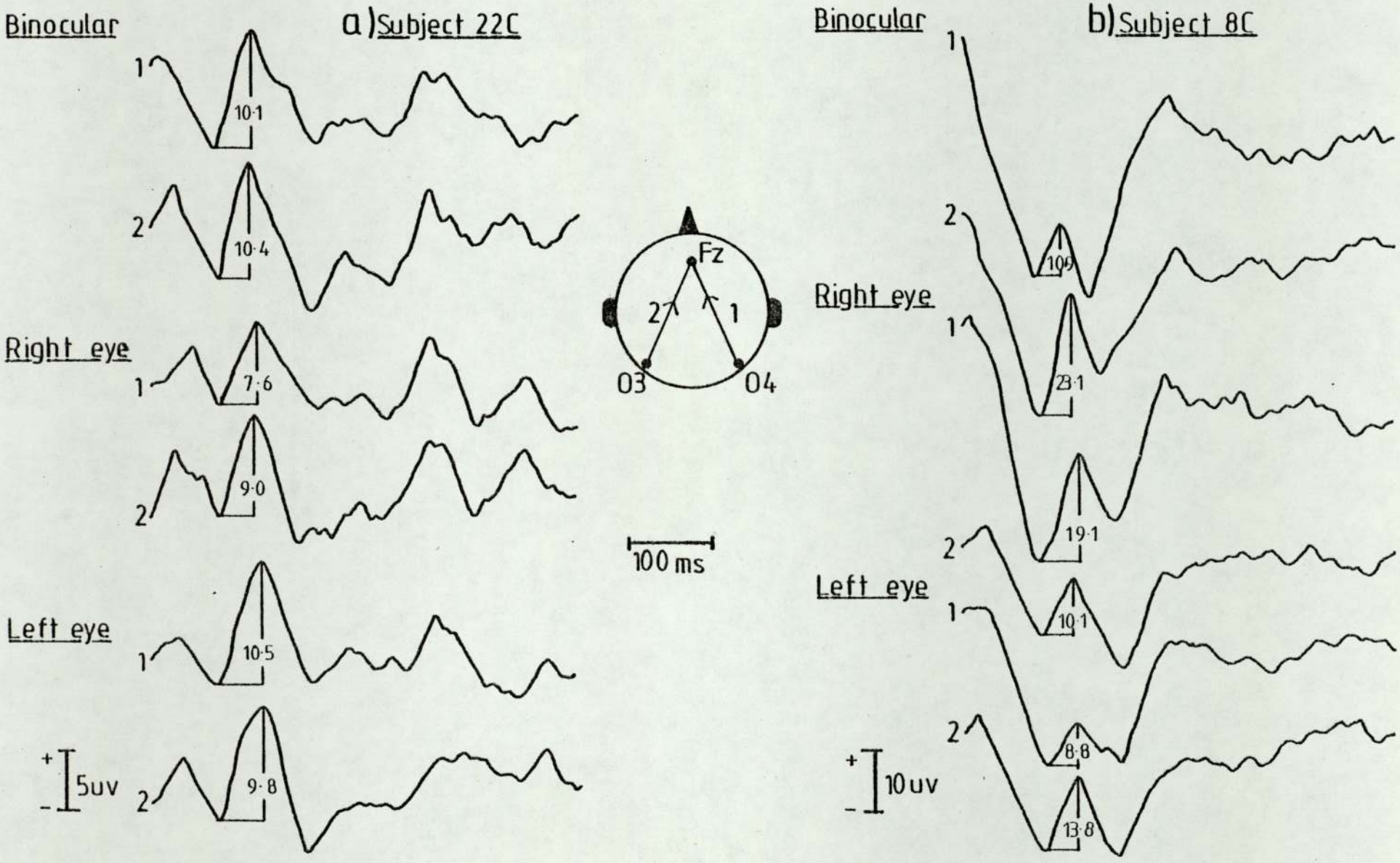

Binocular
a) Subject 18
1
3·6
2
7·5
Right eye
1
4·8
2
10·8
Left eye
1
4·9
2
5·3
+
-
5uv
Fz
2
1
O3
O4
100 ms
b) Subject 8
Binocular
1
20·0
16·0
Right eye
1
15·8
2
8·0
Left eye
1
12·2
2
19·0
+
-
10uv

Figure 6.49

The Pattern Appearance-Disappearance Responses of Control Subjects 22C and 8C

The binocular and monocular responses recorded from electrodes O3 and O4 are shown; the amplitude of CI over each hemisphere is labelled. In (a) Cx = +1.05 uV while in (b) Cx = -7.00 uV indicating contralateral and ipsilateral monocular lateralisation respectively. (Check size 50', 50 sweeps).


Binocular
a) Subject 22C
1
10·1
2
10·4
Right eye
1
7·6
2
9·0
Left eye
1
10·5
2
9·8
+
5uv
-
Fz
2
1
O3
O4
100 ms
Binocular
b) Subject 8C
1
10·9
2
23·1
Right eye
1
19·1
2
10·1
Left eye
1
8·8
2
13·8
+
10uv
-

The mean Cx value of the albino group was -0.33uV (S.E. 1.18) and of the control group -0.82uV(S.E. 1.14). These means $\pm$ 1 S.E. are illustrated graphically in Figure 6.50.

ANOVA on the raw amplitude data produced similar results to those obtained when considering electrodes O1 and O2. There was no interaction between the amplitude of the CI component over the two hemispheres and the eye stimulated in neither the albino or control group. These results are illustrated graphically in Figure 6.51.

6.4.5 Bipolar recordings

As previously described, during the recording of the pattern appearance-disappearance VECPs one averaging channel was devoted to a bipolar recording between electrodes O1 and O2 (O1 referred to O2). Creel et al. (1981a and b) and Apkarian et al. (1983) have reported this to be successful in identifying misrouting in albino subjects. In control subjects, on binocular and monocular stimulation, the bipolar response was reported to remain similar in waveform but, in the albinos, it was found that there was polarity reversal when stimulation was changed from one eye to the other.

Our results confirmed that in the control subjects the bipolar responses recorded on binocular, left and right eye stimulation, although not usually flat, were very similar in waveform. Figure 6.52 illustrates the responses

Figure 6.50

Graphical Illustration of the mean Cx Values ± 1 S.E. with Respect to the Amplitude of CI Recorded at Electrodes O3 and O4 in both the Albino and Control Groups

The Cx values ± 1 S.E. are plotted for both groups.

(See text for further details)

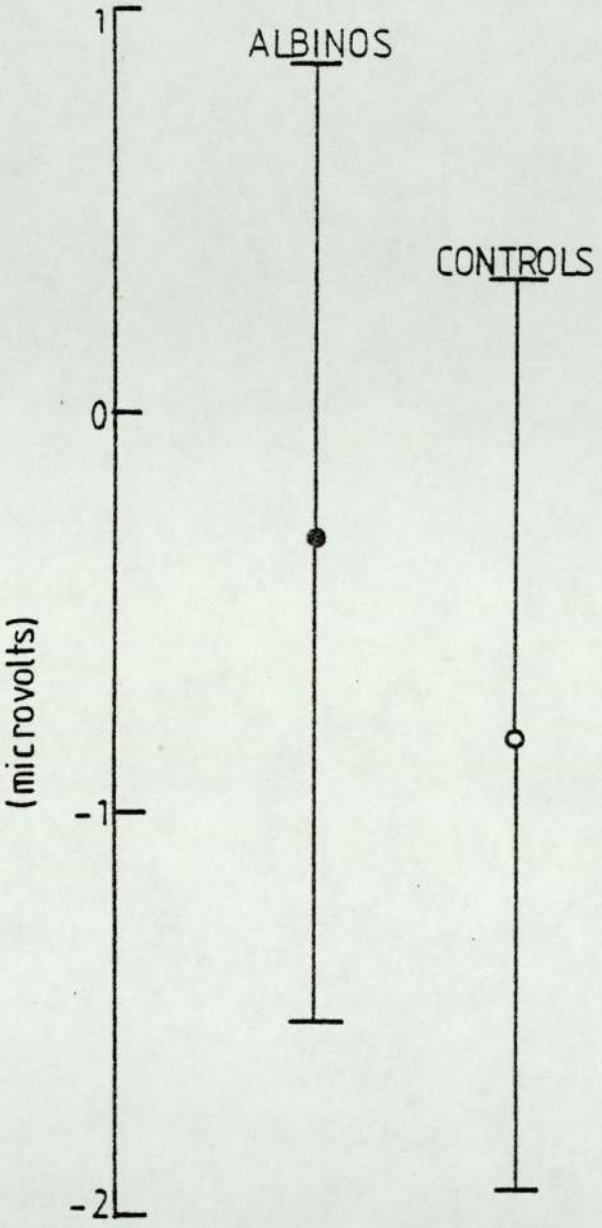

1
0
-1
-2
(microvolts)
ALBINOS
CONTROLS

Figure 6.51

Graphical Illustration of ANOVA Results Obtained Using The Raw CI Amplitude Data from Recordings at O3 and O4 in Both the Albino and Control Groups

The amplitude of the CI component recorded over the right and left hemispheres on binocular and monocular stimulation for both groups are plotted. In neither case was there any interaction between the hemisphere over which the larger CI amplitude was recorded and the eye stimulated.

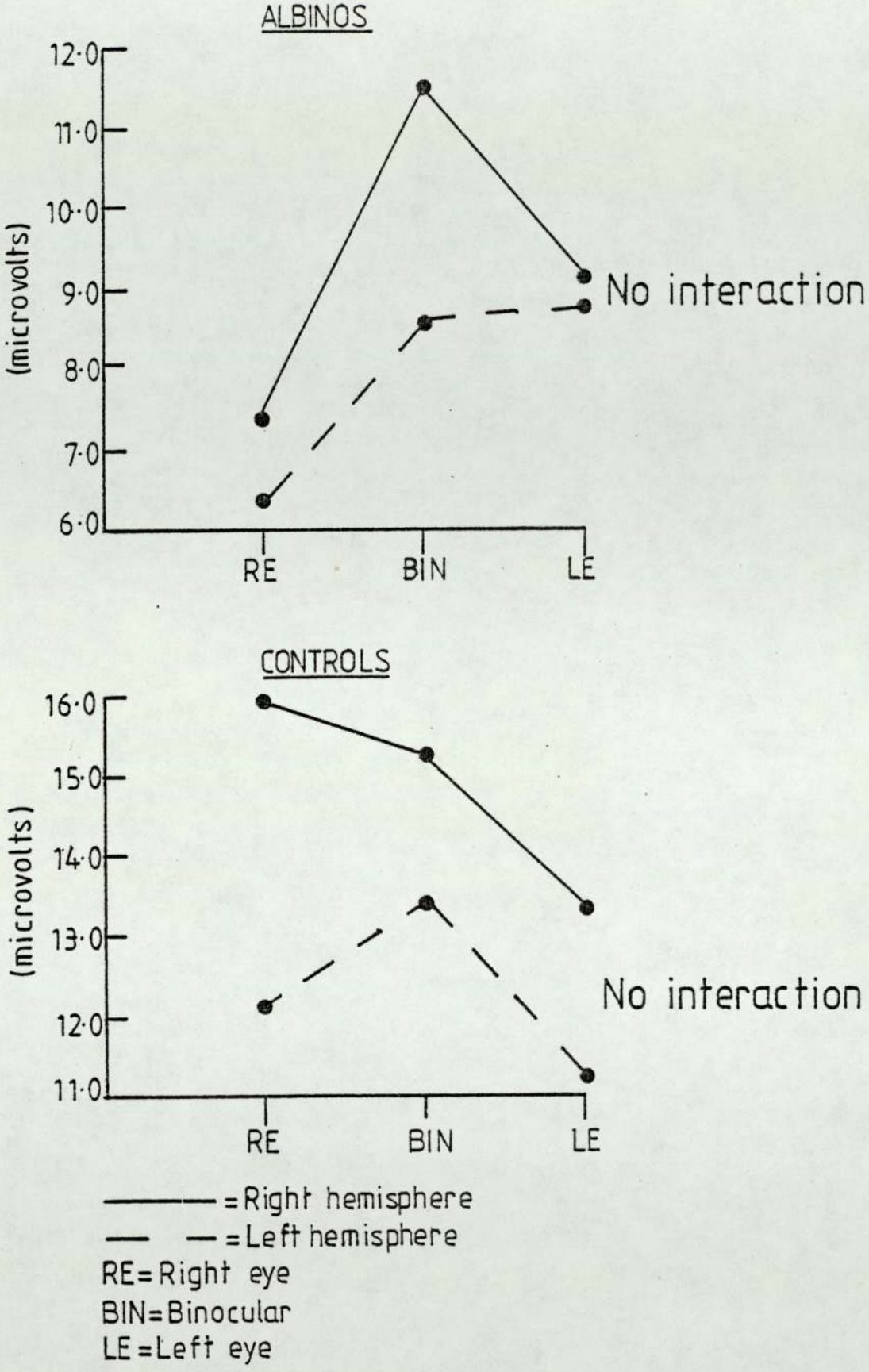
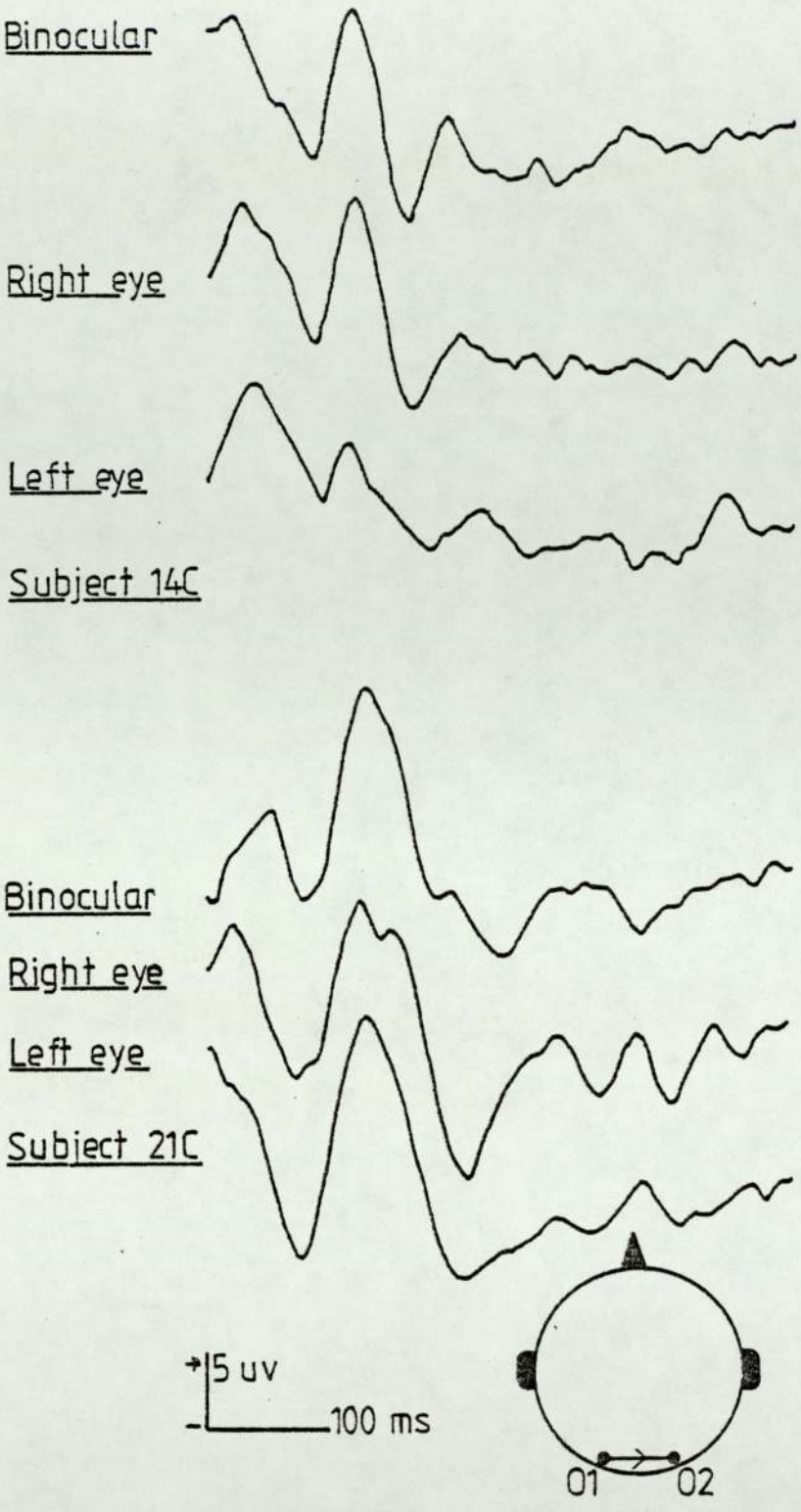

ALBINOS
12·0
11·0
10·0
9·0
8·0
7·0
6·0
(microvolts)
No interaction
RE
BIN
LE
CONTROLS
16·0
15·0
14·0
13·0
12·0
11·0
(microvolts)
No interaction
RE
BIN
LE
——— = Right hemisphere
— — = Left hemisphere
RE = Right eye
BIN = Binocular
LE = Left eye

Figure 6.52

The Bipolar Occipital Pattern Appearance-Disappearance Full-Field Responses of Control Subjects 14C and 21C

The binocular, right and left eye responses recorded from a bipolar occipital derivation (O1-O2) are illustrated. In each subject the three responses, although not flat, have a very similar waveform. (Check size 50'; 50 sweeps).


Binocular
Right eye
Left eye
Subject 14C
Binocular
Right eye
Left eye
Subject 21C
5 uv
100 ms
O1
O2

of two control subjects (14C and 21C) showing this typical result; in both cases the bipolar occipital responses are virtually identical under binocular and monocular conditions. None of the control subjects showed bipolar responses indicative of any form of monocular lateralisation of either a contralateral or ipsilateral nature.

Within the albino group the results, however, were somewhat different. Of the 12 subjects examined 8 (67%) showed a polarity reversal of the monocular O1-O2 bipolar response when stimulation was changed between the two eyes. All recordings were made using O1 referred to O2 and, using this derivation, contralateral lateralisation on monocular stimulation is represented by an upward (positive) deflection on right eye stimulation and a downward (negative) deflection on left eye stimulation. The reverse will be present if ipsilateral lateralisation occurred. On this basis, all 8 subjects who produced monocular polarity reversal at the latency of the CI component showed lateralisation of a contralateral nature; in no case was ipsilateral lateralisation found. The subjects showing this effect are shown in Table 6.14. Two typical examples are shown in Figure 6.53. In some subjects the effect was fairly dramatic (Figure 6.53; subject 9), while in others it was less obvious but nevertheless present (Figure 6.53; subject 14).

Table 6.14

Polarity Reversal of Bipolar, O1-O2, Recordings on Monocular Pattern Appearance-Disapperance Stimulation of the Albinos

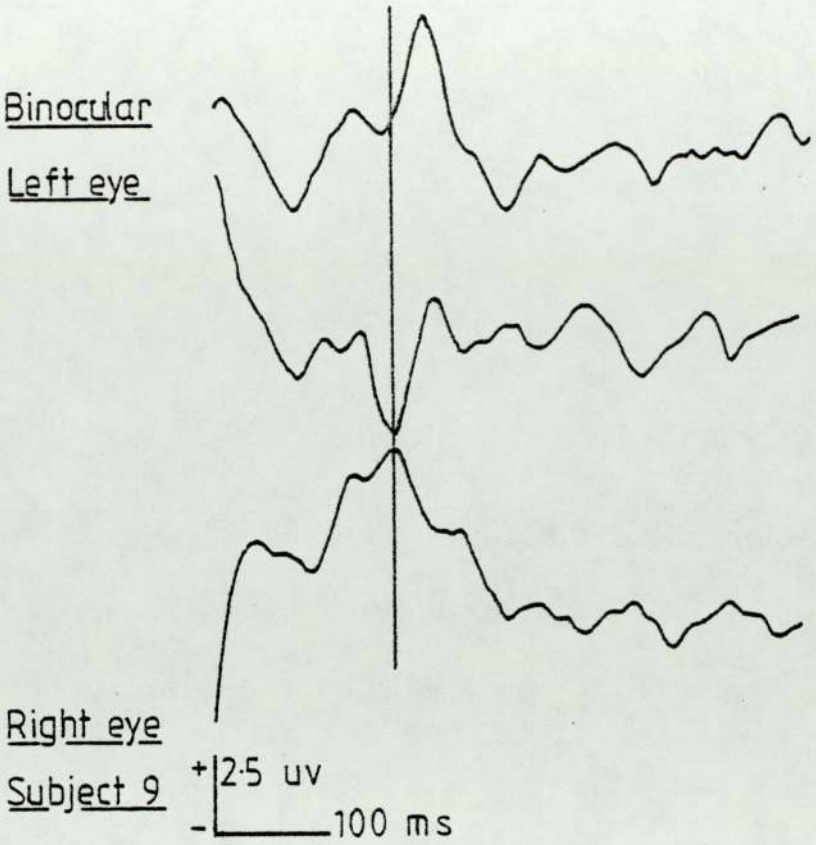
Polarity reversal of the bipolar response on changing stimulation between the two eyes occurred in 8 of the 12 albinos examined. In all these cases the response showed contralateral lateralisation. Four of the subject failed to exhibit this effect. In no subject was ipsilateral lateralisation found. (See text for further details).

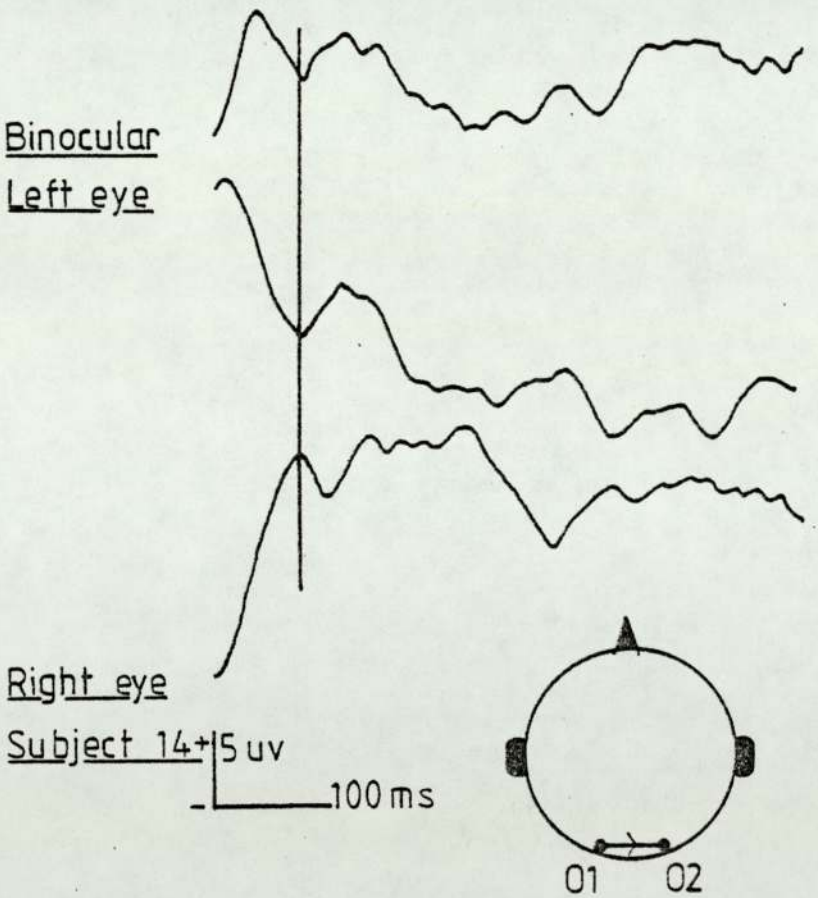
Subject	Polarity Reversal of 01-02 Response on Monocular Stimulation
3	NO
5	NO
7	NO
8	YES (Contralateral)
9	YES (Contralateral)
11	NO
12	YES (Contralateral
14	YES (Contralateral)
17	YES (Contralateral)
18	YES (Contralateral)
21	YES (Contralateral)
22	YES (Contralateral)

Figure 6.53

The Bipolar Occipital Pattern Appearance-Disappearance Full-Field Responses of Albino Subjects 9 and 14

The binocular right and left eye responses recorded from a bipolar occipital derivation (O1-O2) are illustrated. In both subjects the left and right eye responses show polarity reversal (marked by a solid line) indicating contralateral lateralisation on monocular stimulation. (Check size 50'; 50 sweeps).


Binocular
Left eye
Right eye
Subject 9
+
2·5 uv
-
100 ms


Binocular
Left eye
Right eye
Subject 14
+
5 uv
-
100 ms
O1
O2

The monocular bipolar occipital derivations recorded in these albinos were often very similar to those found on monocular half-field stimulation in the control subjects. This can be seen by comparing Figure 6.53 with Figure 6.54 the latter of which illustrates the monocular full-field and half-field responses of two control subjects, 8C and 21C whose half-field responses show clear contralateral lateralisation.

Four of the albinos did not show this monocular polarity reversal (see Table 6.14). In these subjects no clear polarity reversal of either an ipsilateral or contralateral nature was found, although, the responses from the two eyes were not generally similar as found in control subjects (see Figure 6.52). The responses of two such albinos (subjects 3 and 7) are illustrated in Figure 6.55; it can be seen that the polarity reversal illustrated in Figure 6.53 is not obvious in these albinos.

6.4.6 Half-field responses

These were recorded in the albinos primarily to investigate the possibility that in these subjects the monocular whole-field responses are dominated by the response of the nasal retina (temporal half-field) rather than that of the temporal retina (nasal half-field) from which the misrouted fibres arise.

To find out if this was indeed the case the half-field responses were superimposed over the full-field responses.

Figure 6.54

The Monocular Half-Field Pattern Appearance-Disappearance Responses Recorded from a Bipolar Occipital Derivation in Control Subjects 8C and 21C

The left and right half-field responses of both subjects show the polarity reversal evident in the left and right eye responses of the albino subjects shown in Figure 6.53. This polarity reversal is marked by a solid line. (Check Size 50'; 50 sweeps).

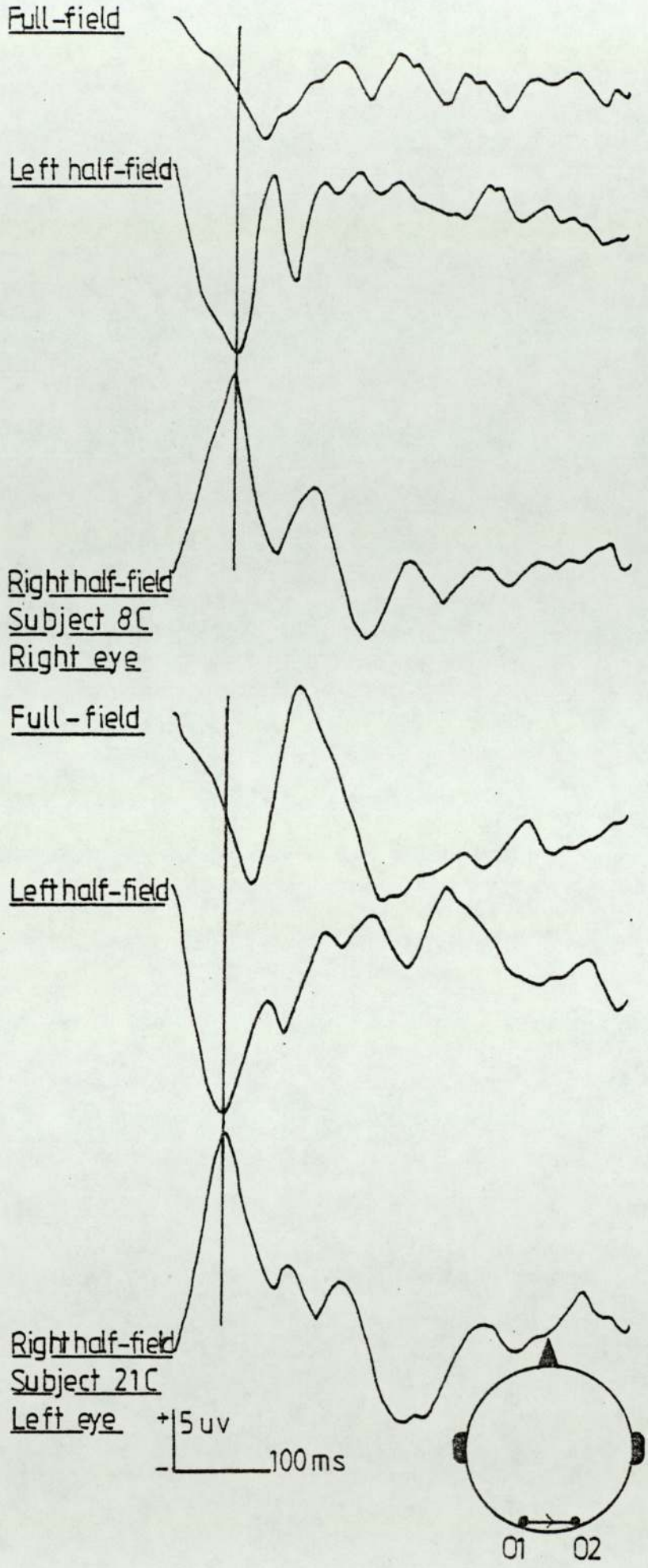
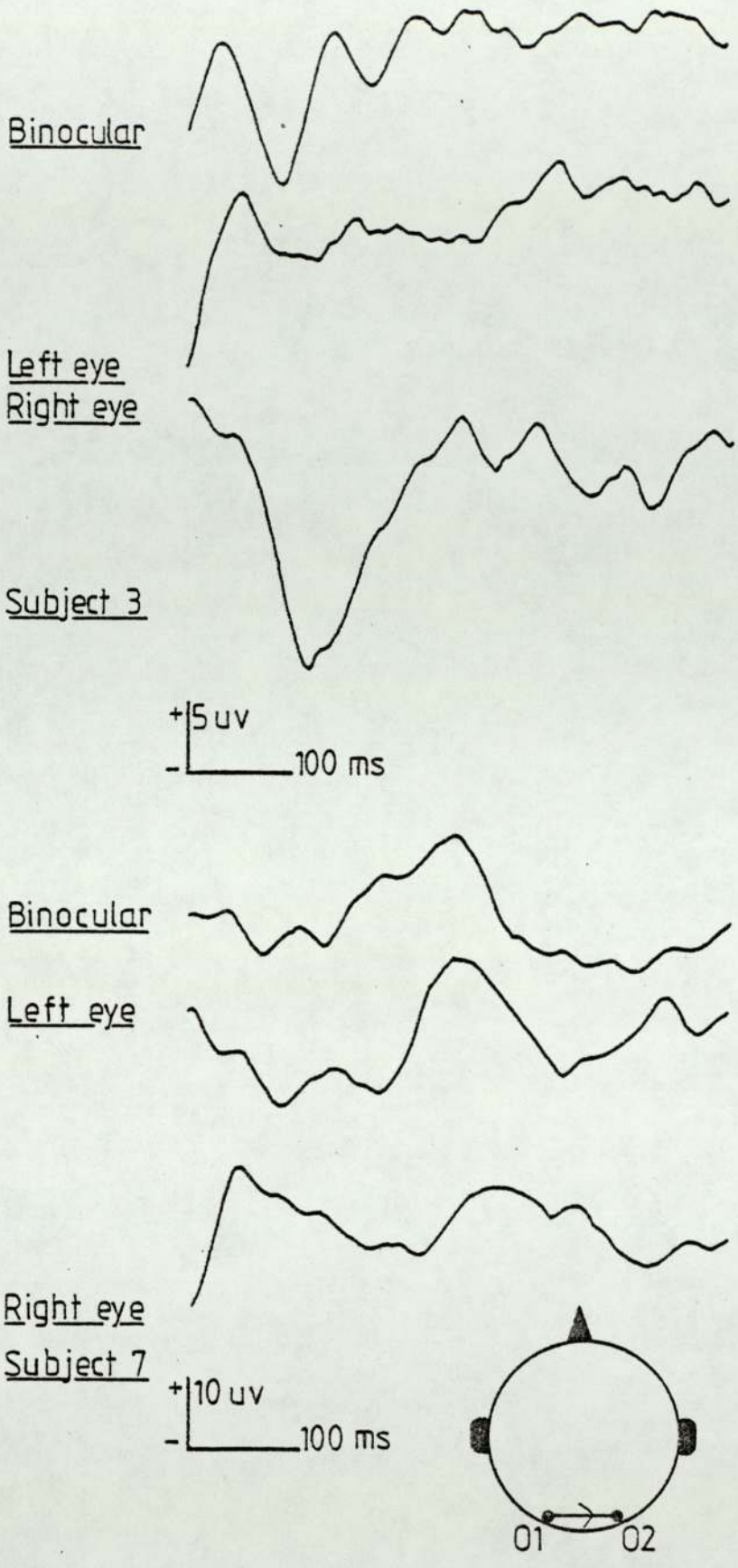

Full-field
Left half-field
Right half-field
Subject 8C
Right eye
Full-field
Left half-field
Right half-field
Subject 21C
Left eye
+
5 uv
-
100 ms
O1
O2

Figure 6.55

The Bipolar Occipital Pattern Appearance-Disappearance Responses of Albino Subjects 3 and 7

Unlike the responses illustrated in Figure 6.53, the monocular full-field responses of these two albinos do not show polarity reversal of either a contralateral or ipsilateral nature. (Check size 50', 50 sweeps).


Binocular
Left eye
Right eye
Subject 3
+
5 uv
-
100 ms
Binocular
Left eye
Right eye
Subject 7
+
10 uv
-
100 ms
O1
O2

Using this method one can estimate if the full-field response more nearly resembles that of the temporal half-field response rather than that on nasal half-field stimulation. In only four subjects could this effect be clearly seen (see Table 6.15) and in some subjects both temporal and hasal half-field responses were poorly defined compared to the full-field potential.

The left eye full and half-field responses of two of the four subjects in whom the effect was seen (subjects 8 and 7) are shown in Figure 6.56 and 6.57. In the remaining albinos the full-field responses were not dominated by those of the nasal retina (an example is shown in Figure 6.58 showing the responses of subject 9) although in no case was the opposite effect seen in which the full-field response more nearly resembled that of the nasal half-field. These half-field responses will be considered further in 6.5.

6.4.7 The pattern appearance-disappearance responses of albino subject 20

The full and half-field responses of this subject are illustrated in Figures 6.59 and 6.60 respectively. On full-field stimulation the responses from the two eyes differed somewhat. This difference is reflected primarily on the relative sizes of the two responses, that of the left eye having a much greater amplitude than that of the right eye. As would be predicted the binocular response

Table 6.15

Half-Field Pattern Appearance-Disappearance Responses of the Albino Subjects

In only four of the twelve subjects did the monocular full-field responses more closely resemble the temporal rather than the nasal half-field responses of the same eye. In the remaining 8 subjects this effect was not seen. (See text for further details).

Subject	Monocular full-field response dominated by temporal half-field response.
3	YES
5	NO
7	YES
8	YES
9	NO
11	NO
12	YES
14	NO
17	NO
18	NO
21	NO
22	NO

Figure 6.56

The Left Eye Full and Half-Field Pattern Appearance-Disappearance Responses of Albino Subject 8

The full, right and left field responses recorded from a transverse row of occipital electrodes are shown. It can be seen that the full-field response is dominated by that of the temporal (left) half-field. The response from the nasal (right) half-field has a quite different waveform with poorly defined components. (Check size 50', 50 sweeps).

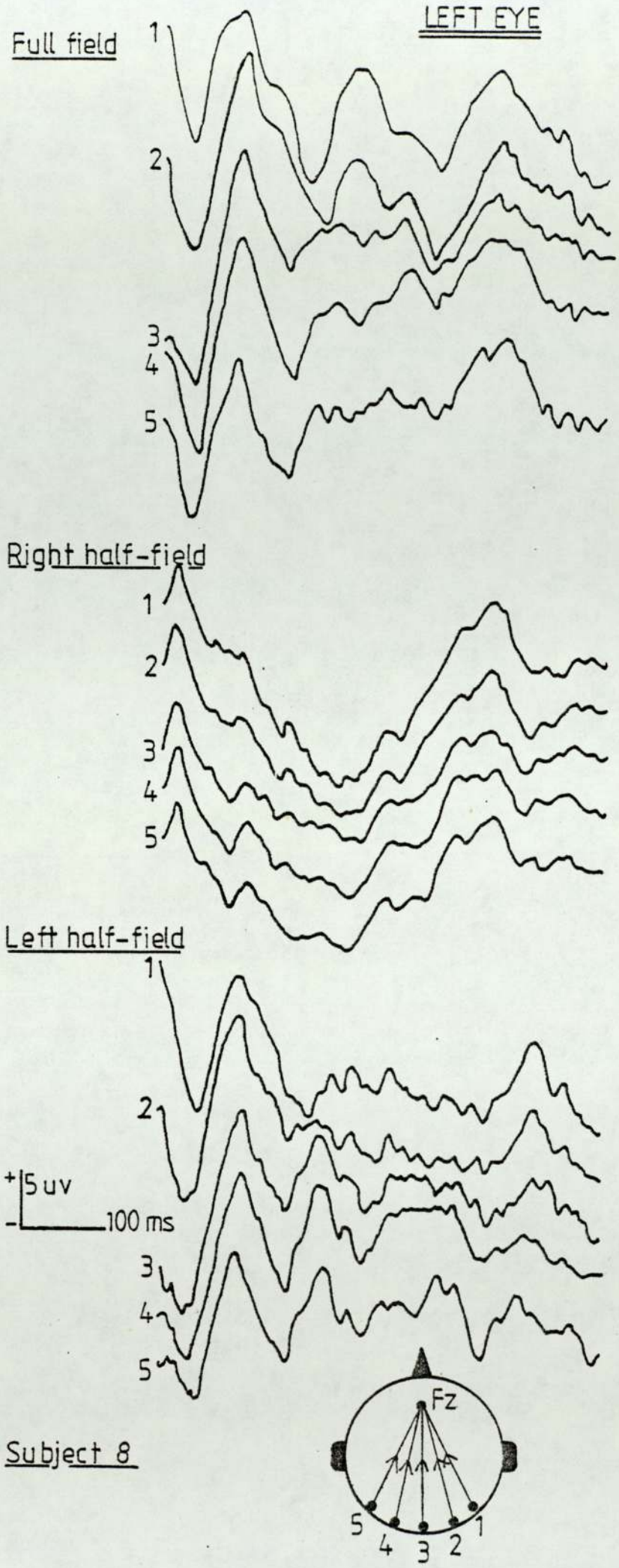

LEFT EYE
Full field
1
2
3
4
5
Right half-field
1
2
3
4
5
Left half-field
1
2
3
4
5
+
5 uv
-
100 ms
Fz
5
4
3
2
1
Subject 8

Figure 6.57

The Right Eye Full and Half-Field Pattern Appearance-Disappearance Responses of Albino Subject 7

The full, right and left field responses recorded from a transverse row of occipital electrodes are shown. As in the case shown in Figure 6.56, the full-field response of this subject is also dominated by that of the temporal (right) half-field while the nasal (left) half-field response is poorly formed. (Check size 50', 50 sweeps).

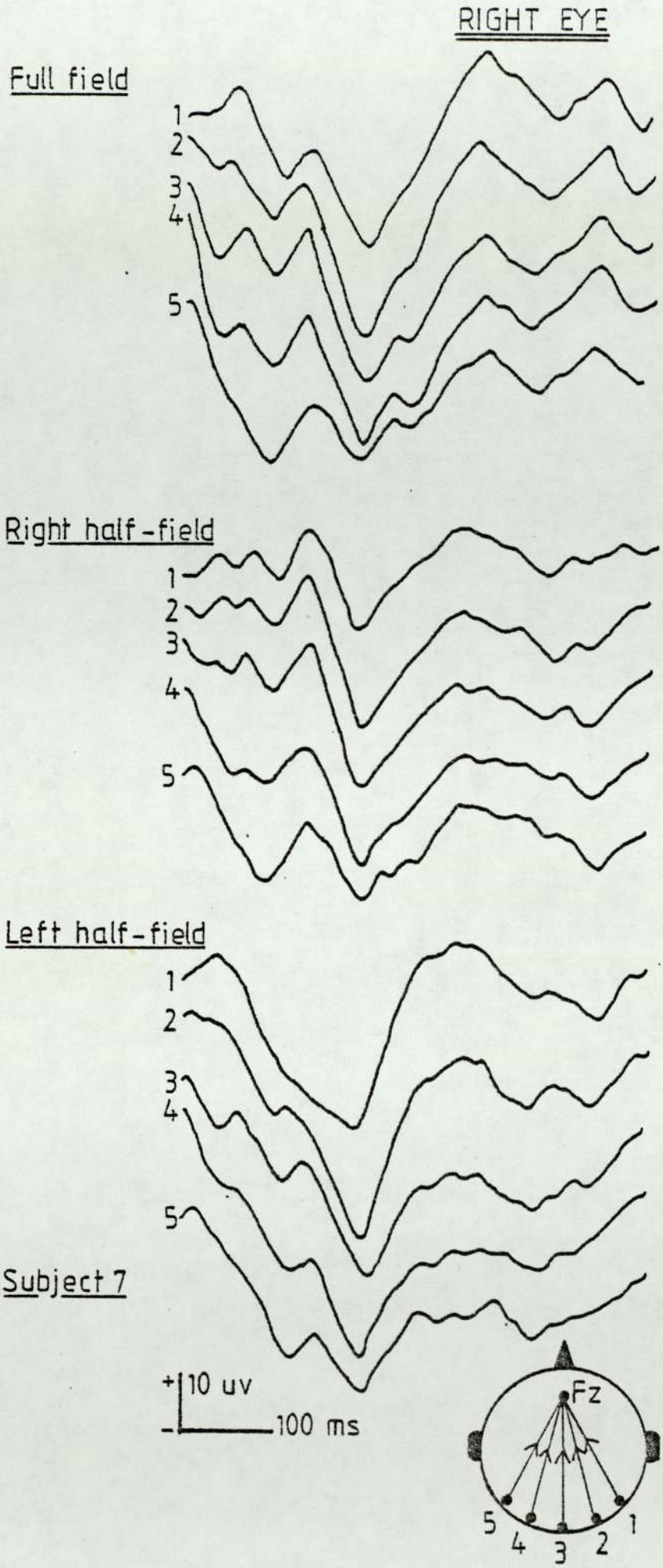

RIGHT EYE
Full field
1
2
3
4
5
Right half-field
1
2
3
4
5
Left half-field
1
2
3
4
5
Subject 7
+
10 uv
-
100 ms
Fz
5
4
3
2
1

Figure 6.58

The Left Eye Full and Half-Field Pattern Appearance-Disappearance Responses of Albino Subject 9

The full, right and left field responses recorded from a transverse row of occipital electrodes are shown. Unlike the responses illustrated in Figures 6.56 and 6.57, the full field potential recorded in this subject is not dominated by that of the temporal (left) half-field. In this albino the two half-fields are very similar in waveform both to each other and to the full field response. (Check size 50', 50 sweeps).

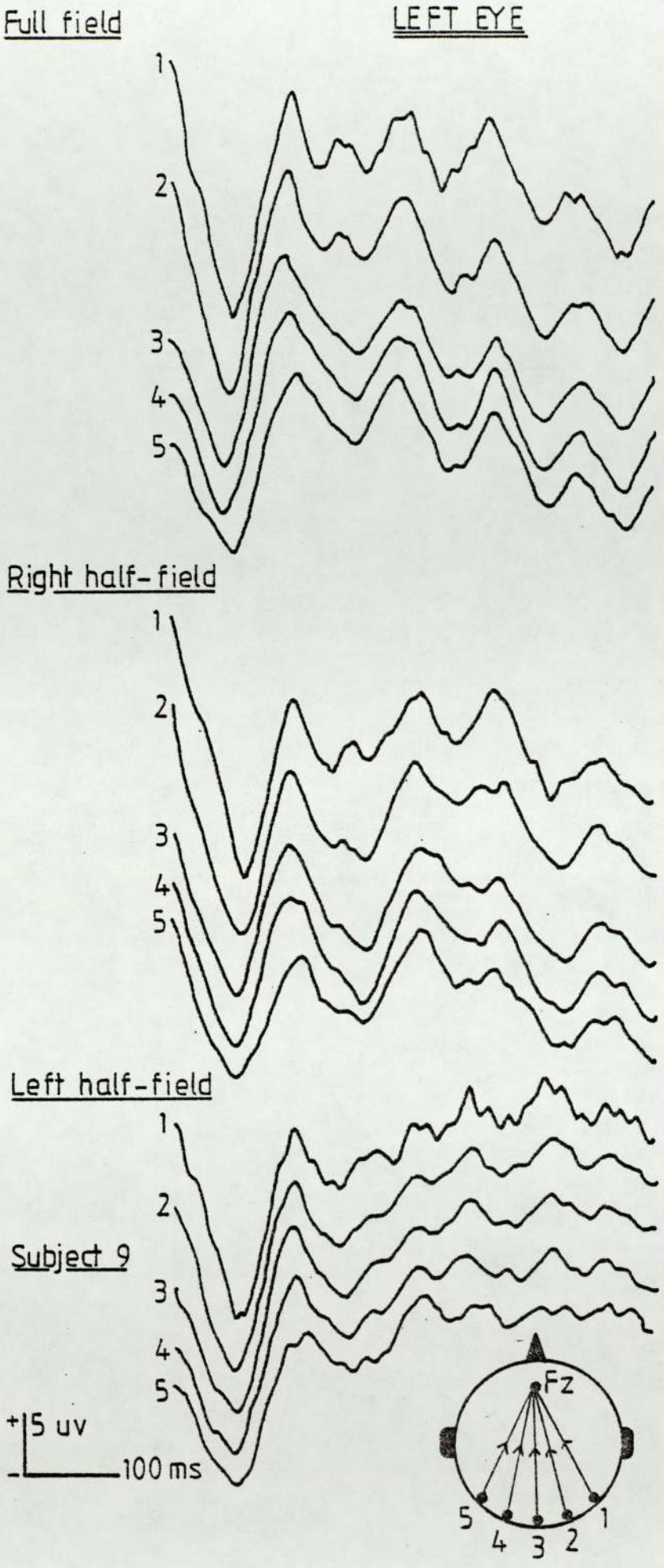

Full field
LEFT EYE
1
2
3
4
5
Right half-field
1
2
3
4
5
Left half-field
1
2
3
4
5
Subject 9
+
5 uv
-
100 ms
Fz
5
4
3
2
1

Figure 6.59

The Full-Field Pattern Appearance-Disappearance Responses of Albino Subject 20

The binocular and monocular responses recorded from a transverse row of occipital electrodes are shown. Clearly, that of the right eye (which showed a visual field defect) is of much reduced amplitude with poorly defined components. As would be expected, the binocular response is dominated by that of the left eye. See text for further details. (Check size 50', 50 sweeps).

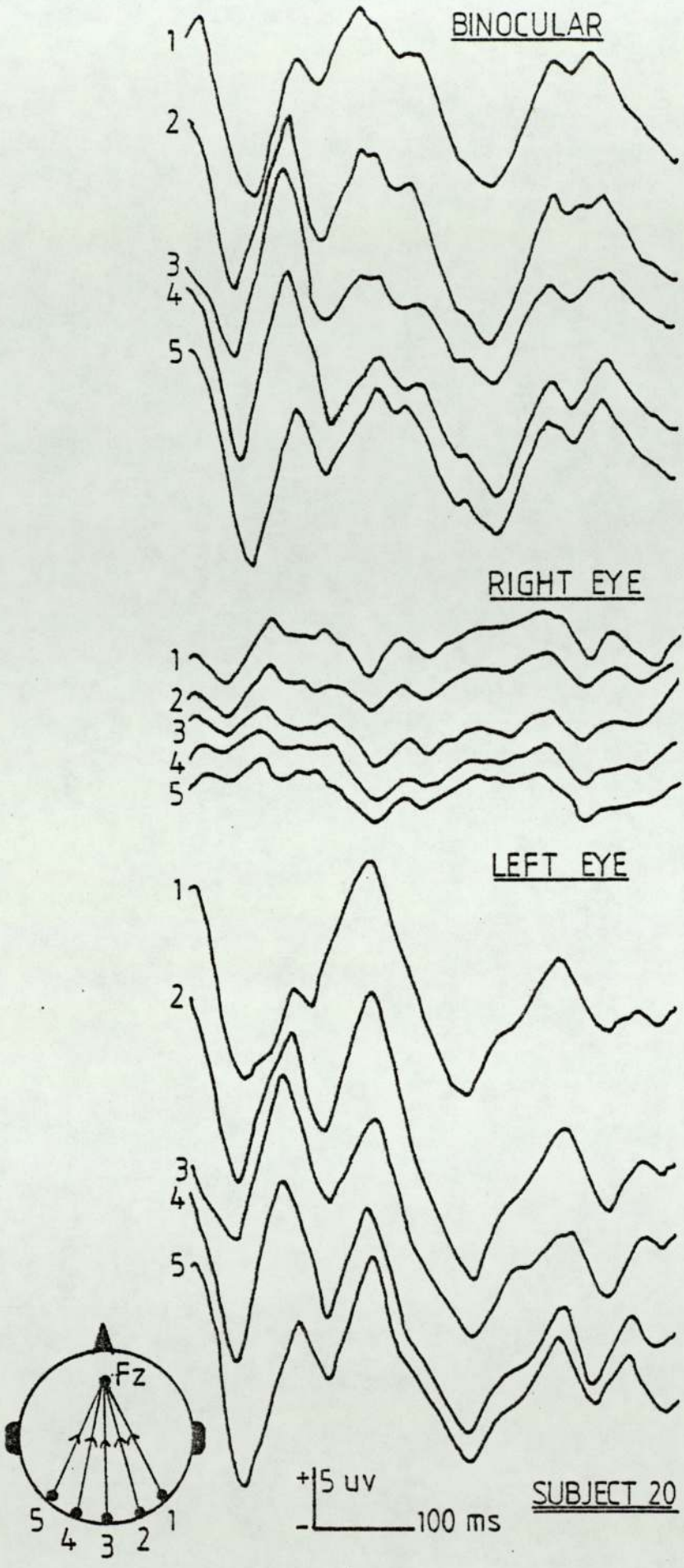
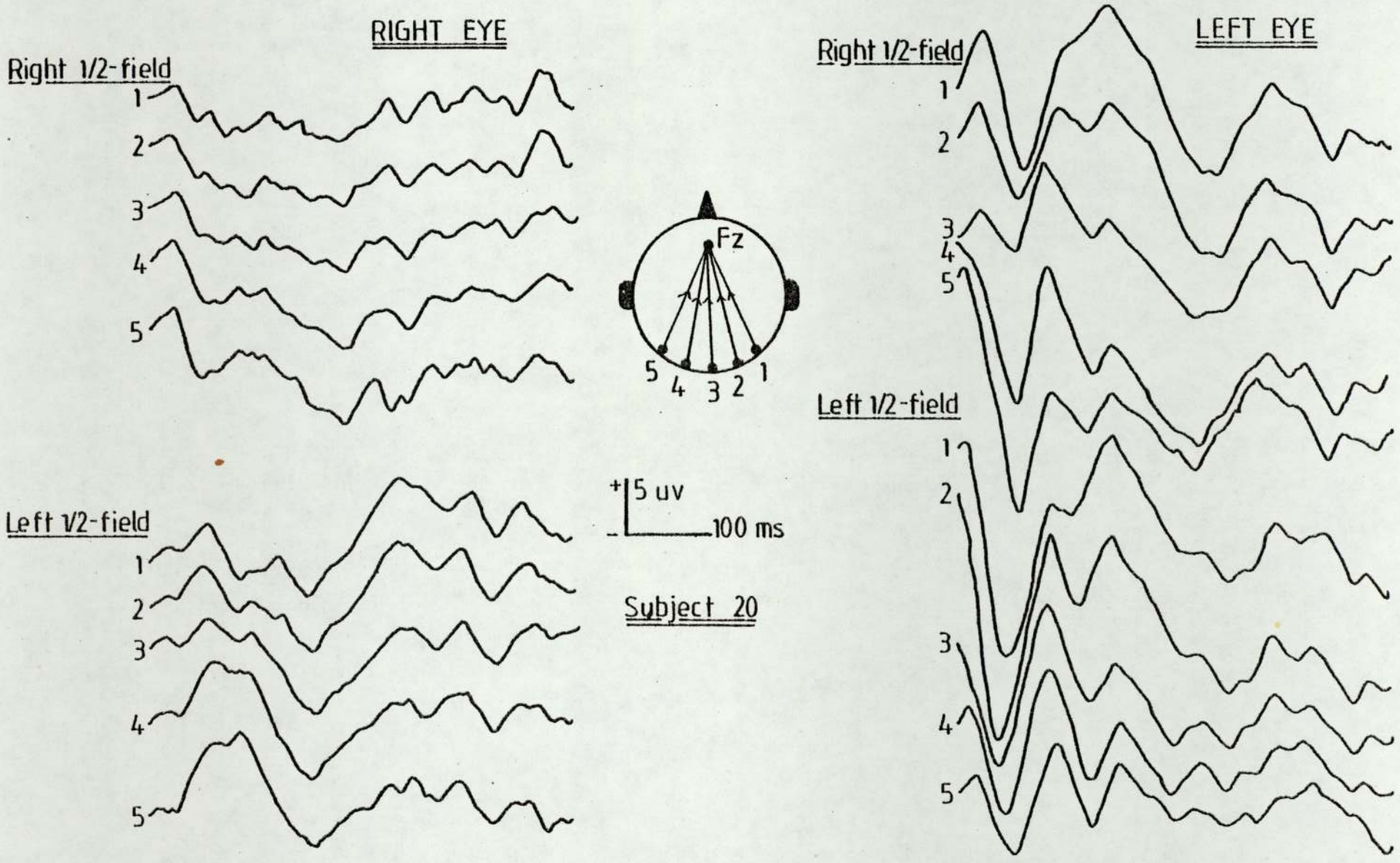

BINOCULAR
1
2
3
4
5
RIGHT EYE
1
2
3
4
5
LEFT EYE
1
2
3
4
5
Fz
5
4
3
2
1
+
5 uv
-
100 ms
SUBJECT 20

Figure 6.60

The Half-Field Pattern Appearance-Disappearance Responses of Albino Subject 20

The two half-field responses from each eye are shown. Again, as in Figure 6.59, the responses from the right eye are of a greatly reduced amplitude with poorly defined components. See text for further details. (Check size 50', 50 sweeps).


RIGHT EYE
LEFT EYE
Right 1/2-field
Left 1/2-field
Right 1/2-field
Left 1/2-field
1
2
3
4
5
Fz
5 4 3 2 1
+ 5 uv
- 100 ms
Subject 20

is dominated by that of the left eye. Clear components can be identified in the binocular and left eye responses with an initial positive wave occurring at around 95ms. However, the potential recorded on right eye stimulation is of such a low amplitude that components are not clearly seen although there is evidence of an early positive component at around 80ms.

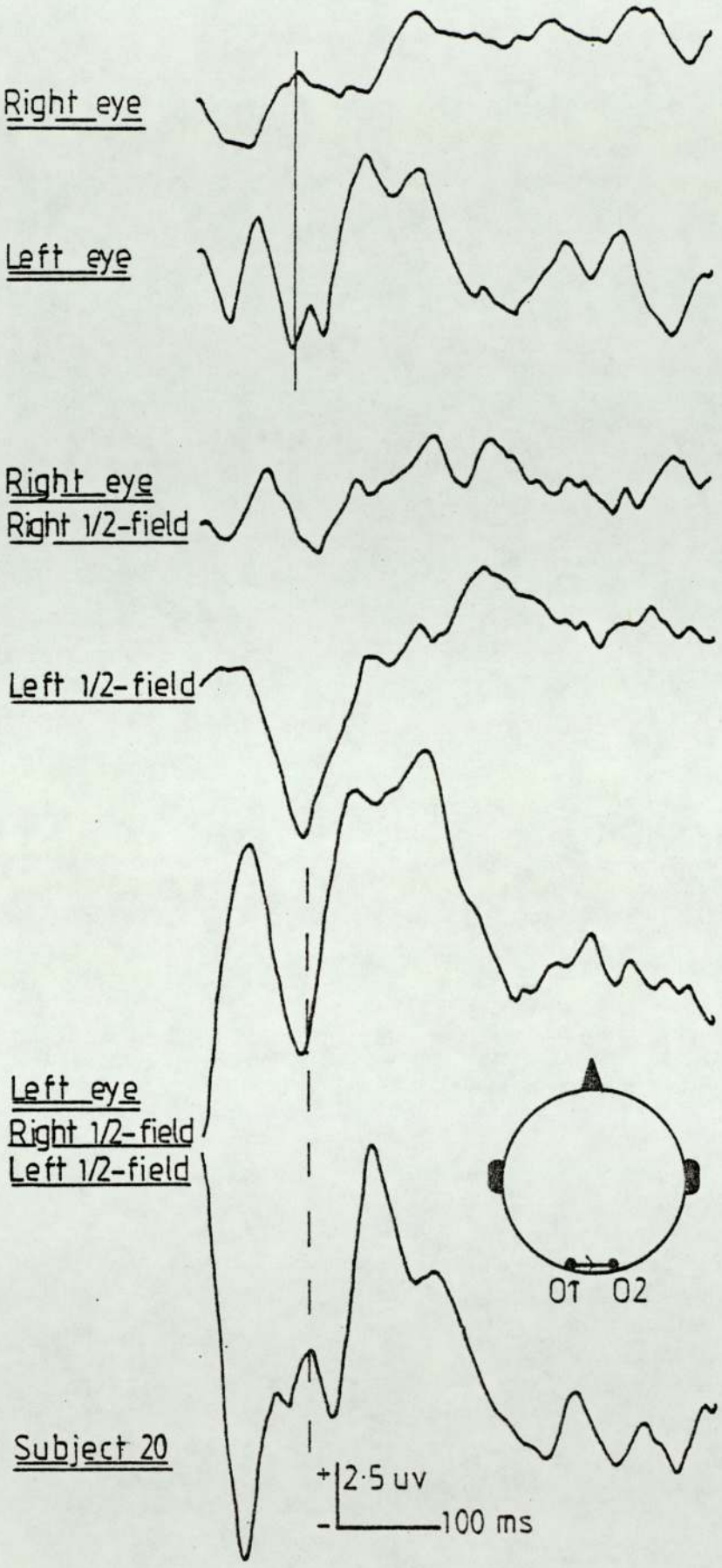
Similarly, on individual half-field stimulation the responses from the right eye are of much smaller amplitude than those from the left eye. In the right eye responses components prove difficult to identify but on comparison the potential on left half-field stimulation has a better waveform than that on right half-field stimulation. This is somewhat contrary to what might be expected as the visual field of this eye showed a left sided defect. The potential recorded from the left eye was of a much larger amplitude with clearly formed components similar to that found on binocular and left eye full-field stimulation. In the half-field responses an initial positive component is seen at around 100ms. On super-imposition of the full and half-field responses from this eye, the full-field potential did not appear to be clearly dominated by that of either the temporal or nasal half-field.

Bipolar recordings (O1-O2) are shown in Figure 6.61. There is some evidence of polarity reversal representing contralateral lateralisation on full-field stimulation of each eye (see solid line) although, again, the potential

Figure 6.61

The Bipolar Pattern Appearance-Disappearance Responses of Albino Subject 20

The monocular full and half-field responses recorded from a bipolar (O1 - O2) montage are shown. The full field responses show some evidence of the predicted contralateral lateralisation (solid line). Half-field stimulation of the left eye also shows the same polarity reversal seen in control subjects (dotted line); this effect is not seen in half-field recordings of the right eye. See text for further details (Check size 50', 50 sweeps).


Right eye
Left eye
Right eye
Right 1/2-field
Left 1/2-field
Left eye
Right 1/2-field
Left 1/2-field
O1 O2
Subject 20
+
2·5 uv
-
100 ms

recorded on right eye stimulation is poorly formed. On half-field stimulation the potentials recorded from the left eye showed polarity reversal (see dotted line) similar to that found on half-field stimulation in control subjects. This effect is not seen on individual half-field stimulation of the right eye.

6.4.8 Summary

Table 6.16 shows the calculated Cx values for each component measure of the full-field pattern appearance-disappearance VECPs recorded from the albinos examined. The results regarding the polarity reversal of the O1-O2 bipolar response are also given in the final column of the table. This table, as such, therefore summarises the results shown in Tables 6.10, 6.11, 6.12, 6.13 and 6.14.

Of the first four columns, clearly no one shows a greater number of positive Cx values than any other. However, in 8 of the 12 subjects contralateral lateralisation on monocular stimulation was evident from the bipolar, O1-O2, recordings.

The results are further summarised in Figure 6.62 and Table 6.17 which summarise in graphical and tabular form the mean Cx values $\pm$ 1 S.E. for each component measure in both the albino and control groups. No measure clearly differentiates the albino group from the control group

Table 6.16

Summary Table of the Albino Full-Field Pattern Appearance-Disappearance VECP Results

The calculated Cx values for the CI latency and amplitude measures at O1, O2 and O3,O4 are shown for each albino subject. The bipolar O1-O2 results shown in Table 6.14 are also given. (See text for further details).

Subject	C_x Values				Polarity Reversal of Bipolar O_1-O_2 Response
	C1 Latency		C1 Amplitude		
	O1 and O2	O3 and O4	O1 and O2	O3 and O4	
3	-3.5	-	-1.05	-	No
5	+4.5	+11.0	0	+0.15	No
7	0	-	+1.55	-	No
8	+9.5	-5.0	-2.45	-7.30	Yes
9	+2.0	+11.0	-0.60	-0.35	Yes
11	+4.0	+7.5	+1.60	+2.65	No
12	-1.0	+13.5	-4.10	-3.65	Yes
14	+1.5	-	-1.40	-	Yes
17	-6.0	-0.5	-0.65	-0.25	Yes
18	-2.0	-1.5	+2.30	+2.80	Yes
21	+2.0	+1.0	-0.85	-1.25	Yes
22	-0.5	-3.5	+1.50	+4.25	Yes

Key: - = Values not measurable (see text for further details).

No = No polarity reversal of the bipolar O1-O2 response when recordings from the two eyes compared.

Yes = Polarity reversal of the bipolar O1-O2 response when recordings from the two eyes compared. In all cases the polarity reversal indicated contralateral lateralisation. (See text for further details).

Figure 6.62

Summary Diagram Showing the mean Cx Values ± 1 S.E. for each Component Measure of the Full Field Patterns Appearance-Disappearance Responses Recorded in Both the Albinos and Their Controls

See text for further details.

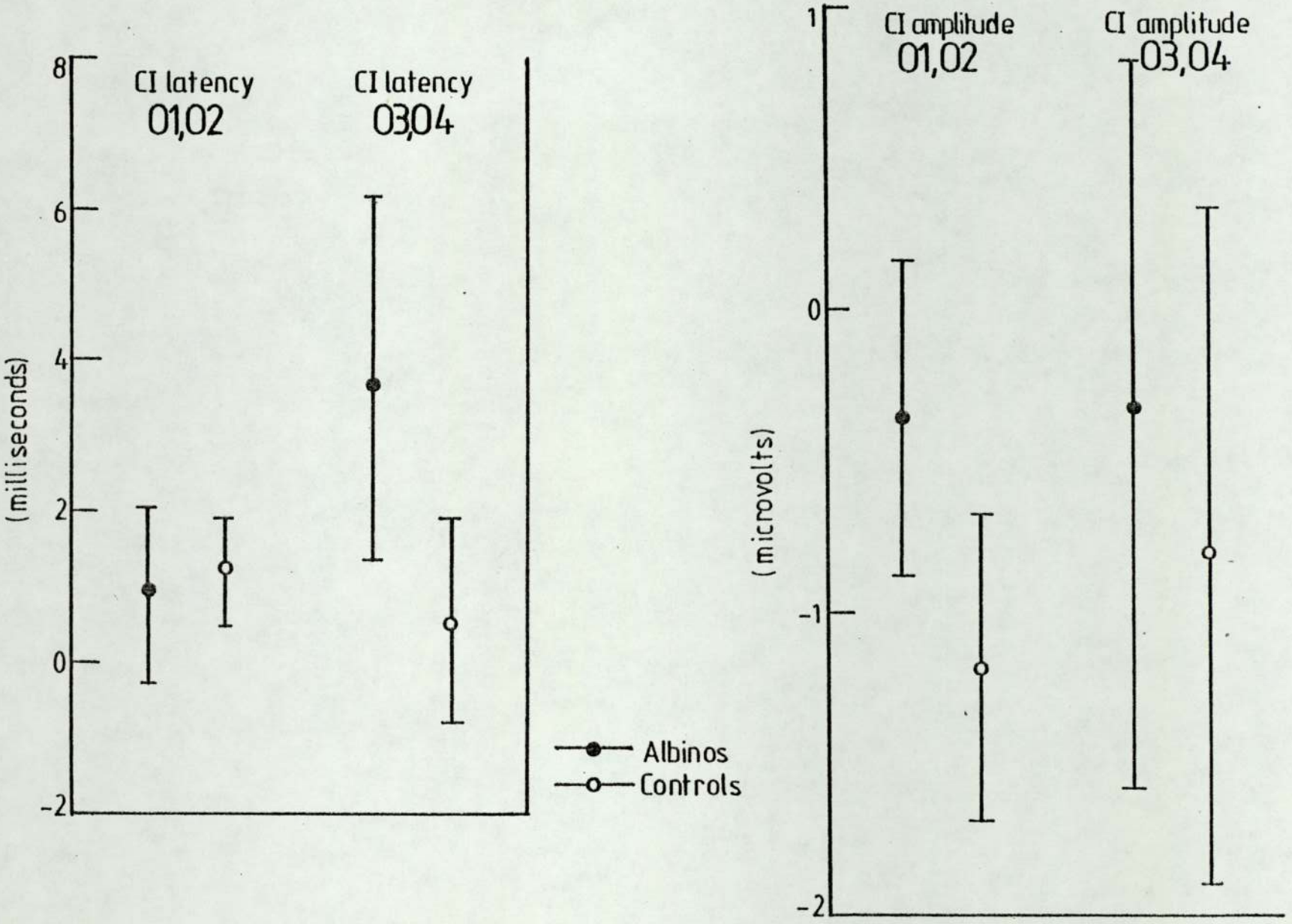

CI latency
01,02
CI latency
03,04
8
6
4
2
0
-2
(milliseconds)
Albinos
Controls
CI amplitude
01,02
CI amplitude
03,04
1
0
-1
-2
(microvolts)

Table 6.17

Summary Table of the Pattern Appearance-Disappearance Mean CI Cx Values ± 1 S.E.

For each component measure the mean Cx values ± 1 S.E. are given for the albino group and their controls. This forms a tabulation of the results illustrated graphically in Figure 6.62. (See text for further details).

Component Measure	Mean Cx Value ± 1 S.E.	
	Albinos	Controls
CI latency (01 and 02)	+0.88 ± 1.17	+1.25 ± 0.74
CI latency (03 and 04)	+3.70 ± 2.35	+0.56 ± 1.42
CI amplitude (01 and 02)	-0.35 ± 0.54	-1.19 ± 0.51
CI amplitude (03 and 04)	-0.33 ± 1.18	-0.82 ± 1.14

as was found when considering the latency of the P2 component of the flash VECP (see Figure 6.31 and Table 6.9). This is reflected in the ANOVA results which showed that:

1) Measurement of the latency and amplitude of the CI component at electrodes O1, O2, O3 and O4 does not show any significant monocular contralateral lateralisation in either the albino or control groups.

2) However, within the control group ANOVA did show that on binocular stimulation the latency of CI at electrodes O3 and O4, but not O1 and O2, was significantly shorter ($p < 0.05$) than on monocular stimulation. Similarly, the amplitude of CI and O1 and O2, but not O3 and O4, was significantly greater ($p < 0.025$) on binocular compared to monocular stimulation. Neither of these findings was evident among the albino population.

With reference to Table 6.16 it can be seen that examination of the O1-O2 bipolar response is more clearly indicative of contralateral lateralisation on monocular stimulation than any single measure of the reference recorded responses; this analysis does not, however, produce a positive result in every case.

Half-field recordings made in the albinos did not really contribute much more information than that obtained on full-field stimulation. In some cases the responses were not clearly formed and that the full-field response is

dominated by that of the temporal half-field was not a universal finding.

6.5 Group data

In order to ascertain whether the results obtained when considering the individual component measures of the VECPs could be illustrated in the form of group data from the albino and control subjects, it was considered advantageous to derive group averages from the two populations. This method of displaying the results may also reveal features not evident in the individual responses.

This proved a simple task. Because the responses recorded from each subject had been stored on floppy discs, individual responses could be recalled and added together using the Nicolet Pathfinder II averager. The results found by this method will now be described for the flash and pattern appearance-disappearance VECPs in turn.

6.5.1 The flash VECP

In turn, the individual binocular, right and left eye responses from each albino and control were added together in order to produce a set of group average responses for each population. The responses of albino 20 displaying the gross visual field defect were excluded from this process.

The resulting group averages for the control group are

illustrated in Figure 6.63. Each response has a smooth waveform and is characterised by a P1, N2, P2 configuration clearly seen over each hemisphere. In each case the asymmetries and asynchronies between the two hemispheres is very small reflecting the insignificant results regarding these characteristics during statistical analysis on the raw data. However, as reflected during statistical analysis the latency of P2 was shorter (by 4-6ms) and the amplitude of N2P2 greater (by 1.1-3.6uV) over each hemisphere on binocular compared to monocular stimulation. The P1 latency and the P1N2 amplitude measures do not show such an effect, although the N2 latency is shorter (by 3-6ms) on binocular stimulation.

The group average responses obtained from the albino data showed somewhat different characteristics. The responses are illustrated in Figure 6.64 where it can be seen that they do not show the smooth waveform found in the controls and that overall the responses are of a lower amplitude. The binocular response shows a clear P2 component of almost identical latency over each hemisphere although of shorter latency than found in the control group. A P1 component is, however, less clearly defined and of a very small amplitude. On monocular stimulation the latency of the P2 component increases but by different amounts dependent upon the eye stimulated.

As shown in Figure 6.64 on stimulation of the right eye a clear P2 component is found over the left hemisphere

Figure 6.63

The Group Average Responses of the Flash VECPs Recorded in the Control Subjects

The binocular and monocular group average responses are shown. The latencies of the P1, N2 and P2 components are labelled with the P1N2 and N2P2 amplitudes. The asymmetries and asynchronies between the two hemispheres are of small magnitudes in each case. (See text for further details).

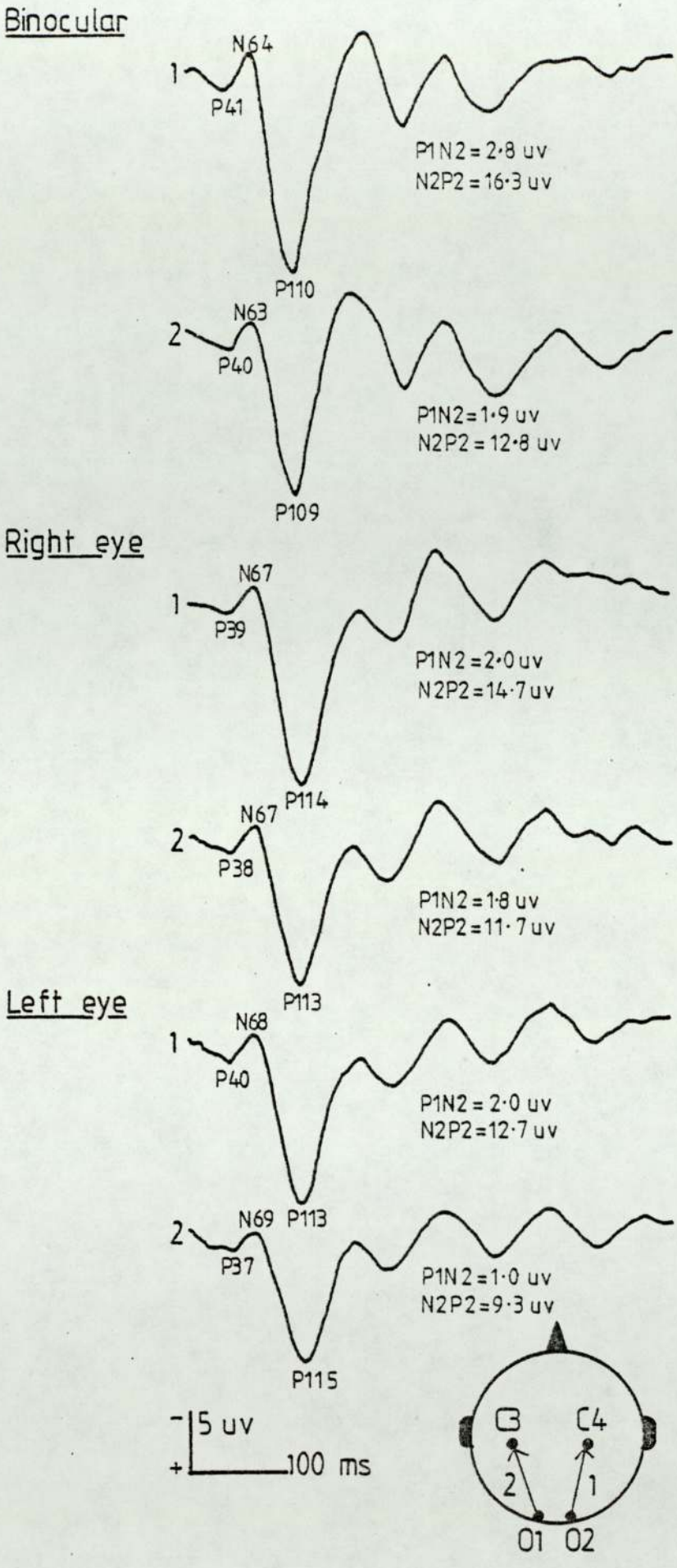
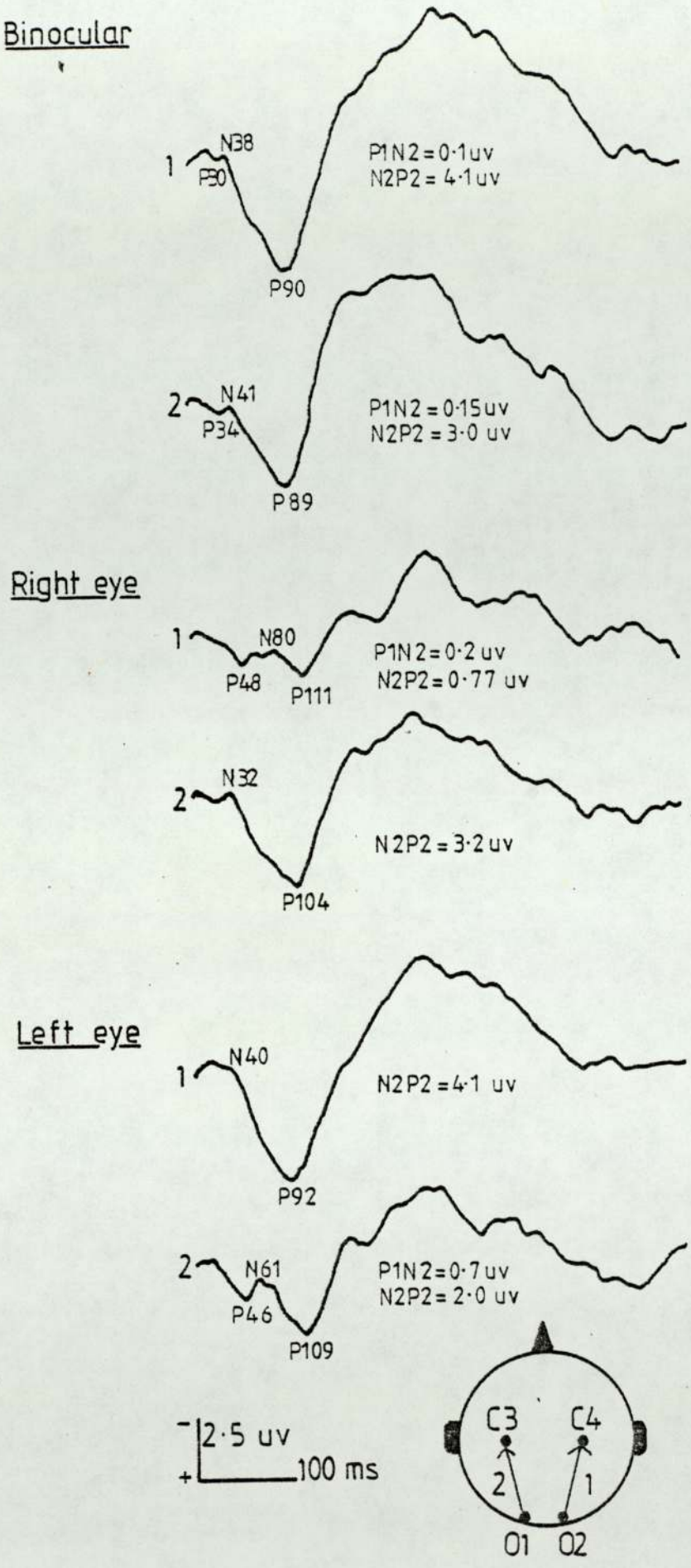

Binocular
1
N64
P41
P110
P1N2 = 2·8 uv
N2P2 = 16·3 uv
2
N63
P40
P109
P1N2 = 1·9 uv
N2P2 = 12·8 uv
Right eye
1
N67
P39
P114
P1N2 = 2·0 uv
N2P2 = 14·7 uv
2
N67
P38
P113
P1N2 = 1·8 uv
N2P2 = 11·7 uv
Left eye
1
N68
P40
P113
P1N2 = 2·0 uv
N2P2 = 12·7 uv
2
N69
P37
P115
P1N2 = 1·0 uv
N2P2 = 9·3 uv
5 uv
100 ms
C3
C4
2
1
O1
O2

Figure 6.64

The Group Average Responses of the Flash VECPs Recorded in the Albino Subjects

The binocular and monocular group average responses are shown. The binocular response is dominated by a bilateral P2 component. The latency of this component is shorter and the N2P2 amplitude greater over the contralateral compared to the ipsilateral hemisphere on monocular stimulation. (See text for further details).


Binocular
1
N38
P30
P90
P1N2 = 0·1uv
N2P2 = 4·1uv
2
N41
P34
P89
P1N2 = 0·15uv
N2P2 = 3·0 uv
Right eye
1
N80
P48
P111
P1N2 = 0·2 uv
N2P2 = 0·77 uv
2
N32
P104
N2P2 = 3·2 uv
Left eye
1
N40
P92
N2P2 = 4·1 uv
2
N61
P46
P109
P1N2 = 0·7 uv
N2P2 = 2·0 uv
2·5 uv
100 ms
C3
C4
2
1
O1
O2

although there is little evidence of a P1 component. In contrast the response over the right hemisphere is characterised by a longer latency and smaller amplitude P2 component preceded by an even smaller P1 component.

On stimulation of the left eye the hemispheric lateralisation is reversed. The poor response over the right hemisphere is replaced by a more prominent P2 component of shorter latency and greater amplitude than on right eye stimulation. In turn, the clear P2 component over the left hemisphere on right eye stimulation is replaced by a less prominent P2 of smaller amplitude and longer latency. However, as on right eye stimulation, the P2 component over this ipsilateral hemisphere is preceded by a P1 component albeit of very small amplitude.

Thus the contralateral hemispheric lateralisation of the VECP on monocular stimulation expected in the albinos is clearly reflected in the group data responses. Both the P2 latency and N2P2 amplitude measures clearly show this effect; within the control group such results are not visible. Surprisingly, within the albino group, however, the P1 component appears to lateralise over the opposite, ipsilateral, hemisphere on monocular stimulation. This result must be considered, however, in the light of the fact that the presumed P1 component is of very small amplitude; the P1N2 component being of only 0.2uV and 0.7uV on stimulation of the right and left eyes respectively.

6.5.2 The pattern appearance-disappearance VECP

As with the flash VECP, the individual responses from the albino and control subjects were added together, again excluding albino subject 20. This produced not only a set of binocular and monocular full-field responses but also a set of individual half-field group averages for the two populations.

The group average responses of the control subjects are illustrated in Figures 6.65, 6.66 and 6.67. The binocular and monocular full-field responses prove very similar in waveform (Figure 6.65). They are characterised by an early negative component at 70-90ms followed by a sharp positive at 120-130ms. This configuration is found at all five electrode sites and is fairly symmetrically placed around the midline.

The monocular half-field responses show a similar although less symmetrical configuration (Figure 6.66). The early negative wave appears to have a shorter latency over the hemisphere contralateral to the half-field stimulation while the later positive component is more clearly formed over the ipsilateral hemisphere. The right and left eye right half-fields have a very similar waveform as do the two left half-fields.

The hemispheric lateralisation of the half-field responses is more clearly seen in the bipolar, O1-O2, recordings (Figure 6.67). As would be expected, the bipolar response

FIGURE 6.65

The Group Average Responses of the Full-Field Pattern Appearance-Disappearance VECPs Recorded in the Control Subjects

The binocular, right and left eye responses are shown. A clear response characterised by a sharp positive wave preceded by an earlier negative is present at all electrode sites and fairly symmetrically placed about the midline. (See text for further details)

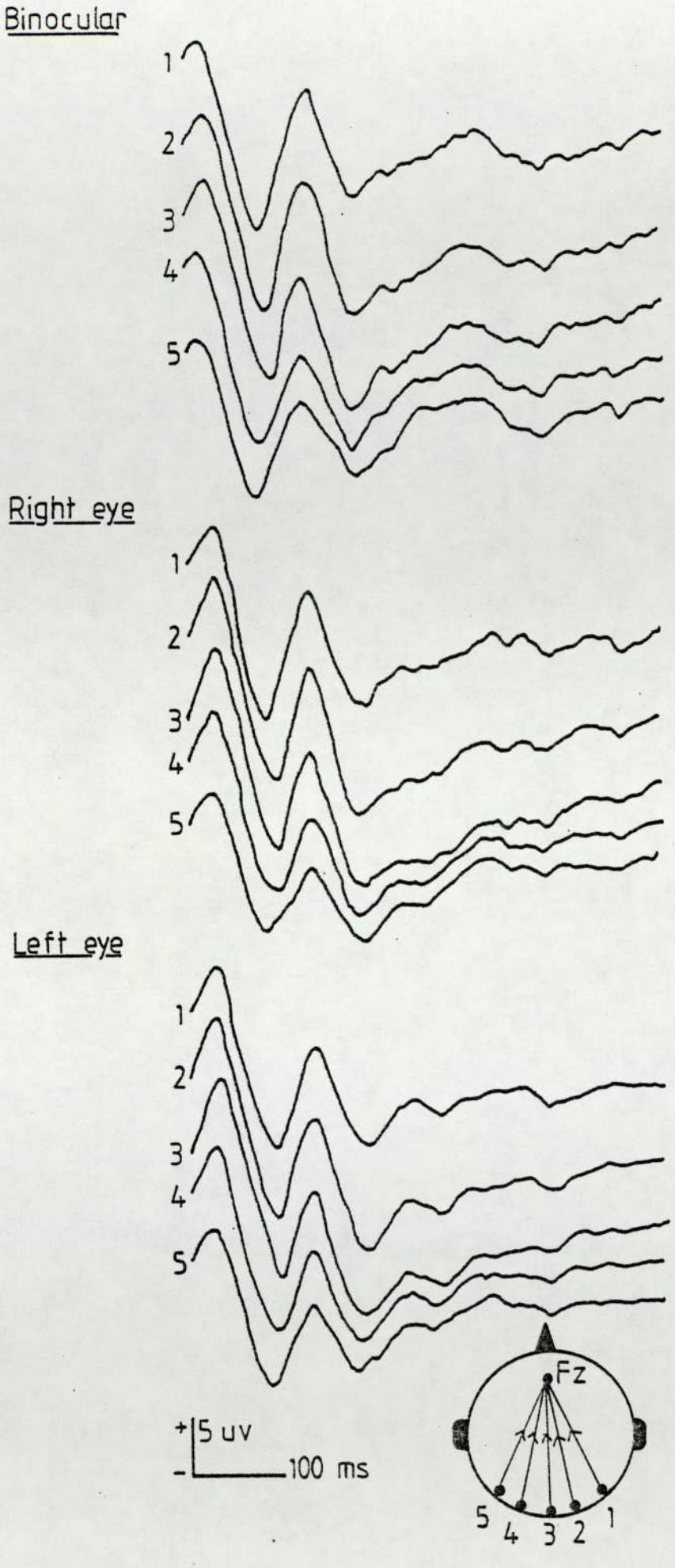

Binocular
1
2
3
4
5
Right eye
1
2
3
4
5
Left eye
1
2
3
4
5
+
5 uv
-
100 ms
Fz
5
4
3
2
1

Figure 6.66

The Group Average Responses of the Half-Field Pattern Appearance-Disappearance VECPs Recorded in the Control Subjects

The responses from individual half-field stimulation of each eye are shown. The latency of the early negative component tends to be shorter over the contralateral hemisphere while the positive component is more clearly formed over the ipsilateral hemisphere. (See text for further details).

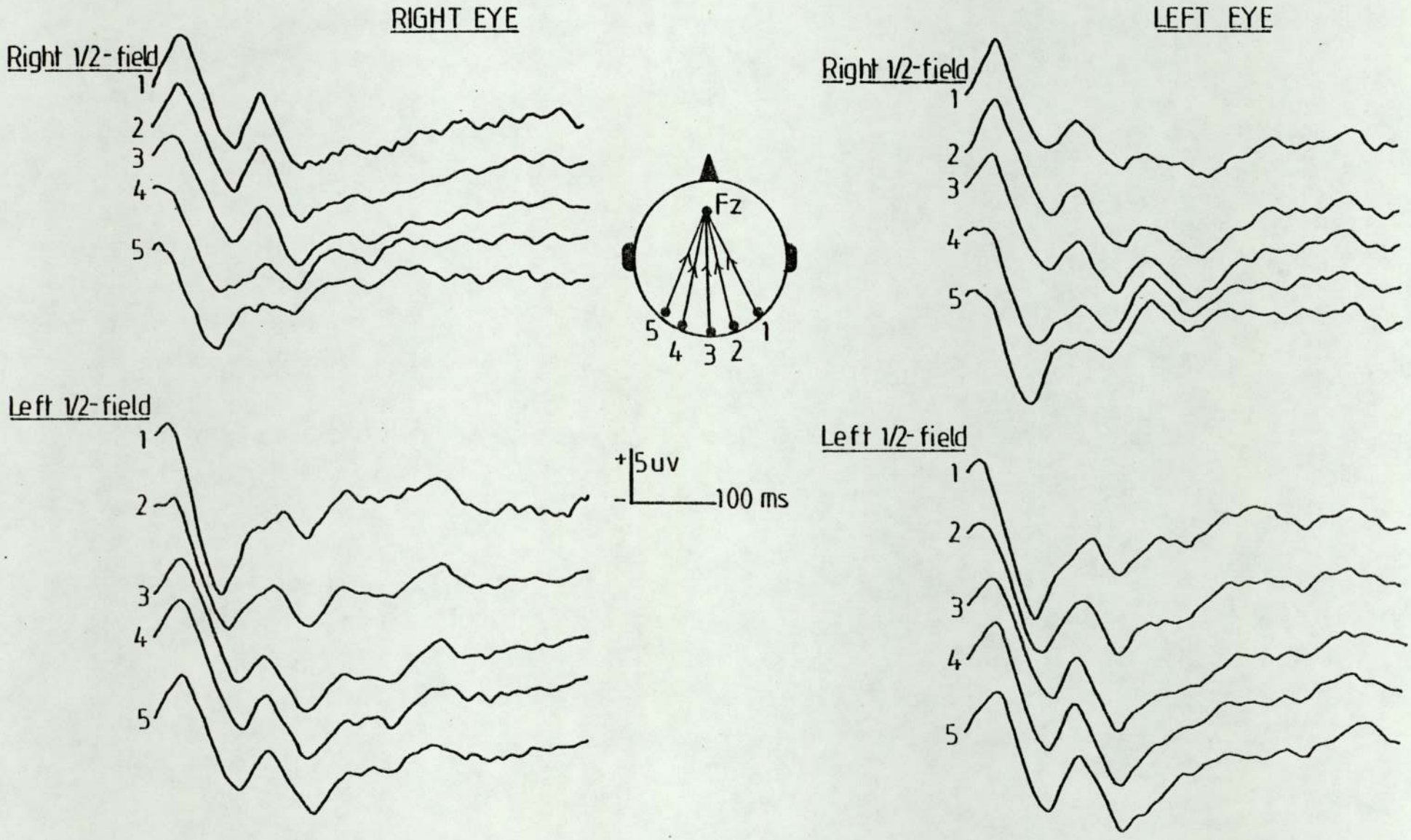
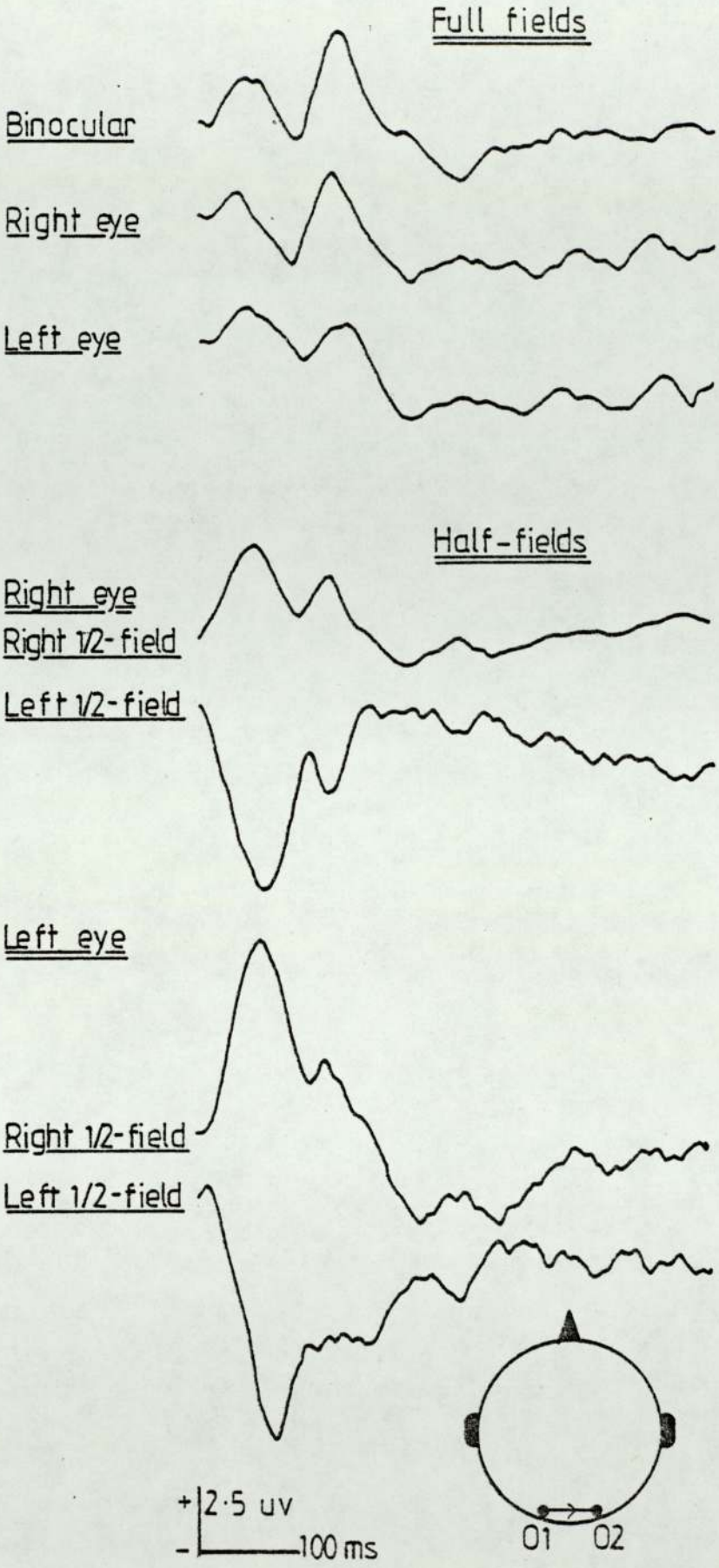

RIGHT EYE
LEFT EYE
Right 1/2-field
Left 1/2-field
Right 1/2-field
Left 1/2-field
1
2
3
4
5
Fz
5 4 3 2 1
+ 5uv
- 100 ms

Figure 6.67

The Group Average Pattern Appearance-Disappearance Responses from Bipolar Recordings in the Control Subjects

As would be expected, the responses on binocular and monocular full field stimulation are almost identical in waveform while on half-field stimulation phase reversal occurs. (See text for futher details).


Full fields
Binocular
Right eye
Left eye
Half-fields
Right eye
Right 1/2-field
Left 1/2-field
Left eye
Right 1/2-field
Left 1/2-field
+
-
2·5 uv
100 ms
O1
O2

recorded on full-field stimulation of the two eyes together and alone are of a very similar waveform. In the half-field recordings a phase reversal of the responses recorded from the two half-fields occurs on right and left eye stimulation.

The group average responses from the albino subjects are shown in Figures 6.68, 6.69 and 6.70. These responses are not, on the whole, as smooth or clearly defined as those of the control subjects but general features can be seen. The full-field responses (Figure 6.68) are dominated by a positive wave (CI) sometimes, but not always, preceded by an earlier negative component. The responses recorded from each of the five electrodes are not as similar as those found in the control group and illustrated in Figure 6.65 and at the two outer electrodes, O3 and O4, a clear positive component is not consistently found. Generally, the latency of this CI component is somewhat shorter on monocular stimulation (78-100ms) compared to binocular stimulation (145-150ms). At electrodes O1 and O2 a clear CI is found although on monocular stimulation there is no obvious contralateral lateralisation of this component by either latency or amplitude. However, the initial deflection in the recordings is much larger over the left hemisphere on right eye stimulation and over the right hemisphere on left eye stimulation.

The half-field responses have, generally, an even poorer configuration (Figure 6.69); the identification of individual components is very difficult. However, by comparing

FIGURE 6.68

The group average responses of full-field pattern appearance-disappearance VECPs recorded in the albino subjects

The responses are somewhat dominated by an early positive (CI) component which is, however, poorly formed at the pair of outer electrodes (O3 and O4). By visual inspection neither the latency or amplitude of this CI component is seen to lateralise contra-laterally on monocular stimulation.

(see text for further details)

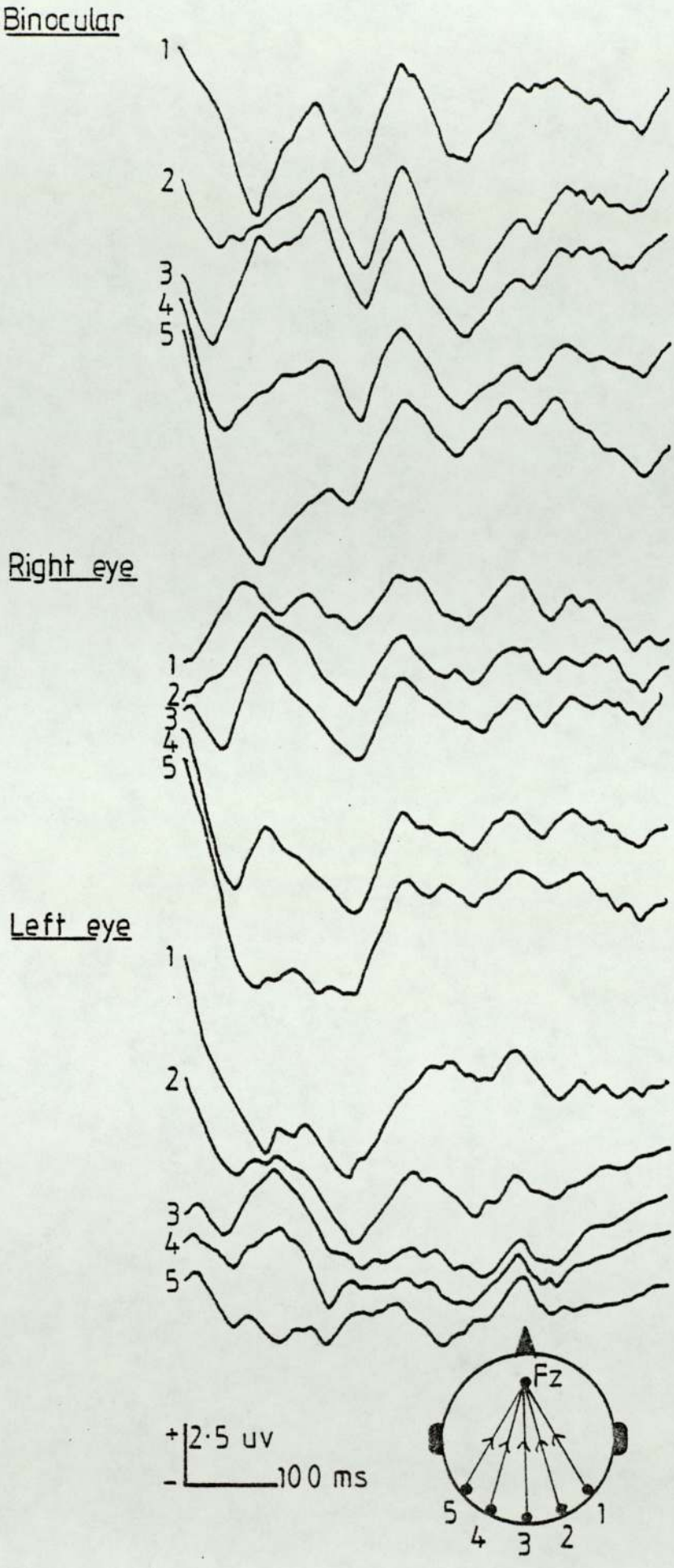

Binocular
1
2
3
4
5
Right eye
1
2
3
4
5
Left eye
1
2
3
4
5
+
2·5 uv
-
100 ms
Fz
5
4
3
2
1

Figure 6.69

The Group Average Responses of the Half-Field Pattern Appearance-Disappearance VECPs Recorded in the Albino Subjects

At all of the electrode sites the response is not as clearly formed as found in the controls. In particular the nasal field response from the two eyes (right eye, left half-field; left eye, right half-field) have a poor configuration. In general the monocular full field responses (Figure 6.68) more closely resemble those of the temporal field recording from that eye. (See text for further details).

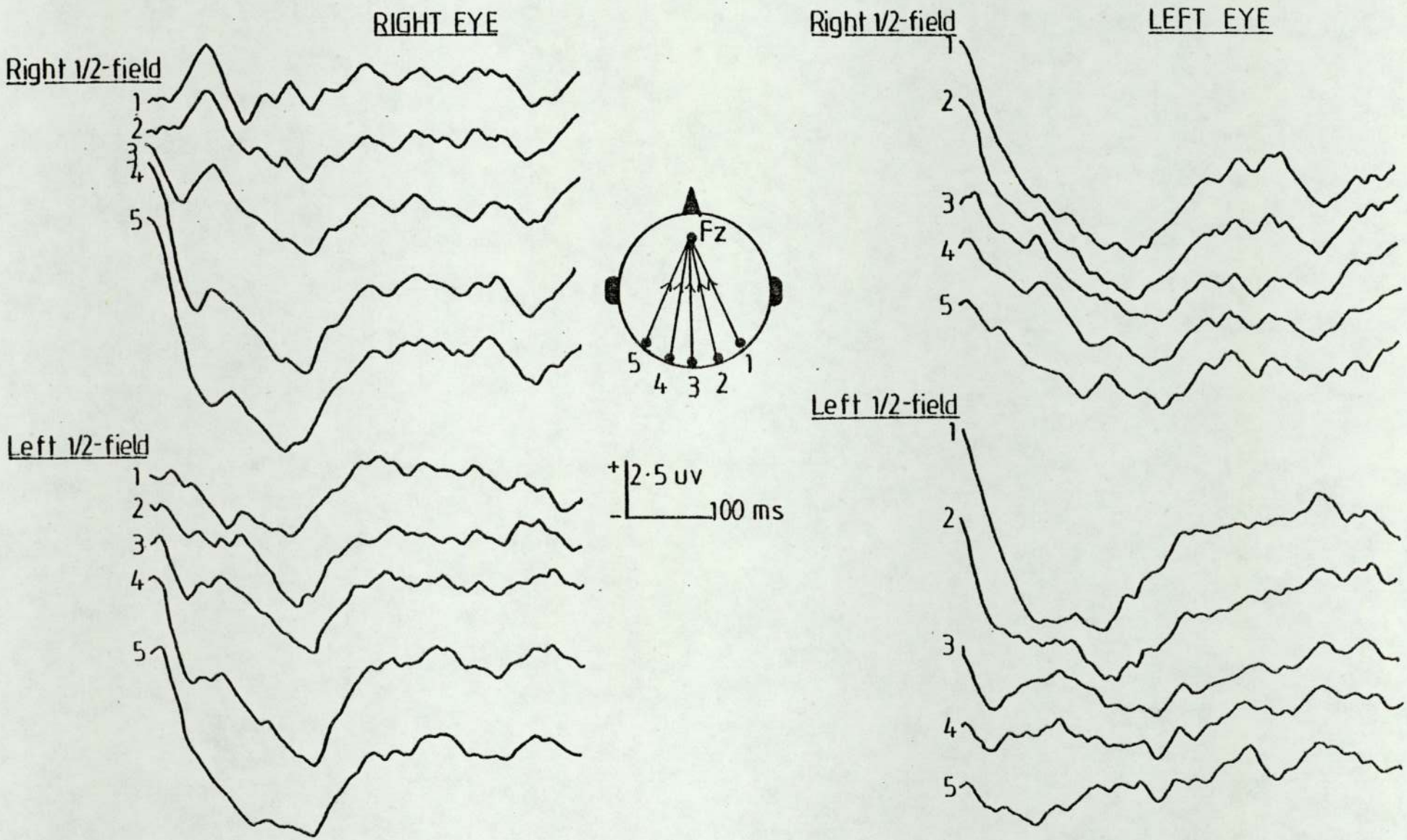
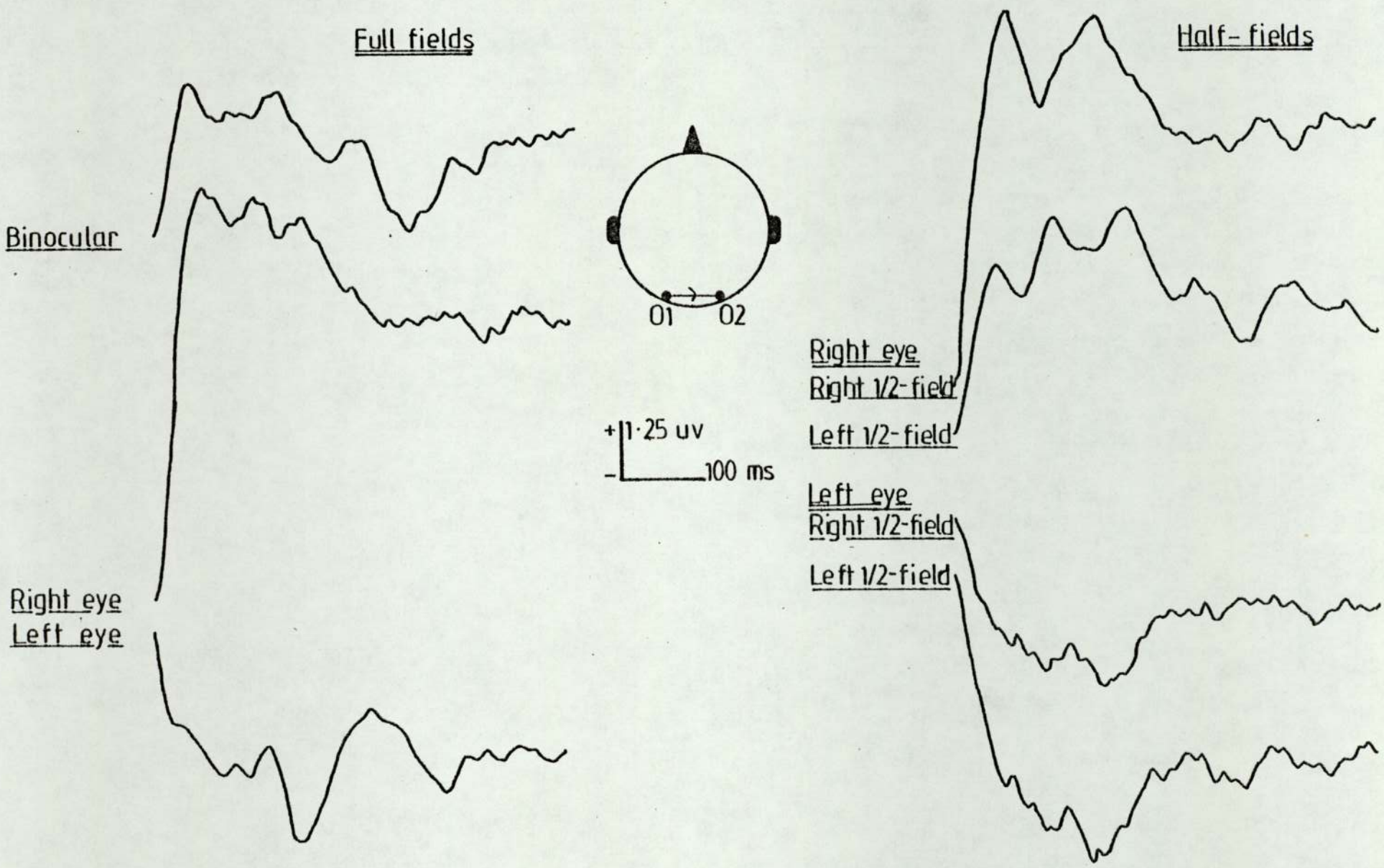

RIGHT EYE
LEFT EYE
Right 1/2-field
Left 1/2-field
Right 1/2-field
Left 1/2-field
1
2
3
4
5
Fz
5 4 3 2 1
+
-
2·5 uv
100 ms

FIGURE 6.70

The Group Average Pattern Appearance-Disappearance Responses from Bipolar Recordings in the Albino Subjects

Clearly the responses from full field stimulation of the two eyes show polarity reversal indicative of contralateral lateralisation. However, this phase reversal which is seen in half-field recordings from the control subjects is not visible in those of the albino responses. The bipolar recordings from the latter actually resemble the full-field bipolar responses. (see text for further details)


Full fields
Half-fields
Binocular
Right eye
Left eye
O1
O2
+
1·25 uv
-
100 ms
Right eye
Right 1/2-field
Left 1/2-field
Left eye
Right 1/2-field
Left 1/2-field

this illustration with Figure 6.68 it can be seen that there is a general trend for the full field monocular responses to be somewhat dominated by those of the individual temporal half-fields (i.e. right eye full field dominated by the right half-field response and the left eye dominated by the left half-field). Although this is only a trend it is further supported by the poor formation of the two nasal half-field responses.

The bipolar, O1-O2, recordings (Figure 6.70) give added information about the monocular full field responses. The initial part of the two responses, one from each eye, show the polarity reversal expected but difficult to predict from the reference recordings. The half-field responses do not show the clear phase reversals seen in the control group average although there is some evidence of its occurrence in the right eye half-field responses. However, on the whole, the two half-field responses from each eye are quite similar both to each other and the full-field bipolar response from that eye.

6.5.3 Summary

The presentation of group averages both confirms and adds to the results obtained when considering the individual responses from the two populations.

The flash VECP is shown to lateralise over the contralateral hemisphere on monocular stimulation in the albino but not the control group. This lateralisation is by both P2 latency

and N2P2 amplitude. No such effect is seen in the pattern appearance-disappearance reference recordings from the albinos although contralateral lateralisation on monocular stimulation is visible in a bipolar, O1-O2, recording. There is a trend for the individual full-field responses from the albinos to be dominated by that of the temporal half-field and the bipolar responses on half-field stimulation do not show the clear phase reversals seen in the control group.

CHAPTER SEVEN

7 RESULTS III : THE VISUALLY EVOKED SUBCORTICAL POTENTIAL

VESPs were successfully recorded in 22 of the albinos and their controls. Unfortunately subject 16, a 6 years old male oculocutaneous albino became too distressed for reliable recording to take place (note this was also the subject whose V.As could also not be measured). As in the previous chapter the responses recorded from albino 20 who displayed the gross visual field defect will be considered separately in section 7.6.

7.1 VESPs recorded in the albino population

Prior to the commencement of recordings it had been predicted that in the presence of the typical albino misrouting, the VESP should lateralise contralaterally on monocular stimulation. However, at an early stage in the study it became evident that this would not be a consistent finding.

The very first albino subject examined, number 11, clearly showed this monocular contralateral lateralisation; the VESPs of this subject are shown in Figure 7.1 (note that in all of the following VESP illustrations the initial few milliseconds of the responses are deleted due to contamination by a flash artifact). However, in contrast, one of the following subjects examined, albino 17, clearly showed the opposite, i.e. ipsilateral, lateralisation on monocular stimulation; the VESPs of this subject are illustrated in

Figure 7.1

The VESPs of Albino Subject 11

The responses recorded on binocular and monocular stimulation are shown. The binocular responses of this subject are not well formed, particularly on the left. On monocular stimulation, however, a VESP is seen on the contralateral channel, that ipsilaterally being unclear. (Flash intensity 8, 5 flashes per second, 750 sweeps).

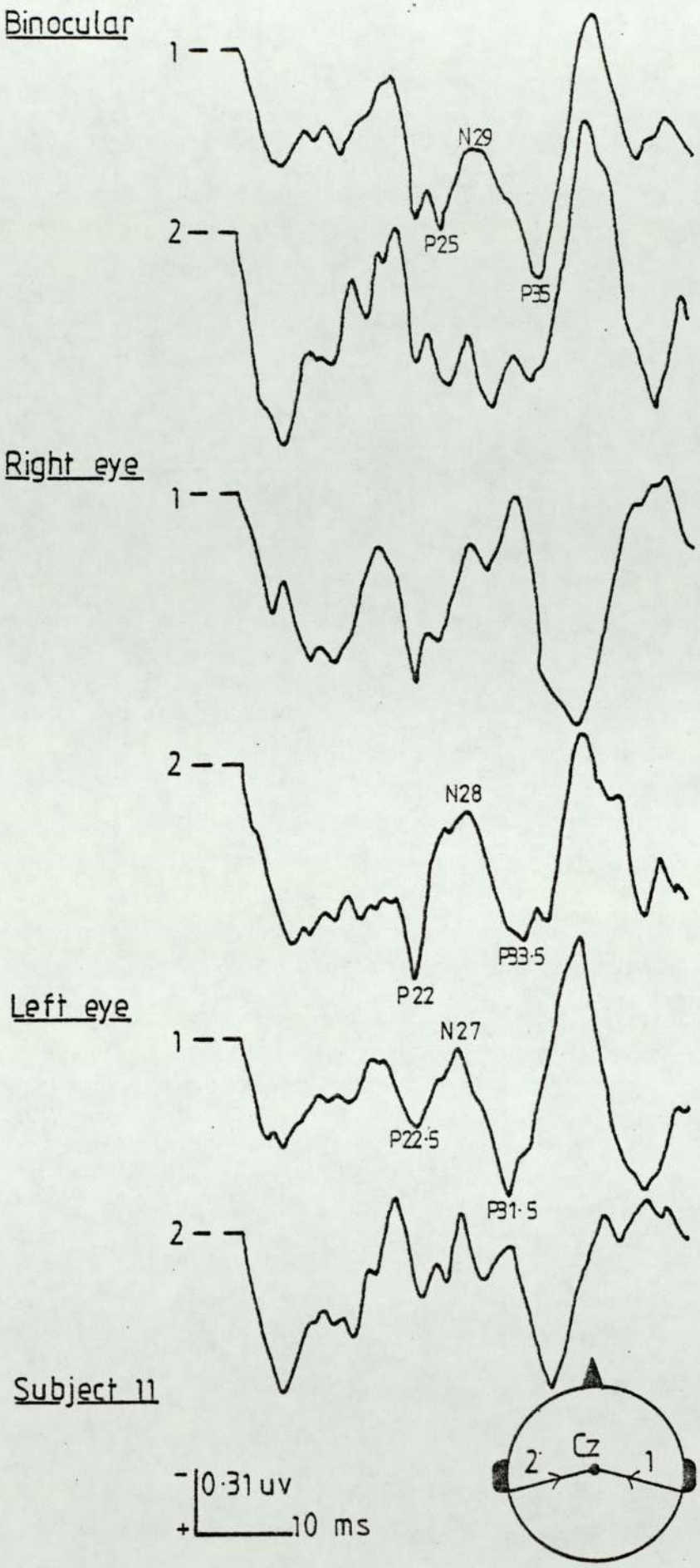

Binocular
1
N29
2
P25
P35
Right eye
1
2
N28
P33·5
P22
Left eye
1
N27
P22·5
P31·5
2
Subject 11
0·31 uv
10 ms
Cz
2
1

Figure 7.2.

This pattern whereby some albinos showed contralateral and others ipsilateral monocular lateralisation repeated itself throughout the study. In order to check the repeatability of these contrasting lateralisations, the VESPs of each subject were repeated during each examination and the responses of albinos 11 and 17 recorded under identical conditions some 2 and 6 months after the initial examination respectively. These repeated recordings are shown in Figures 7.3 and 7.4 and, by comparison with Figures 7.1 and 7.2 respectively it can be seen that the lateralisations found were stable over several months. The responses of these two albinos also show two features commonly seen within the albino population. In some subjects a clear bilateral binocular response was not always recordable (see Figure 7.1) while in other albinos such responses were clearly present (see Figures 7.2 and 7.4). On monocular stimulation it was also often found that no response could be recognised on the channel over which the VESP did not lateralise. This is clearly see on the right eye stimulation of subject 17 (see Figures 7.2 and 7.4). On each occasion a clear VESP is seen over the right hemisphere but that over the left is indefinable and variable. This latter feature was prevalent among the albino population and often lateralisation of the monocular responses could be confirmed by the superimposition of repeated responses; the lateralisation is then characterised by the consistency and repeatability of the response on one channel in conjunction with an inconsistent or even non-

Figure 7.2

The VESPs of Albino Subject 17

The responses recorded on binocular and monocular stimulation are shown. In contrast to that found in Subject 11 (See Figure 7.1), the binocular responses of this subject are well formed bilaterally. In addition the response shows clear ipsilateral lateralisation on monocular stimulation with poorly formed responses contralaterally. (Flash intensity 8, 5 flashes per second, 750 sweeps).

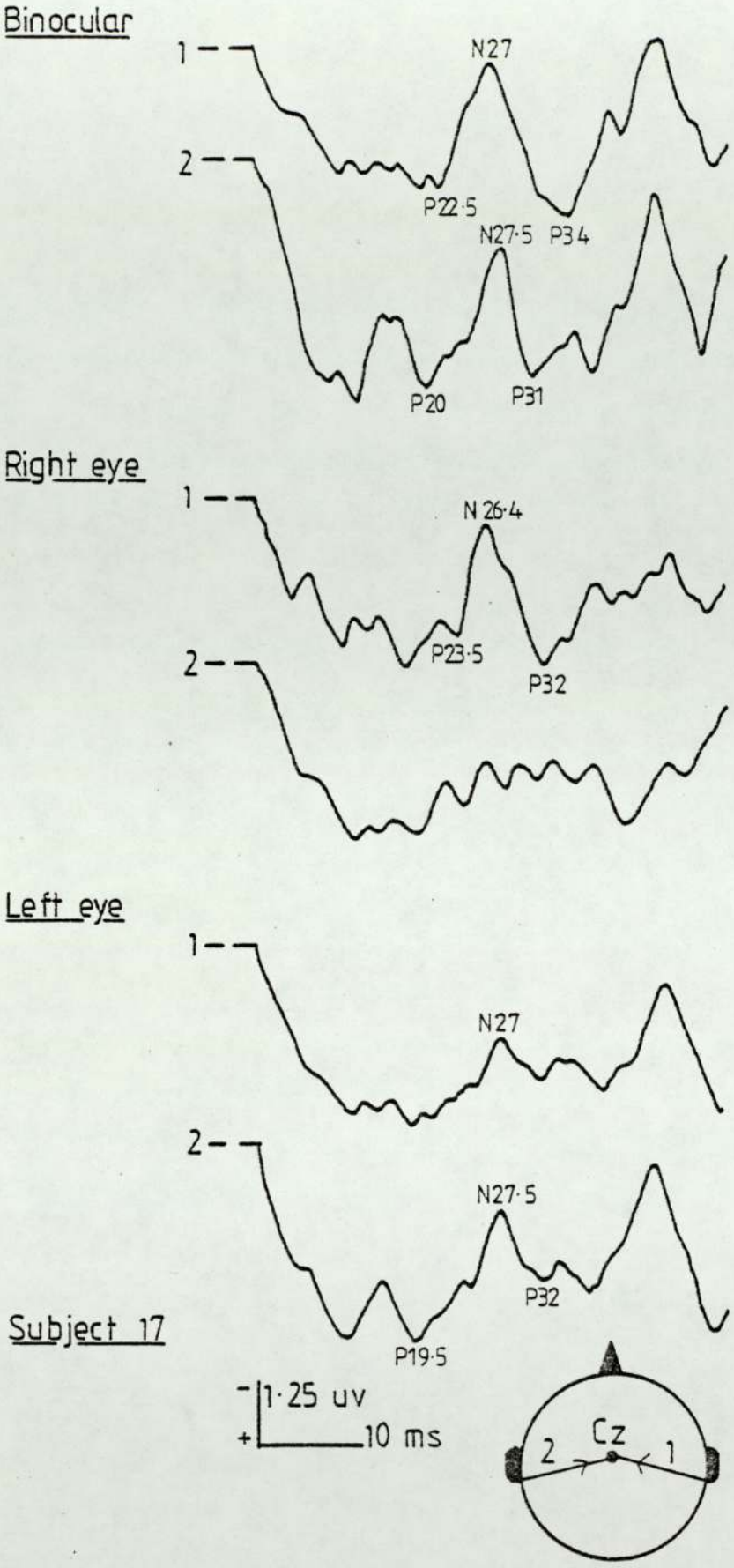

Binocular
1
2
N27
P22·5
N27·5
P34
P20
P31
Right eye
1
2
N 26·4
P23·5
P32
Left eye
1
2
N27
N27·5
P32
P19·5
Subject 17
1·25 uv
10 ms
Cz
2
1

FIGURE 7.3

Repeated VESP Recordings from Albino 11

These responses were recorded 2 months after those shown in Figure 7.1. On this occasion the binocular responses were somewhat better formed and on monocular stimulation clear contralateral lateralisation is again present. The latencies of the VESP components shown here and in Figure 7.1 are very similar proving the repeatability of the responses. (Flash intensity 8, 5 flashes per second, 750 sweeps)

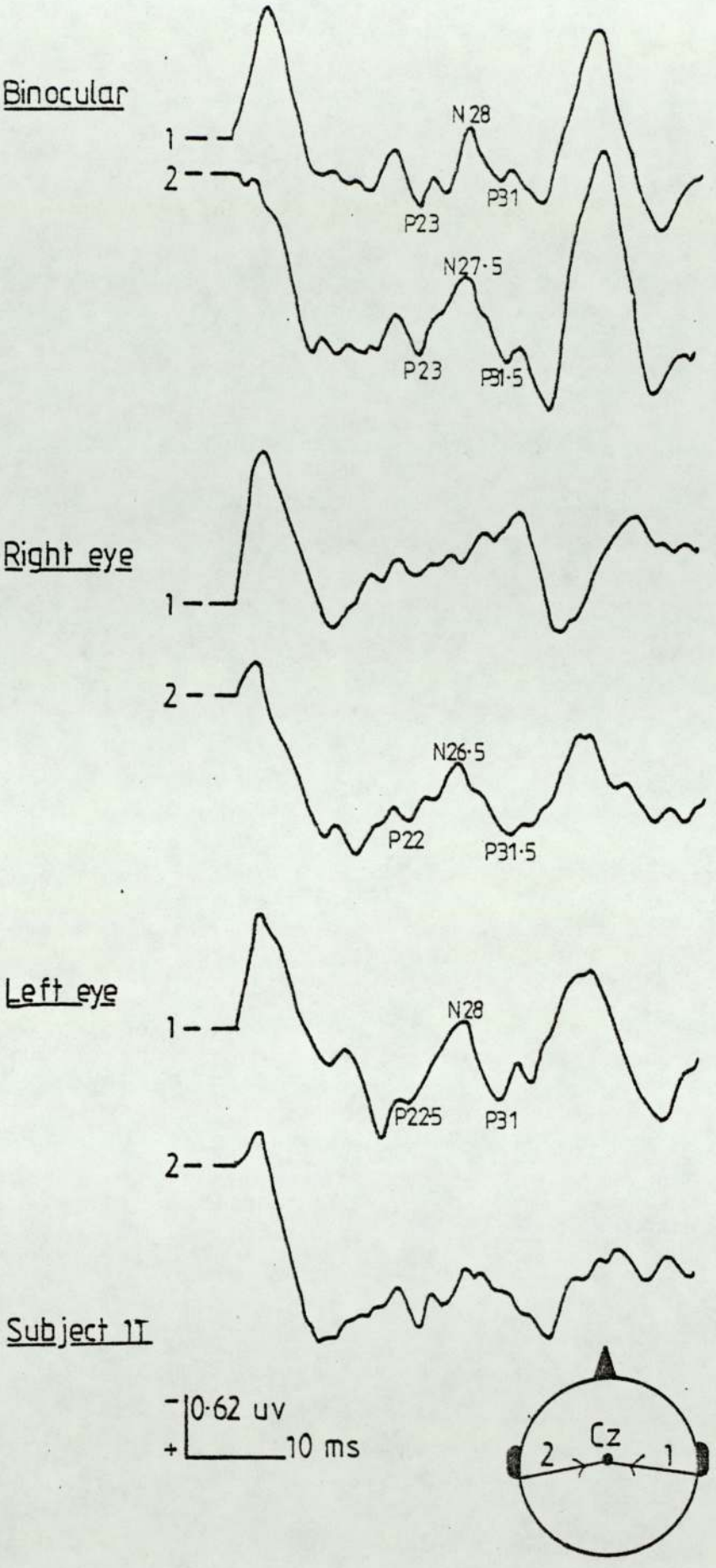
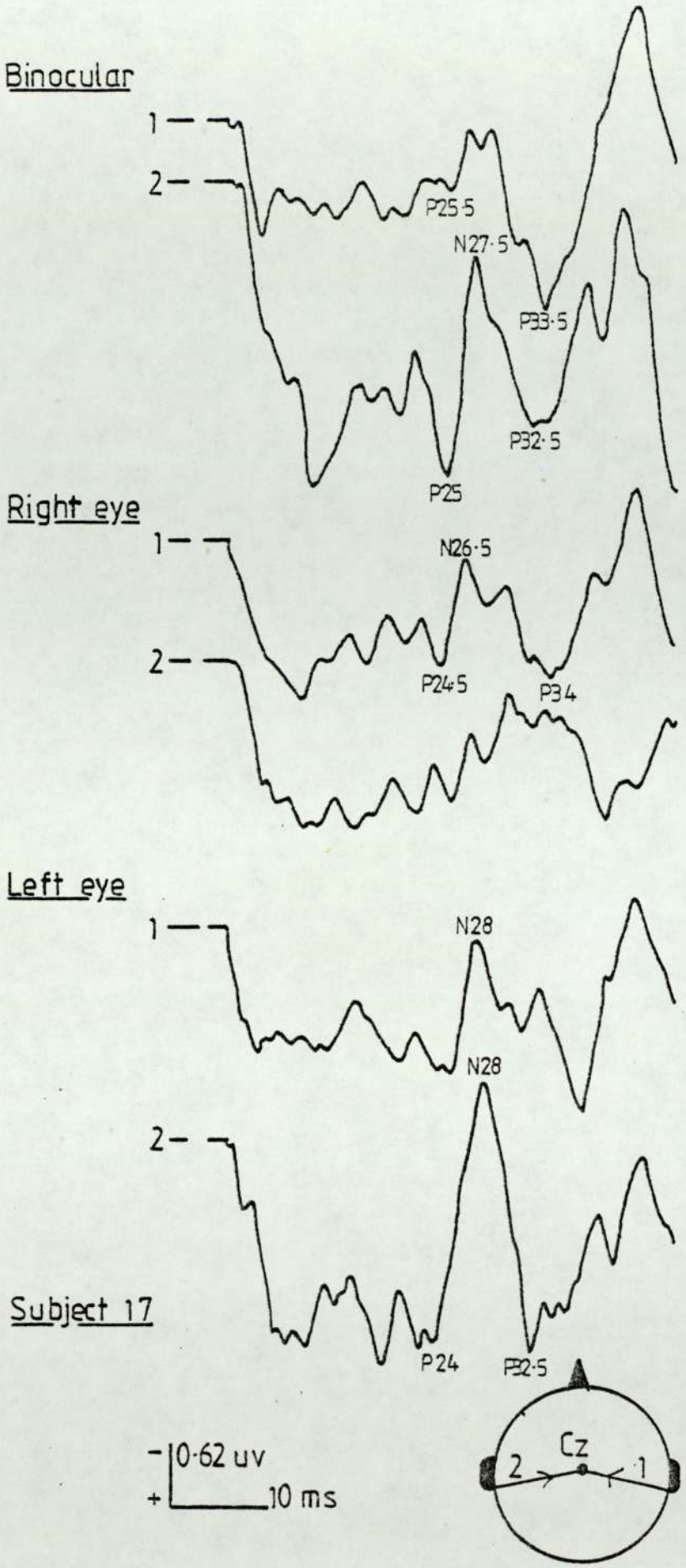

Binocular
1
2
N28
P23
P31
N27·5
P23
P31·5
Right eye
1
2
N26·5
P22
P31·5
Left eye
1
2
N28
P225
P31
Subject 1I
0·62 uv
10 ms
Cz
2
1

Figure 7.4

Repeated VESP Recordings from Albino 17

These responses were recorded 6 months after those shown in Figure 7.2. Here, again, ipsilateral lateralisation on monocular stimulation is found The VESP, had similar component latencies on the two occasions. (Flash intensity 8, 5 flashes per second, 750 sweeps).


Binocular
1
2
P25·5
N27·5
P33·5
P32·5
P25
Right eye
1
N26·5
2
P24·5
P34
Left eye
1
N28
N28
2
Subject 17
P24
P32·5
0·62 uv
10 ms
Cz
2
1

existent VESP on the opposite channel. This effect is shown in Figure 7.5 which shows repeated responses on stimulation of the right eye of albino 10. By superimposition it can be seen that the only consistent response is seen over the right hemisphere while that over the left is variable.

7.2 VESPs recorded in the control population

Responses were successfully recorded in all of the control subjects although often the responses were not as clearly defined as seen within the albinos. In the majority of the control subjects bilateral VESPs were recorded on both binocular and monocular stimulation although in some a small amount of monocular lateralisation, of both the contralateral and ipsilateral type was thought to be present.

7.3 Analysis of the results

7.3.1 Gross observations

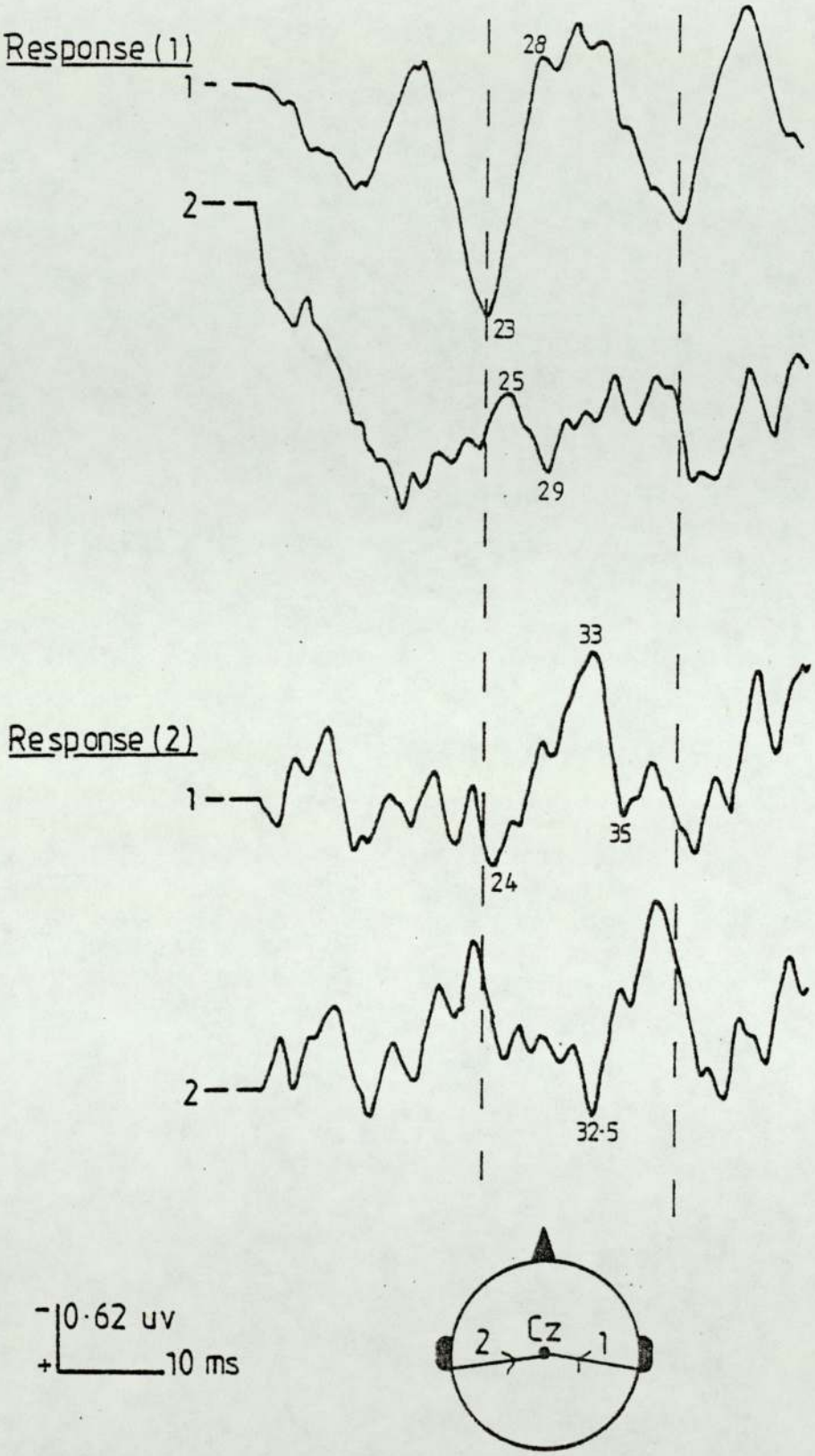
By reference to Figures 7.1 to 7.5 it can be seen that in some albinos monocular lateralisation of the VESP was easily evaluated by gross observation of the responses recorded and, therefore, this method of analysis was the first attempted. A method was used to enable each subject (both albinos and controls) to be categorised into contralateral, ipsilateral or no lateralisation groups on the basis of their VESP responses. To reduce the effects of scorer bias a 'blind' scorer was used to assess the responses

Figure 7.5

The Right Eye VESPs of Albino Subject 10

The right eye responses shown here were recorded on the same occasion some minutes apart. The two responses show how superimposition of responses aids in the interpretation of VESP lateralisation. In this case the response lateralises ipsilaterally. The VESP recorded on the right channel has a clear and repeatable waveform while that on the left is a variable and poorly formed response. (Flash intensity 8, 5 flashes per second, 750 sweeps).

Subject 10 - Right eye



using the following method.

The traces from the albinos and their controls were randomly mixed and given to the scorer. The latter was asked to give each subject a score of contralateral, ipsilateral or no lateralisation of the VESP on monocular stimulation along with any comments about the responses presented. The results of this are shown in Table 7.1 and as can be seen this method of evaluation was not totally successful.

Of the albino group only 4 (19%) were clearly categorised as contralateral and 8 (38%) ipsilateral while one subject (5%) showed no monocular lateralisation. Of the control group 5 (24%) were categorised as contralateral, 7 (33%) as ipsilateral and 4 (19%) as no lateralisation. However, the responses of 8 (38%) of the albinos and 5 (24%) of the controls could not be clearly categorised into one of the above groups (these subjects are shown by a '?' in Table 7.1).

Consequently, this method of analysis was not successful and more detailed examination of the response amplitudes was undertaken.

7.3.2 Amplitude analysis

To undertake this form of analysis the VESPs were treated in a similar fashion to the VECPs: Cx values were calculated for each subject's responses such that a positive Cx value indicates contralateral lateralisation and a negative Cx

Table 7.1

Gross Observations on the Lateralisation of the VESPs In the Albino and Control Populations

A blind scorer attempted to classify each subjects' responses into contralateral, ipsilateral or no lateralisation groups. As can be seen many subjects were not easily classified. (See text for further details).

SUBJECT	VESP LATERALISATION	
	ALBINO	CONTROL
I	I	I
2	?	C
3	?	I
4	=	C
5	C	I
6	I	=
7	C	=
8	?	=
9	I	I
10	I	=
11	C	?
12	?	I
13	?	C
14	I	I
15	?	?
17	I	?
18	I	?
19	C	C
21	I	C
22	?	?
23	?	I

Key: C - Contralateral lateralisation on Monocular Stimulation

I - Ipsilateral lateralisation on Monocular Stimulation

= - No consistent lateralisation on Monocular Stimulation

? - Response not easily classified into one of the above groups

value ipsilateral lateralisation on monocular stimulation. This could only be performed with respect to the amplitudes of the responses. As discussed previously, in some subjects a response on one recording channel could not be clearly defined and hence a latency shift could not be stated with certainty. In these cases, however, the amplitude of the response on this channel could be defined as being of zero microvolts thus enabling a Cx value to be calculated.

For this purpose the VESPs were divided into two component measures; an initial positive-negative followed by a negative-positive. These will be referred to as P23-N28 and N28-P34 respectively using the terminology of Harding and Rubinstein (1980a) and illustrated in Figure 7.6.

Using the positive and negative Cx values as indications of contralaterality or ipsilaterality respectively, a 2 x 2 contingency table could be formed of the results.

1) The P23-N28 amplitude

Table 7.2 shows the calculated Cx values found in the albinos and their controls for this measure of the VESPs recorded. Nine (43%) of the albinos show a positive Cx value and 12 (57%) a negative value. Eleven (52%) of the controls showed a positive Cx value and 10 (48%) a negative value.

Consequently both ipsilateral and contralateral lateralisations were present among both the albinos and controls.

Figure 7.6

The VESP Components Measured During Results Analysis

A typical VESP recorded from a single channel is shown.
The P23N28 and N28P34 amplitudes are indicated.
(See text for further details).

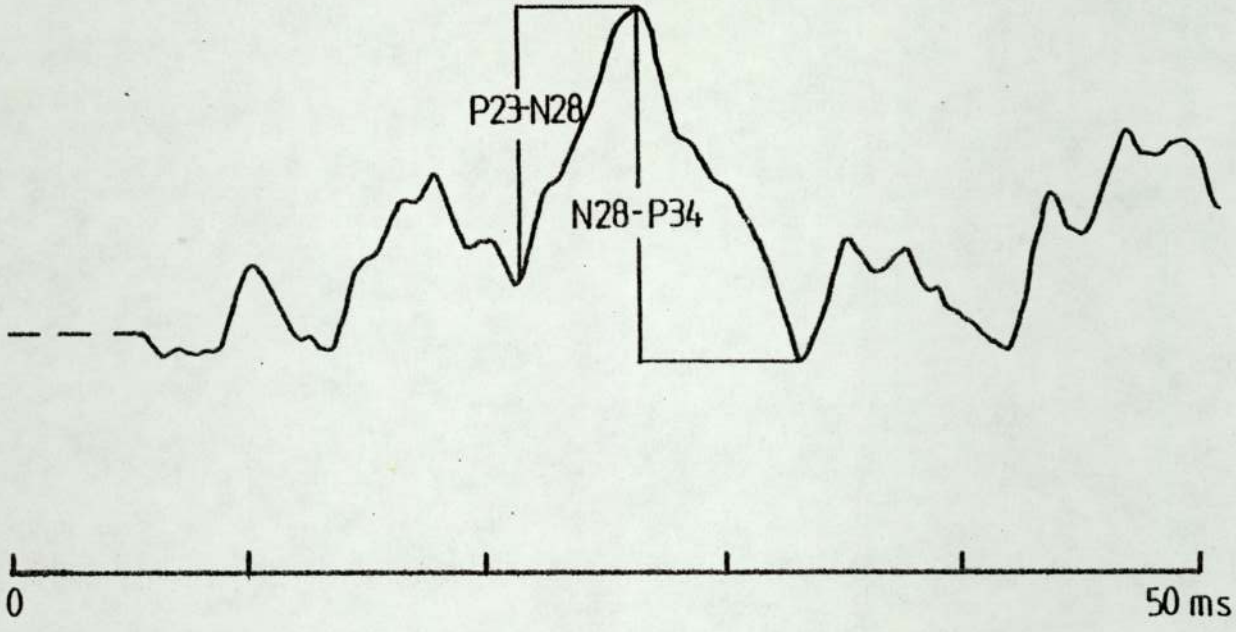

P23-N28
N28-P34
0
50 ms

Table 7.2

The Cx Values for the P23N28 Amplitude Measure In the Albino and Control Groups

The Cx value (in uV) for each subject was calculated; a positive figure indicates contralateral and a negative figure ipsilateral monocular lateralisation. (See text for further details).

Subject	Cx (P23-N28 Amplitude)	
	Albino	Control
1	-0.40	+0.06
2	-0.14	-0.07
3	-1.42	-0.88
4	+0.15	+0.72
5	+0.46	-0.06
6	-0.58	-0.02
7	+0.48	+0.17
8	+0.48	+0.38
9	-0.06	-0.20
10	-1.08	+0.04
11	+0.69	+0.31
12	+0.61	-0.55
13	-0.29	+0.60
14	-0.80	-0.26
15	-0.33	-0.15
17	-1.12	-0.01
18	-0.60	+0.57
19	+1.35	+0.58
21	-0.38	+0.56
22	+0.17	+0.40
23	+0.41	-0.47

This is illustrated in Figures 7.7 and 7.8. The former illustrates the VESPs of albinos 5 and 14 who displayed contralateral (Cx = + 0.46uV) and ipsilateral (Cx = - 0.80uV) lateralisation respectively. Similarly, Figure 7.8 shows the VESPs of control subjects 19C and 23C who showed contralateral (Cx = + 0.58uV) and ipsilateral (Cx = - 0.47uV) lateralisation respectively.

Among the albino group the average Cx value was -0.11uV (S.E. 0.15) and among the controls +0.08uV (S.E. 0.09); this is illustrated in Figure 7.9. By visual inspection it did seem that the size of the lateralisations were greater in the albino group compared to the controls and in order to confirm this separate average Cx values were calculated for the contralateral and ipsilateral lateralisations of both groups. Within the albino group the average positive Cx value was +0.50uV (S.E. 0.12) and within the controls +0.37uV (S.E. 0.07); the average negative Cx value among the albino group was -0.60uV (S.E. 0.12) and within the controls -0.27uV (S.E. 0.09). These results do seem to indicate the trend for clearer lateralisation among the albino group; the results are illustrated in Figure 7.10.

A 2 x 2 contingency table was formed of the positive and negative Cx value results (see Table 7.3) and a chi-square test of association was found to be not significant ($x^2 = 0.38$).

2) The N28-P34 amplitude

Table 7.4 shows the calculated Cx values for the albinos

FIGURE 7.7

The VESPs of albino subjects 5 and 14

The binocular and monocular responses are shown. (a) illustrates the responses of albino 5 whose VESPs showed contralateral monocular lateralisation of P23N28 (Cx = +0.46uV). In contrast (b) shows the responses of albino 14 whose VESPs showed ipsilateral lateralisation (Cx = -0.80uV). (Flash intensity 8, 5 flashes per second, 750 sweeps).

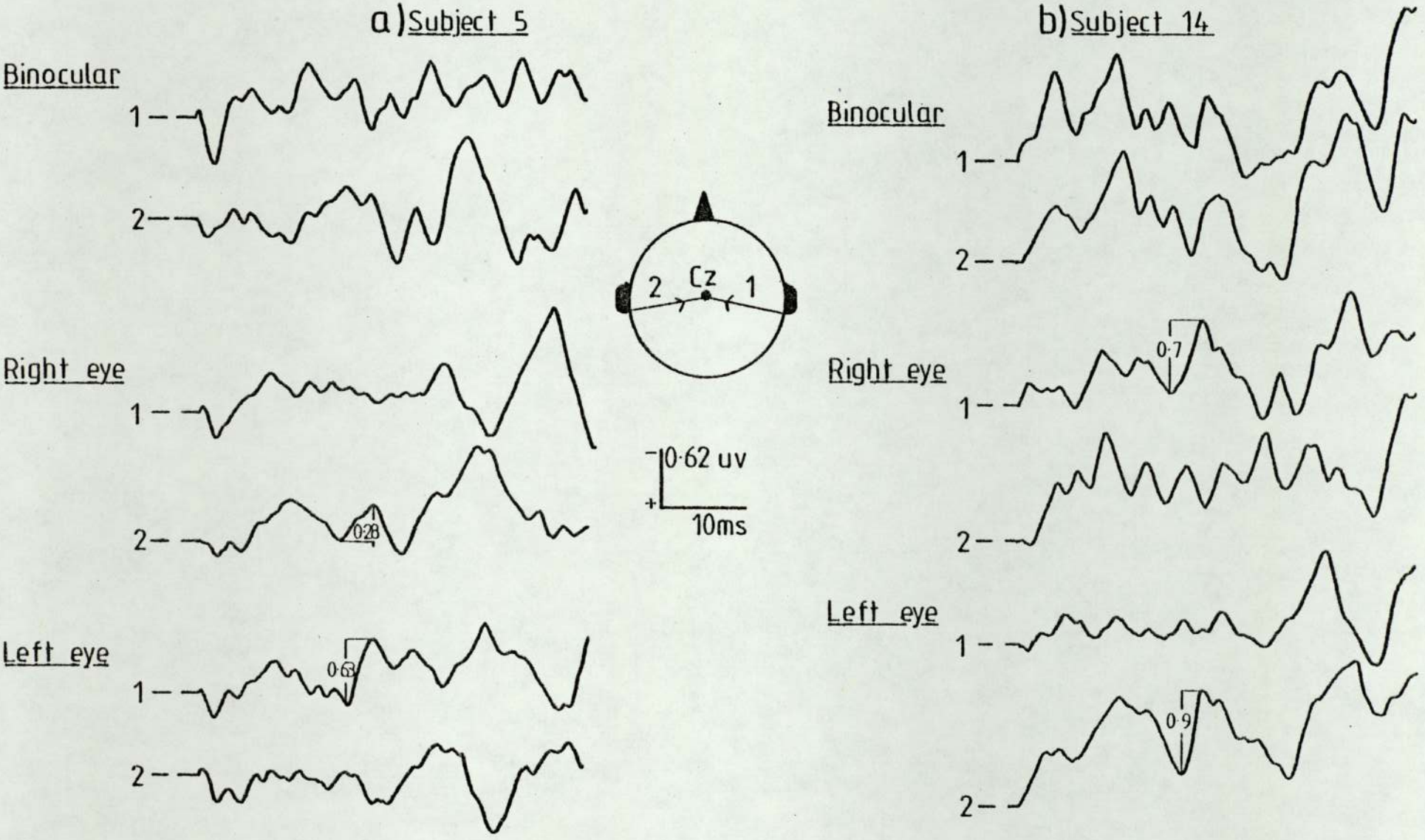

a) Subject 5
Binocular
1
2
Right eye
1
2
0·28
Left eye
1
0·63
2
2
Cz
1
0·62 uv
10ms
b) Subject 14
Binocular
1
2
Right eye
0·7
1
2
Left eye
1
0·9
2

Figure 7.8

The VESPs of Control Subjects 19C and 23C

The binocular and monocular responses are shown. (a) illustrates the responses of subject 19C in whom P23N28 showed contralateral monocular lateralisation (Cx = +0.58 uV). In contrast (b) shows the responses of subject 23C who showed ipsilateral lateralisation (Cx = -0.47 uV). (Flash intensity 8, 5 flashes per second, 750 sweeps).

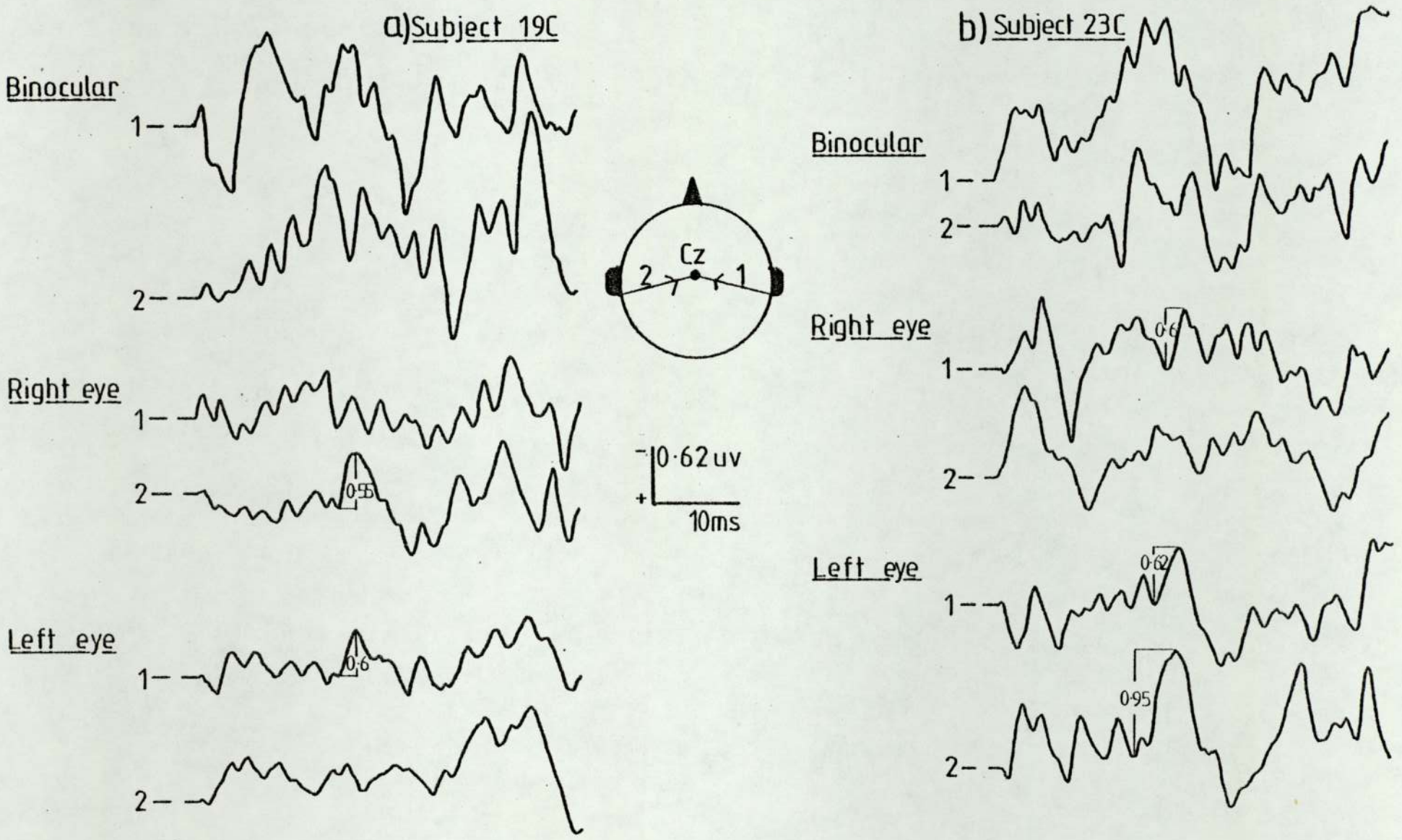

a) Subject 19C
Binocular
1–
2–
Right eye
1–
2–
0·55
Left eye
1–
0·6
2–
Cz
2
1
0·62 uv
10ms
b) Subject 23C
Binocular
1–
2–
Right eye
0·6
1–
2–
Left eye
0·62
1–
0·95
2–

Figure 7.9

The Mean P23N28 Cx Values $\pm$ 1 S.E.

The mean Cx Values $\pm$ 1 S.E. with respect to the P23N28 measure in the albino and control groups are shown. (See text for further details).

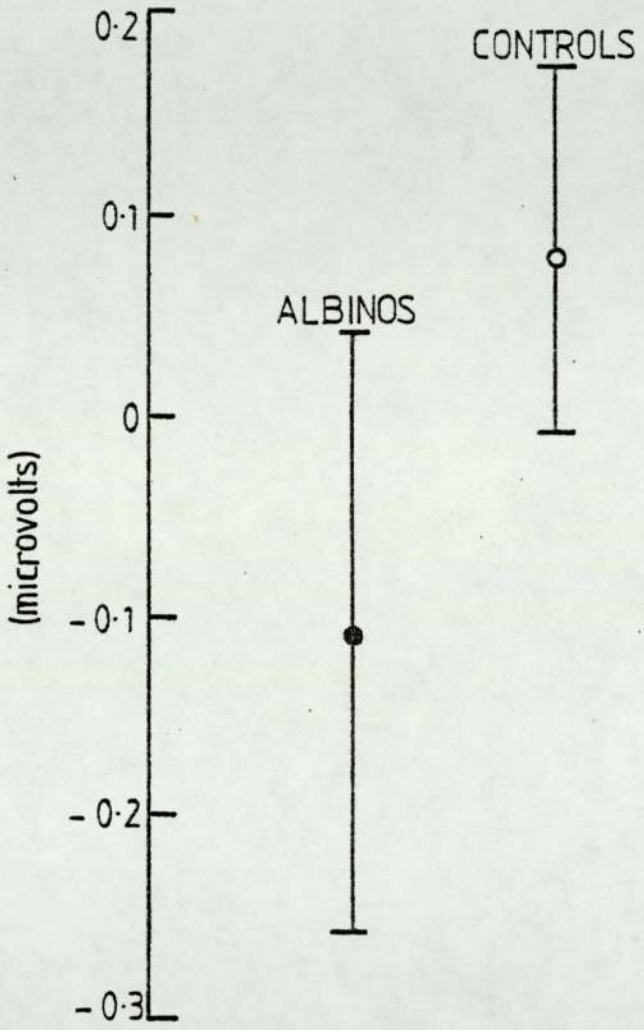

0·2
0·1
0
- 0·1
- 0·2
- 0·3
(microvolts)
ALBINOS
CONTROLS

Figure 7.10

The Mean Positive and Negative P23N28 Cx Values ± 1 S.E.

In this instance the mean Cx values for the albinos and controls were calculated for the original positive and negative values separately. The trend towards a greater amount of lateralisation, both of the contralateral and ipsilateral type, within the albino group compared to the controls is indicated. (See text for further details).

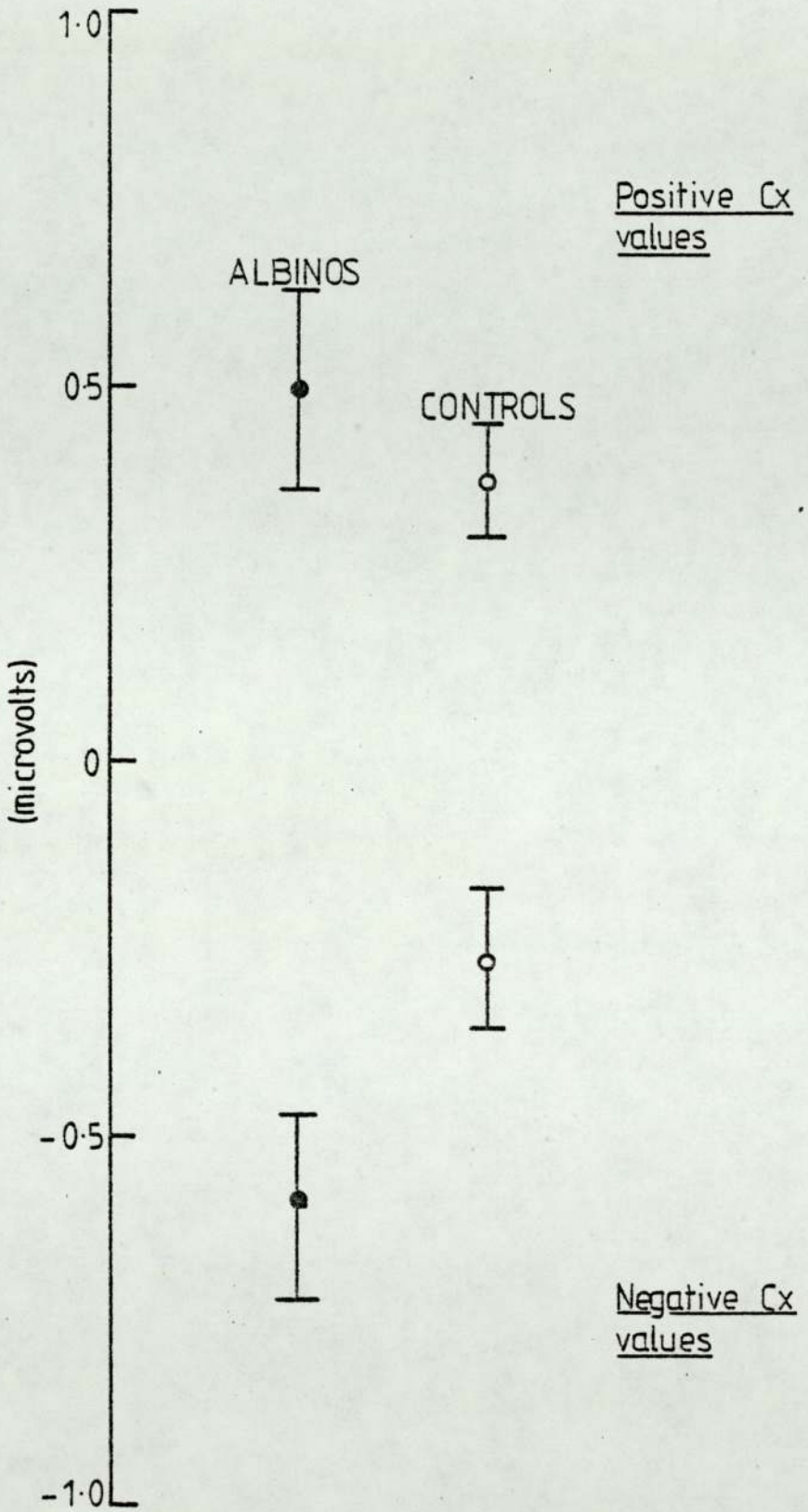

1·0
0·5
0
-0·5
-1·0
(microvolts)
ALBINOS
CONTROLS
Positive Cx values
Negative Cx values

Table 7.3

Contingency Table Formulated from the P23N28 Data

A 2 x 2 contingency table is shown formed from the results in Table 7.2 (See text for further details).

	ALBINOS	CONTROLS
CONTRALATERAL	9	11
IPSILATERAL	12	10

and their controls with respect to this measure. Nine (43%) of the albinos show a positive Cx value and 12 (57%) a negative value. Eight (38%) of the controls showed a positive Cx value and 13 (62%) a negative value. Consequently, as when considering the P23-N28 amplitude, both contralateral and ipsilateral lateralisations were present among the albino and control populations. This is illustrated in Figures 7.11 and 7.12. The former shows the VESPs of albino subjects 12 and 10 who showed contralateral (Cx = + 0.17uV) and ipsilateral (Cx =-1.00uV) monocular lateralisation respectively. Similarly Figure 7.12 illustrates the responses of control subjects 19C and 13C who also showed contralateral (Cx + 0.90uV) and ipsilateral (Cx = -0.13uV) lateralisations respectively.

Within the albino group the average Cx value was - 0.09uV (S.E. 0.15) and among the controls + 0.02uV (S.E. 0.11); this is illustrated in Figure 7.13. By dividing the albinos and controls in positive and negative value groups the results again seemed to indicate that the lateralisations seen within the albino group were greater than those within the control group. Among the albinos the average positive Cx value was +0.56uV (S.E. 0.17) and among the controls +0.39uV (S.E. 0.16). The average negative Cx value among the albino group was -0.57uV (S.E. 0.11) and among the controls -0.24uV (S.E. 0.07). These results are illustrated in Figure 7.14.

A 2 x 2 contingency table was formed of the positive and

Table 7.4

The Cx Values for the N28P34 Amplitude Measure In the Albino and Control Groups

The Cx value (in uV) for each subject was calculated; a positive figure indicates contralateral and a negative figure ipsilateral monocular lateralisation.

(See text for further details)

Subject	Cx (N28-P34 Amplitude)	
	Albino	Control
1	-0.46	+0.20
2	-0.03	+0.15
3	-0.59	-0.88
4	+0.04	+0.14
5	+0.36	-0.13
6	-0.31	+0.09
7	+0.46	-0.09
8	+0.81	-0.08
9	-0.56	-0.20
10	-1.00	-0.18
11	+0.80	-0.15
12	+0.17	-0.67
13	-0.25	-0.13
14	-0.75	-0.06
15	-0.43	-0.01
17	-1.37	-0.28
18	-0.78	+0.12
19	+1.68	+0.90
21	-0.32	+1.45
22	+0.25	+0.48
23	+0.44	-0.28

Figure 7.11

The VESPs of Albino Subjects 12 and 10

The binocular and monocular responses are illustrated (a) shows the responses of albino 12 in whom N28P34 lateralised contralaterally on monocular stimulation (Cx = +0.17 uV). In contrast (b) shows albino 10 who displays ipsilateral monocular lateralisation. (Cx = -1.00 uV). (Flash intensity 8, 5 flashes per second, 750 sweeps).

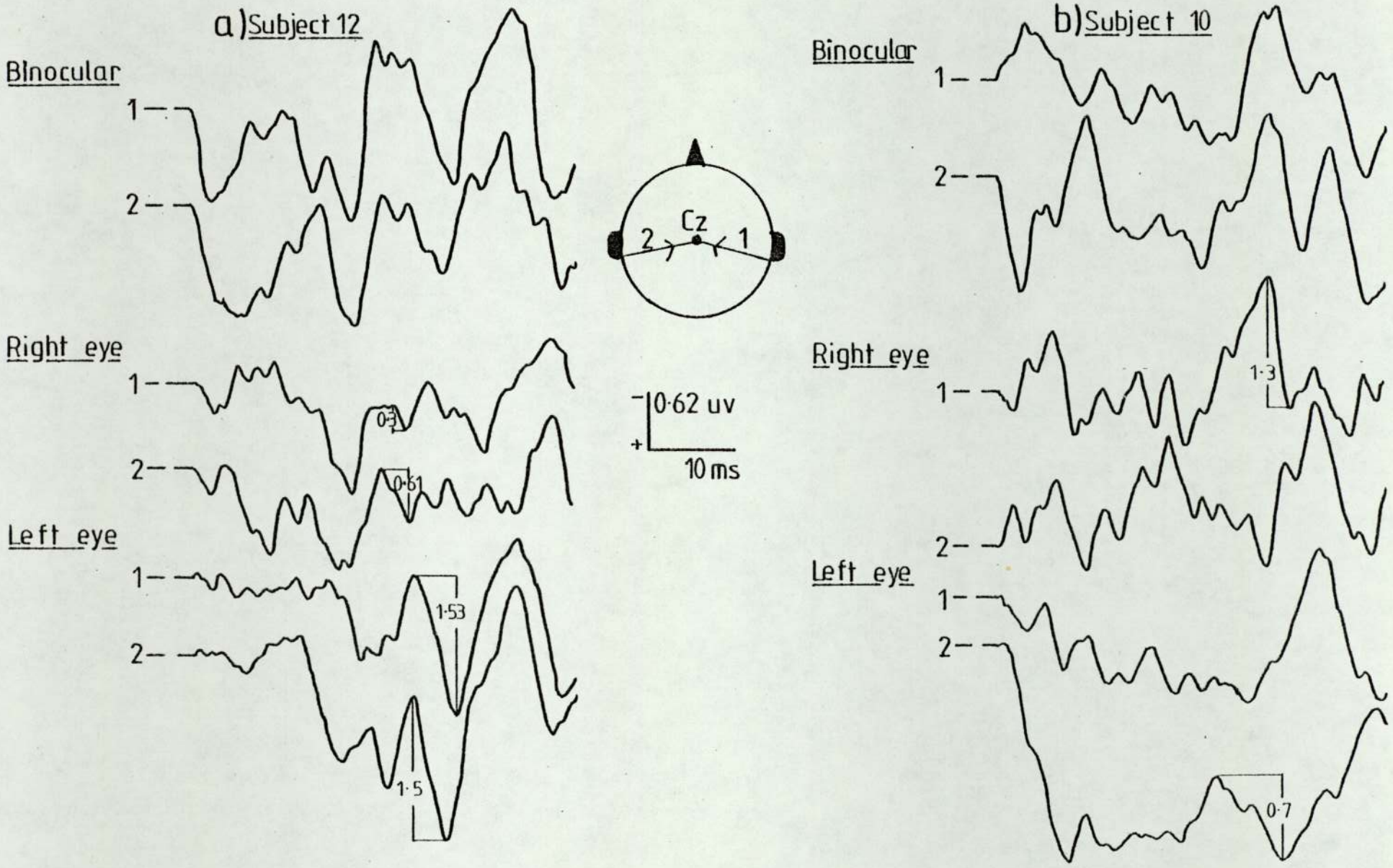

a) Subject 12
Binocular
1
2
Right eye
1
2
Left eye
1
2
0·3
0·61
1·53
1·5
Cz
2
1
0·62 uv
10 ms
b) Subject 10
Binocular
1
2
Right eye
1
2
Left eye
1
2
1·3
0·7

Figure 7.12

The VESPs of Control Subjects 19C and 13C

The binocular and monocular responses are shown. Subject 19C whose responses are shown in (a) displayed contralateral lateralisation of N28P34 (Cx = +0.90 uV) Subject 13C shown in (b) displayed ipsilateral lateralisation of this measure (Cx = -0.13 uV). (Flash intensity 8, 5 flashes per second, 750 sweeps).

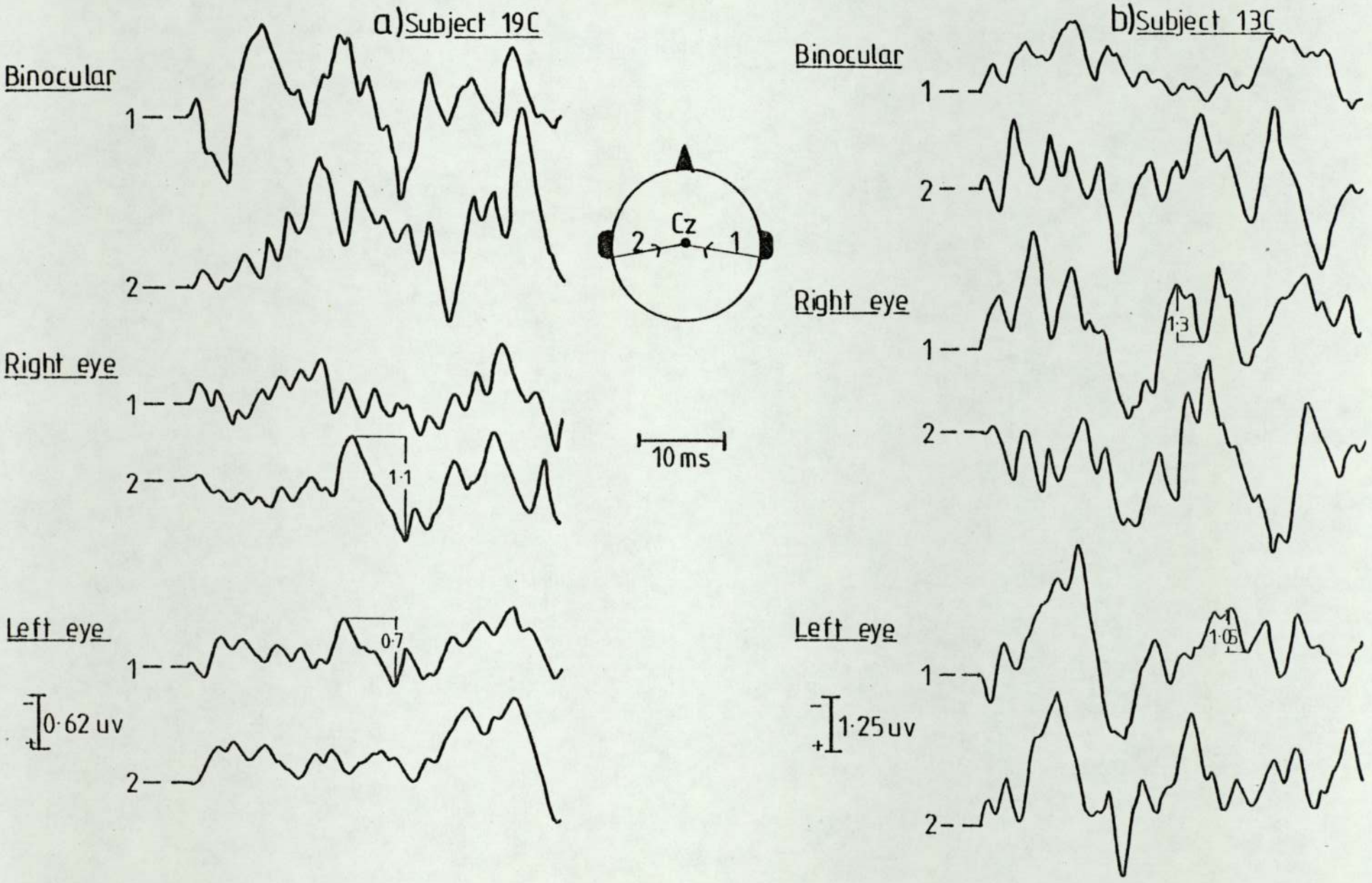

a) Subject 19C
Binocular
1
2
Right eye
1
2
1·1
Left eye
1
0·7
0·62 uv
2
Cz
2
1
10 ms
b) Subject 13C
Binocular
1
2
Right eye
1·3
1
2
Left eye
1
1·05
1·25 uv
2

Figure 7.13

The Mean N28P34 Cx Values $\pm$ 1 S.E.

The mean Cx values $\pm$ 1 S.E. with respect to the N28P34 measure in the albino and control groups are shown. (See text for further details).

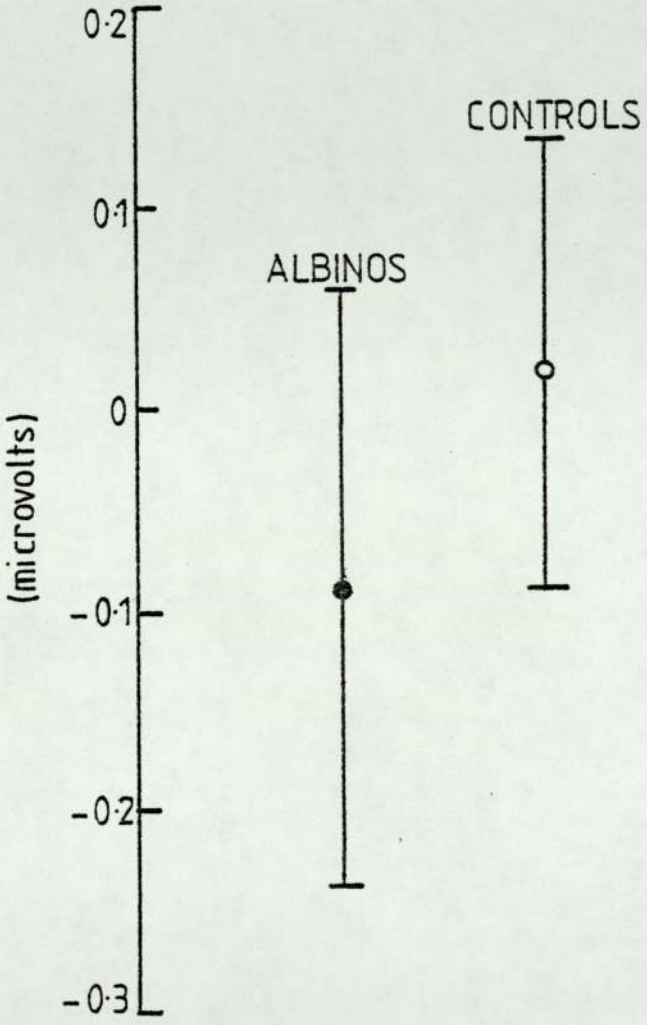
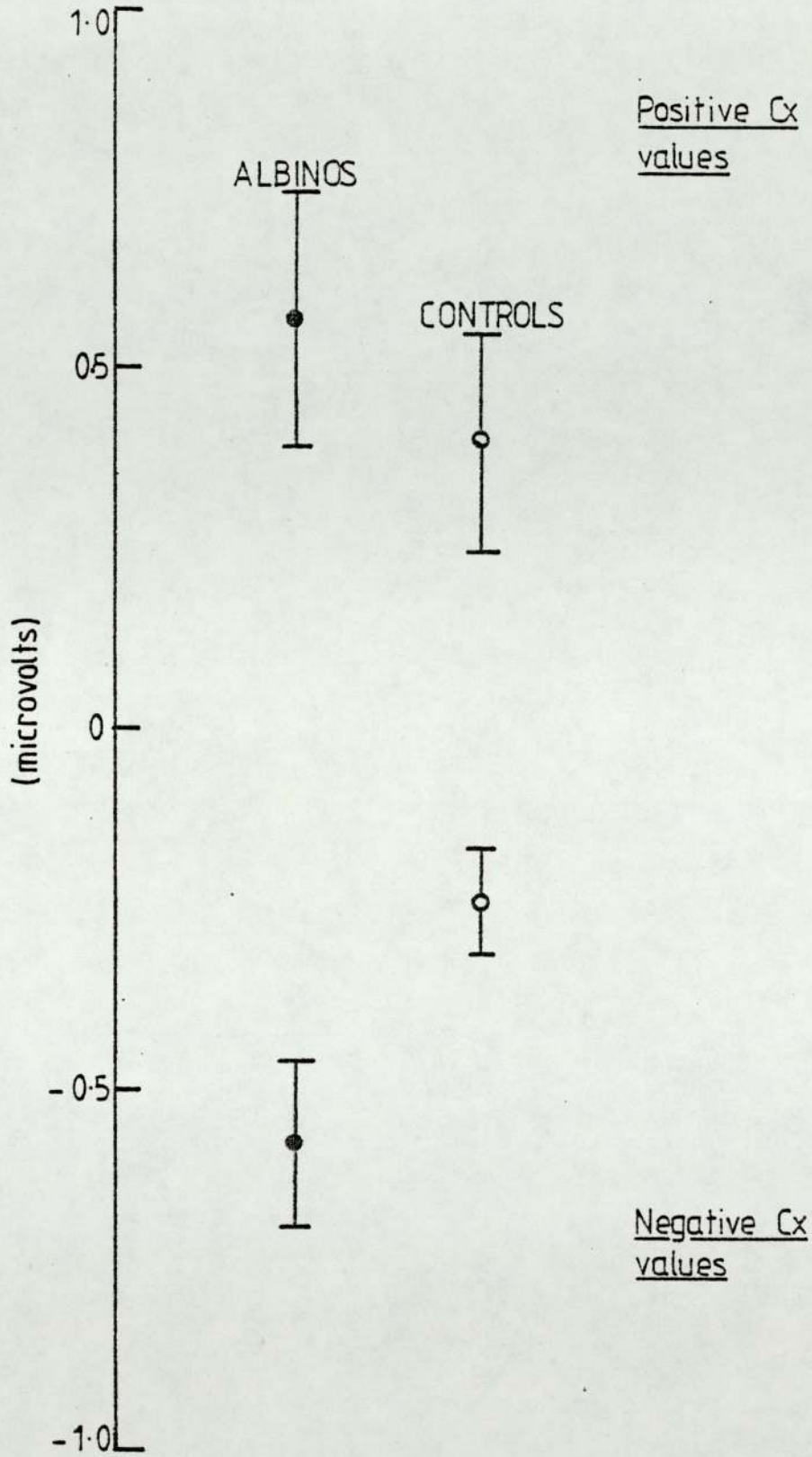

0·2
0·1
0
-0·1
-0·2
-0·3
(microvolts)
ALBINOS
CONTROLS

Figure 7.14

The Mean Positive and Negative N28P34 Cx Values ± 1 S.E.

As shown in Figure 7.10, in this instance the mean Cx values for the albinos and controls were calculated for the original positive and negative values separately. The trend towards a greater amount of lateralisation, both contralateral and ipsilateral, within the albino group compared to controls is indicated. (See text for further details).


1·0
0·5
0
-0·5
-1·0
(microvolts)
ALBINOS
CONTROLS
Positive Cx values
Negative Cx values

negative Cx value results (see Table 7.5) and a chi-square test of association was found to be not significant ($x^2 = 0.1$).

By comparing Tables 7.2 and 7.4 it can be seen that in each albino P23-N28 and N28-P34 underwent consistent contralateral or ipsilateral monocular lateralisation, i.e. if P23-N28 showed contralateral lateralisation so did N28-P34 and similar an ipsilateral lateralisation of P23-N28 occurred in conjunction with ipsilateral lateralisation of N28-P34. On this basis the VESP of each albino can be defined as undergoing either contralateral or ipsilateral lateralisation. This, however, is not true within the control group. Some of these subjects did show consistent monocular lateralisation of the two amplitude measures but others showed contralateral lateralisation of one parameter with ipsilateral lateralisation of the other. This is summarised in Table 7.6. Here it can be seen that 9 (43%) of the albinos showed contralateral and 12 (57%) ipsilateral monocular lateralisation of the VESP. Of the controls 6 (29%) showed contralateral and 8 (38%) ipsilateral lateralisation. The remaining 7 (33%) showed no clear lateralisation; 5 (24%) showed contralateral lateralisation of P23-N28 and ipsilateral lateralisation of N28-P34 while 2 (9%) showed ipsilateral lateralisation of P23-N28 and contralateral lateralisation of N28-P34.

7.4 The VESP/VECP relationship

The previous section described how the lateralisation

Table 7.5

Contingency Table Formulated from the N28P34 Data

A 2 x 2 contingency is shown formed from the results in Table 7.4. (See text for further details).

	ALBINOS	CONTROLS
CONTRALATERAL	9	8
IPSILATERAL	12	13

Table 7.6

Summary of the Results on the Lateralisation of the VESP in the Albinos and Controls

In each albino components P23N28 and N28P34 lateralised consistently in either a contralateral or ipsilateral direction. This was also true of some of the control group but in others one measure lateralised contra-laterally and the other ipsilaterally. (See text for further details).

Subject	VESP Lateralisation	
	Albino	Control
1	I	C
2	I	I/C
3	I	I
4	C	C
5	C	I
6	I	I/C
7	C	C/I
8	C	C/I
9	I	I
10	I	C/I
11	C	C/I
12	C	I
13	I	C/I
14	I	I
15	I	I
17	I	I
18	I	C
19	C	C
21	I	C
22	C	C
23	C	I

Key:-

C = Contralateral monocular lateralisation of the VESP

I = Ipsilateral monocular lateralisation of the VESP

I/C = Ipsilateral monocular lateralisation of P23-N28 component of the VESP but contralateral lateralisation of the N28-P34 component

C/I = Contralateral monocular lateralisation of the P23-N28 component of the VESP but ipsilateral lateralisation of the N28-P34 component.

of the VESP of each albino subject could be clearly defined as contralateral or ipsilateral in nature. Because of this it is possible to compare these results to those found in the VECP recordings, notably the results with regard to the latency of the flash VECP P2 component, the only measure of the VECPs recorded which showed statistically significant contralateral lateralisation within the albino group. Table 7.7 shows the monocular lateralisation found in each albino both with regard to the latency of the P2 component and the VESP. It can be seen that the results are not totally concordant. Some albinos whose VECP showed contralateral lateralisation, showed ipsilateral lateralisation of the VESP and, moreover, the two whose VECP showed ipsilateral lateralisation actually showed contralateral lateralisation of the VESP. These results indicate the independence of the two responses, and presumably their independent sources.

7.5 Topographical studies

Further evidence for the independence of the VECP and VESP was obtained during topographical studies of the scalp distribution of the VESP. Such examination was initially undertaken to confirm the existence of two forms of albino lateralisation. For this purpose two albinos were chosen for investigation these being subject 11 and 17 whose VESPs had been shown to consistently show contralateral and ipsilateral monocular lateralisation respectively (see Section 7.1).

The array of scalp electrodes used was similar to that

Table 7.7

Relationship between the Lateralisation of the VESP and P2 Component of the Flash VECP in the Albino Group.

The lateralisation of the VESP on the basis of the P23N28 and N28P34 amplitude measures and the latency of the P2 flash VECP component is given for each albino subject. (See text for further details).

SUBJECT	MONOCULAR LATERALISATION	
	P2 Latency	VESP
1	C	I
2	C	I
3	C	I
4	C	C
5	I	C
6	C	I
7	I	C
8	C	C
9	C	I
10	C	I
11	C	C
12	C	C
13	C	I
14	C	I
15	C	I
17	C	I
18	C	I
19	C	C
21	C	I
22	C	C
23	C	C

Key: C = Contralateral lateralisation on monocular stimulation.

I = Ipsilateral lateralisation on monocular stimulation.

employed by Harding and Rubinstein (1980a) and Rubinstein (1981) during the early VESP studies. Anterior-posterior and transverse montages were used; these are illustrated schematically in Figure 7.15.

In each montage high mastoid electrodes were included as routinely employed in VESP recordings (these are referred to in following figures as A1 and A2). In the anterior-posterior montage additional electrodes were attached at F7, F8, T5, T6, O1 and O2. In the transverse montage half-distance electrodes were employed at T3½, T4½, CP3, CP4, CP5 and CP6 (Harding and Rubinstein 1980a; Rubinstein and Harding 1981).

The VESPs were recorded using the parameters described previously and with Cz as the common reference. As recordings could only take place on 8 channels at any one time, separate recordings were made from the anterior-posterior and transverse montages. Binocular and monocular responses were recorded each repeated twice using each montage to check repeatability.

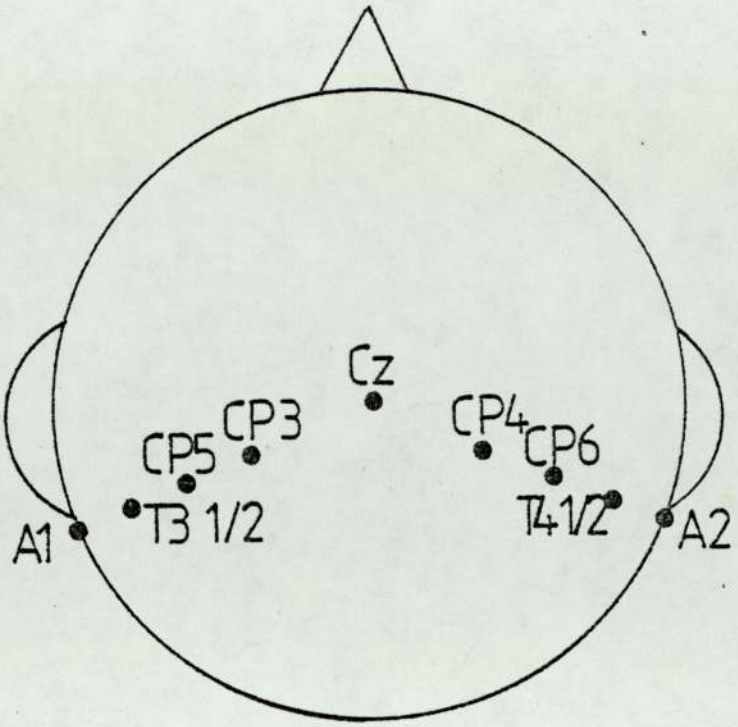
To aid interpretation of the following diagrams, the P23 and P34 components of the VESPs are approximately indicated by dotted lines. All transverse recordings are drawn from right to left with the top trace representing that from A2 and the final trace A1. Anterior-posterior recordings are drawn in a clockwise direction commencing at F8, i.e. from right anterior to right posterior then left posterior

Figure 7.15

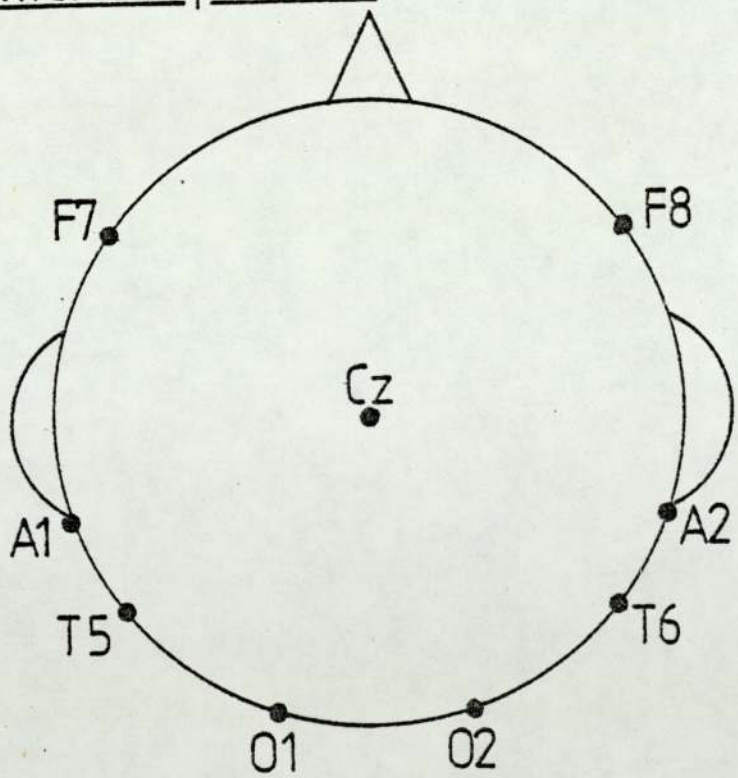
Electrode Sites Used for Topographical Investigations of the VESP

See text for further details.

Transverse



Anterior – posterior



to left anterior.

7.5.1 Transverse recordings

The VESPs recorded on binocular stimulation using this derivation in the two albinos are illustrated in Figure 7.16. As found on previous occasions the response from subject 11 was not as clearly defined as that from subject 17. In the former the VESP is clearer over the left compared to the right with a decrease in amplitude from A1 to the midline while in the latter a response is visible on every channel with greater amplitude at sites A1, A2, T3½ and T4½ with a gradual reduction from more centrally placed electrodes.

The monocular responses of subject 11 are shown in Figure 7.17 and, as expected, contralateral lateralisation of the response was present. On stimulation of the right eye clear VESPs are only present on the four channels recording over the left hemisphere; over the right hemisphere the response is virtually absent. On stimulation of the left eye the responses over the left hemisphere are less clearly defined while over the right a VESP is apparent. In both monocular responses a second lateralisation feature is also present. The later and larger components of the response show clear polarity reversal about the midline on each occasion. This reversal itself changes in polarity when stimulation is changed from one eye to the other.

The monocular responses from the transverse row of occipital

Figure 7.16

The Binocular VESPs Recorded Using a Transverse Montage in Albinos 11 and 17

The binocular responses of each subject are shown. The VESP (between the dotted lines) of subject 11 is not as clear as that of subject 17. See text for further details. (Flash intensity 8, 5 flashes per second, 500 sweeps).

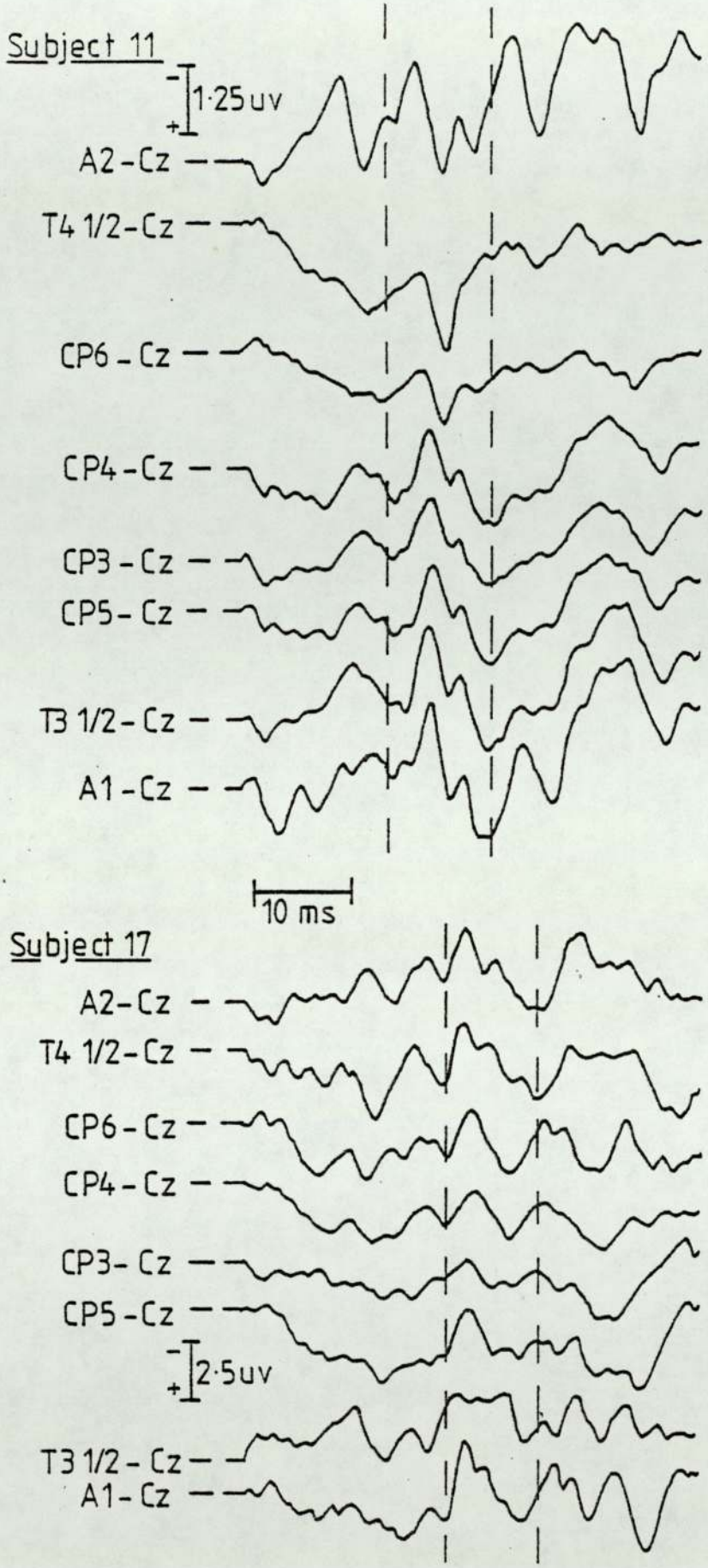
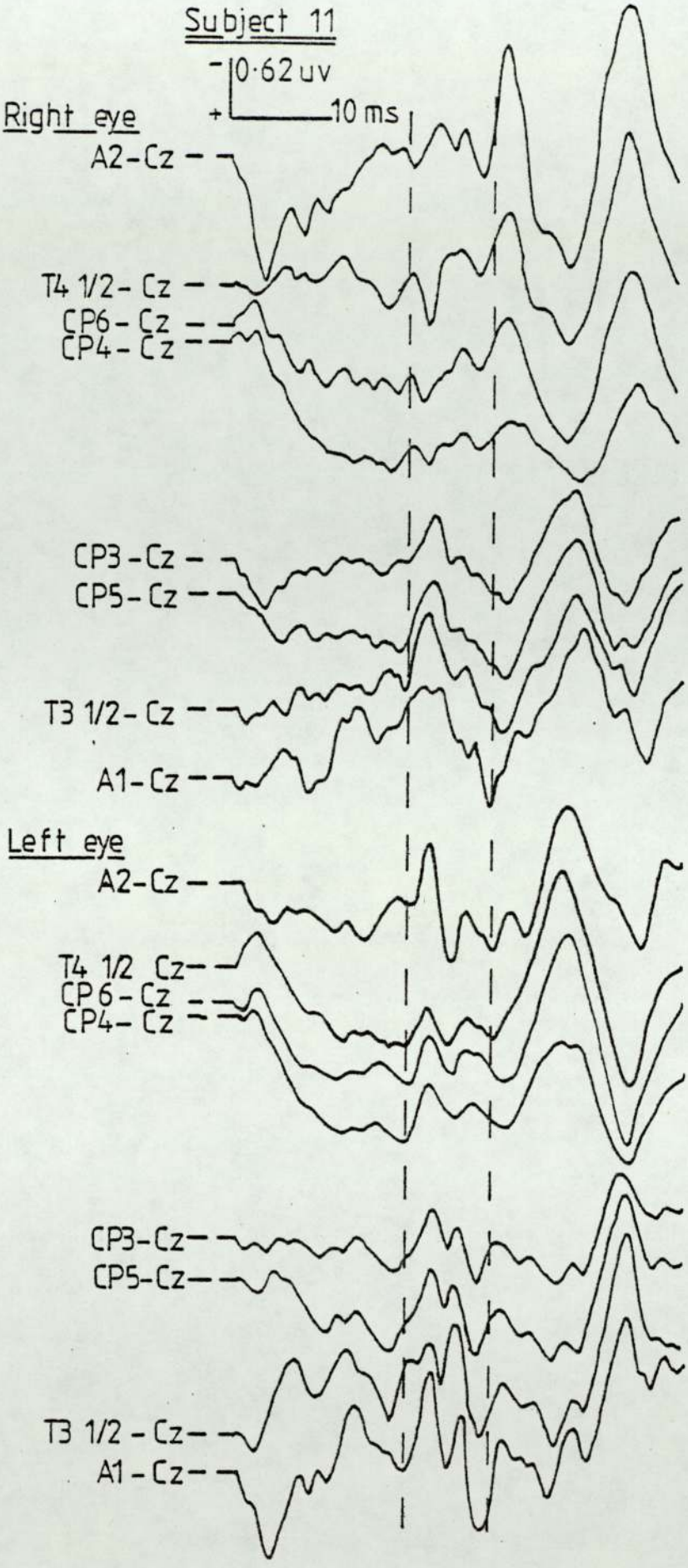

Subject 11
1·25 uv
A2 - Cz
T4 1/2 - Cz
CP6 - Cz
CP4 - Cz
CP3 - Cz
CP5 - Cz
T3 1/2 - Cz
A1 - Cz
10 ms
Subject 17
A2 - Cz
T4 1/2 - Cz
CP6 - Cz
CP4 - Cz
CP3 - Cz
CP5 - Cz
2·5 uv
T3 1/2 - Cz
A1 - Cz

Figure 7.17

The Monocular VESPs Recorded from a Transverse Montage in Albino 11

The VESP (between the dotted lines) is seen to lateralise contralaterally on monocular stimulation. In addition the later part of the response undergoes polarity reversal about the midline. See text for further details. (Flash intensity 8, 5 flashes per second, 500 sweeps).


Subject 11
0·62 uv
10 ms
Right eye
A2-Cz
T4 1/2-Cz
CP6-Cz
CP4-Cz
CP3-Cz
CP5-Cz
T3 1/2-Cz
A1-Cz
Left eye
A2-Cz
T4 1/2 Cz
CP6-Cz
CP4-Cz
CP3-Cz
CP5-Cz
T3 1/2-Cz
A1-Cz

electrodes in subject 17 are shown in Figure 7.18. Here, as expected, clear ipsilateral lateralisation of the VESP is seen the VESP being only definable in each case over the four channels ipsilateral to the eye stimulated. The polarity reversal about the midline of the later components seen in subject 11 is also present in the responses of this albino.

7.5.2 Anterior-posterior recordings

The binocular responses recorded from the two albinos using this montage are shown in Figure 7.19. Again the responses of subject 17 are clearer than those from subject 11. The recordings from the two frontally placed electrodes (F7 and F8) show large deflections representing the ERG (Harding and Rubinstein 1980a; Rubinstein and Harding 1981). At the more posteriorly placed sites (O1 and O2) recording from the occipital cortices a large late positive component (indicated by the solid line in Figure 7.19) is seen.

This component is present with a lesser amplitude at T5 and T6 but is absent at derivations A1, A2, F7 and F8.

The monocular responses of albino 11 are shown in Figure 7.20. The ERG recorded at F7 and F8 shows ipsilateral lateralisation while the VESP shows the expected contralateral lateralisation. Similarly, the occipital response also shows contralateral lateralisation (see solid line). The late positive component seen over both hemispheres on binocular

Figure 7.18

The Monocular VESPs Recorded from a Transverse Montage in Albino 17.

The VESP (between dotted lines) lateralises ipsilaterally on monocular stimulation. In addition the later part of the response undergoes polarity reversal about the midline. See text for further details. (Flash intensity 8, 5 flashes per second, 500 sweeps).

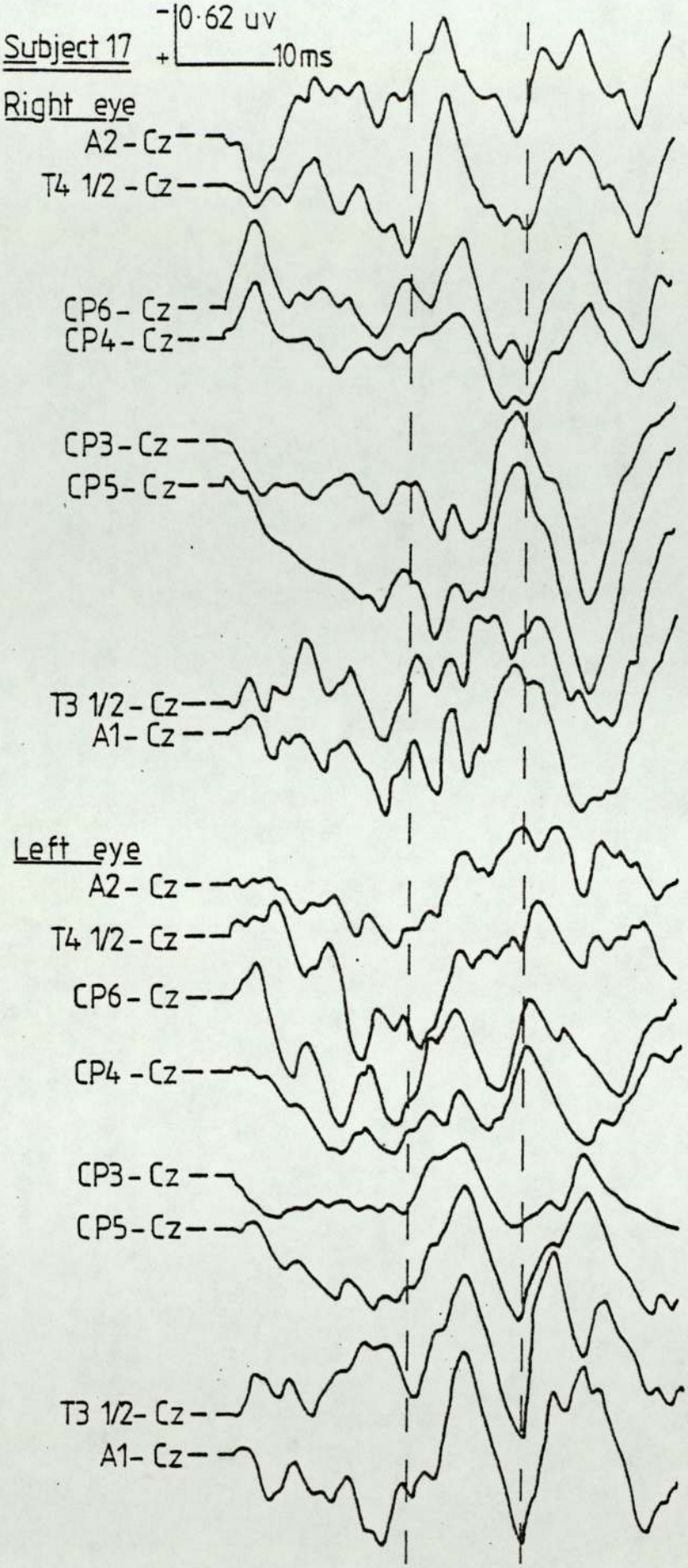

Subject 17
0·62 uv
10 ms
Right eye
A2 - Cz
T4 1/2 - Cz
CP6 - Cz
CP4 - Cz
CP3 - Cz
CP5 - Cz
T3 1/2 - Cz
A1 - Cz
Left eye
A2 - Cz
T4 1/2 - Cz
CP6 - Cz
CP4 - Cz
CP3 - Cz
CP5 - Cz
T3 1/2 - Cz
A1 - Cz

FIGURE 7.19

The Binocular VESPs Recorded Using an Anterior-Posterior Montage in Albinos 11 and 17

The VESP is shown between the dotted lines. The frontal electrodes F7 and F8 record the ERG while the occipital electrodes O1 and O2 record a late bilateral positive wave shown by the solid line. See text for further details. (Flash intensity 8, 5 flashes per second, 500 sweeps)

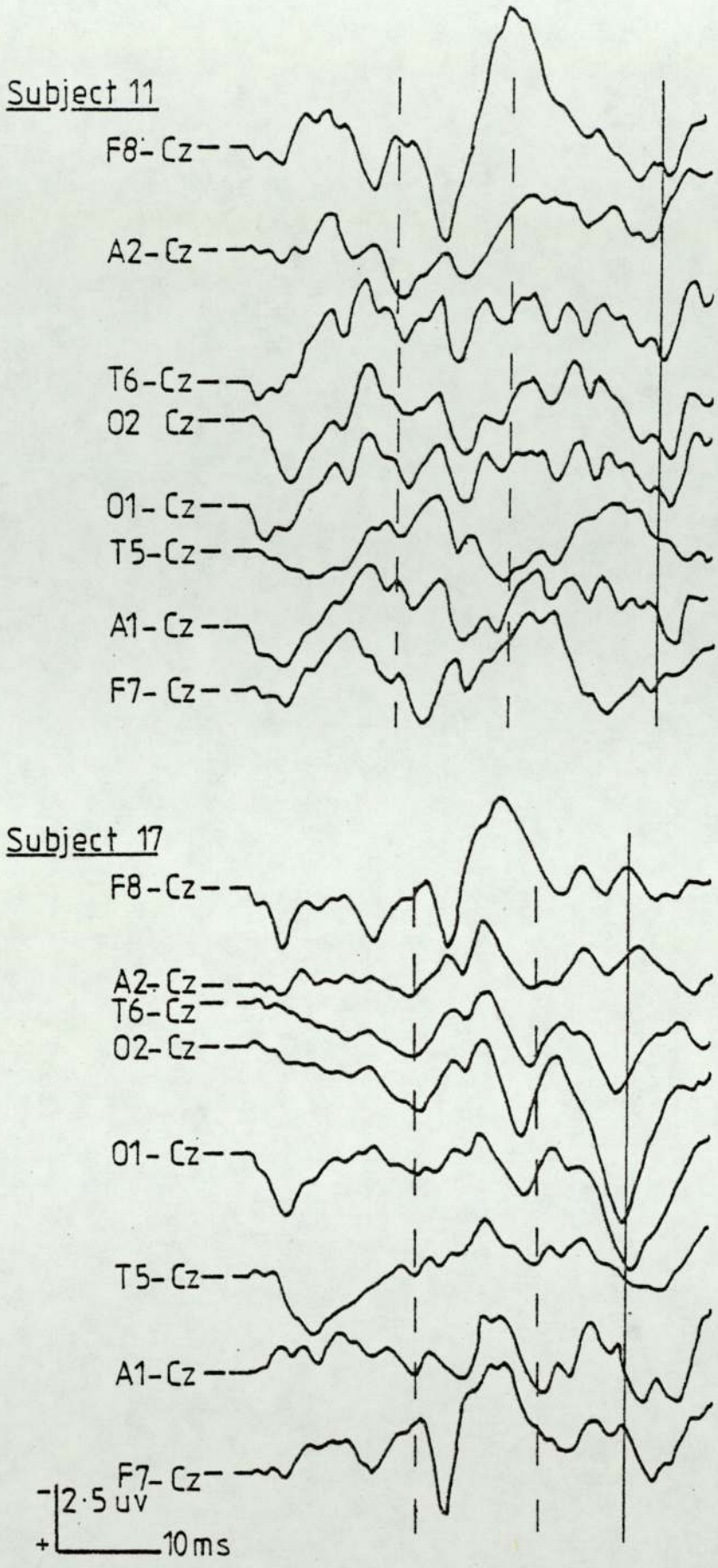
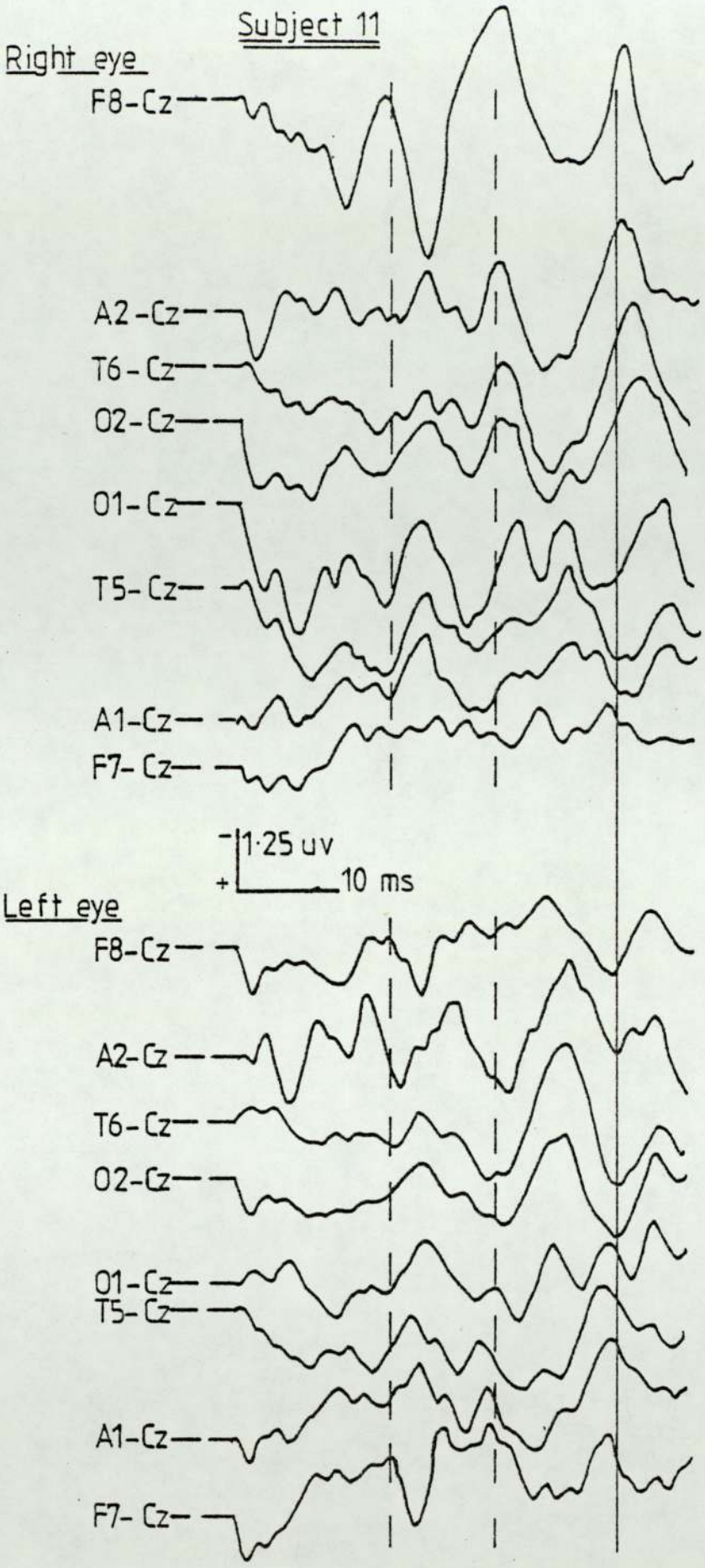

Subject 11
F8-Cz
A2-Cz
T6-Cz
O2 Cz
O1-Cz
T5-Cz
A1-Cz
F7-Cz
Subject 17
F8-Cz
A2-Cz
T6-Cz
O2-Cz
O1-Cz
T5-Cz
A1-Cz
F7-Cz
2·5 uv
10 ms

Figure 7.20

The Monocular VESPs Recorded Using an Anterior Posterior Montage in Albino 11

The VESP (between the dotted lines) undergoes contralateral lateralisation on monocular stimulation. The ERG recorded at electrodes F7 and F8 shows ipsilateral lateralisation while the late positive recorded at O1 and O2 shows contralateral lateralisation (solid line). See text for further details. (Flash intensity 8, 5 flashes per second, 500 sweeps).


Subject 11
Right eye
F8-Cz
A2-Cz
T6-Cz
O2-Cz
O1-Cz
T5-Cz
A1-Cz
F7-Cz
1·25 uv
10 ms
Left eye
F8-Cz
A2-Cz
T6-Cz
O2-Cz
O1-Cz
T5-Cz
A1-Cz
F7-Cz

stimulation is only present contralaterally on monocular stimulation. The ipsilateral response is poorly formed with a tendency towards replacement by a negative wave giving the impression of polarity reversal.

The monocular responses of subject 17 are shown in Figure 7.21. As found in subject 11 the ERG shows ipsilateral lateralisation. In addition clear ipsilateral lateralisation of the VESP is seen. However the response from the occipital region shows contralateral lateralisation. As indicated by the solid line a clear late positive component is only found contralaterally with a negative component on ipsilateral channels.

A final check on the lateralisation of the VESP was then undertaken. The bipolar A1-A2 binocular and monocular responses were derived for albinos 11 and 17 from the many responses previously recorded and stored on floppy discs. This removes possible influence from the reference electrode Cz and should confirm that two opposing forms of the VESP lateralisation are indeed present within the albino population. Typical examples of the resulting bipolar responses are shown in Figure 7.22.

In albino 11 contralateral lateralisation of the response is seen with polarity reversal of the right and left eye responses. In subject 17 polarity reversal is also found between the two monocular responses but the direction of the reversal is precisely opposite to that found in subject 11 and indicative of ipsilateral monocular lateralisation.

Figure 7.21

The Monocular VESPs Recorded Using an Anterior Posterior Montage in Albino 17

The VESP (between the dotted lines) shows ipsilateral monocular lateralisation as does the ERG recorded at F7 and F8. However, the occipital late positive shown by the solid line undergoes contralateral lateralisation. See text for further details. (Flash intensity 8, 5 flashes per second, 500 sweeps).

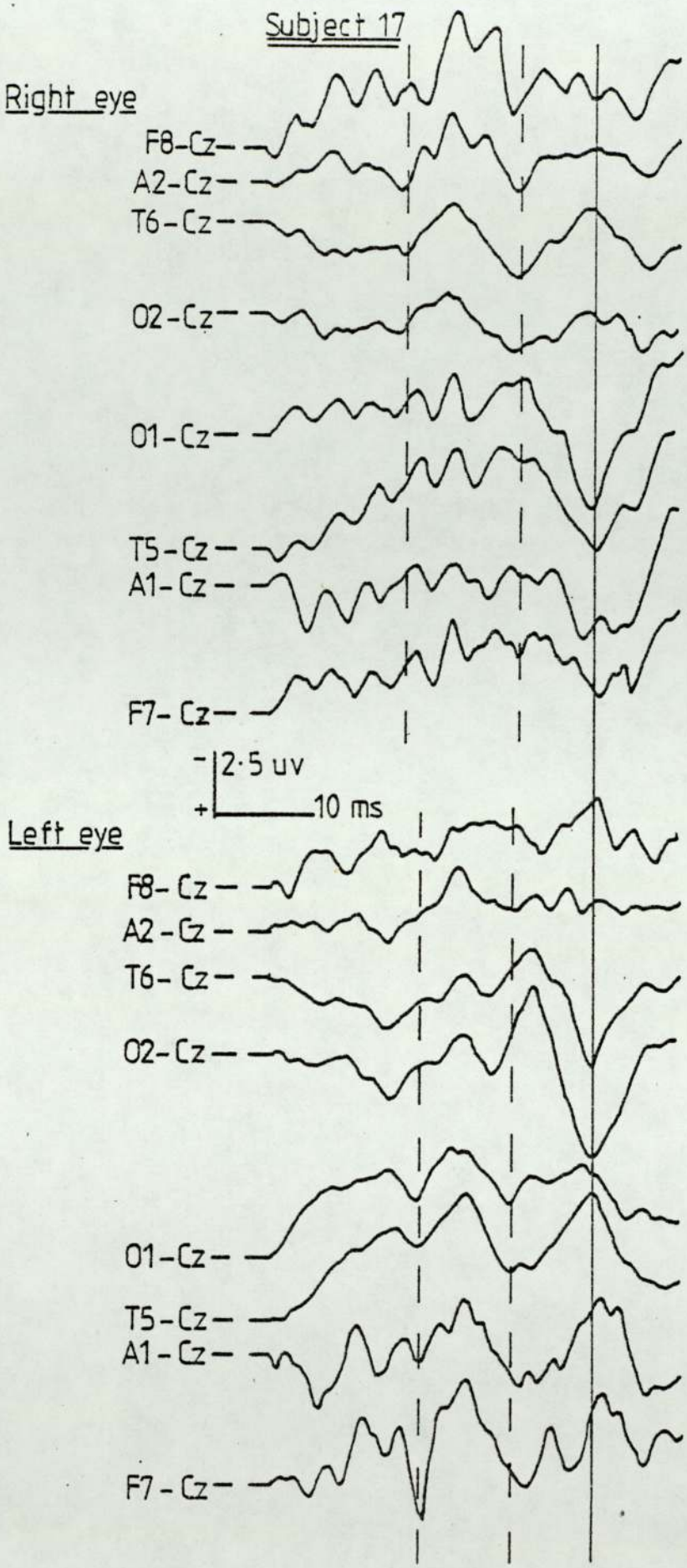
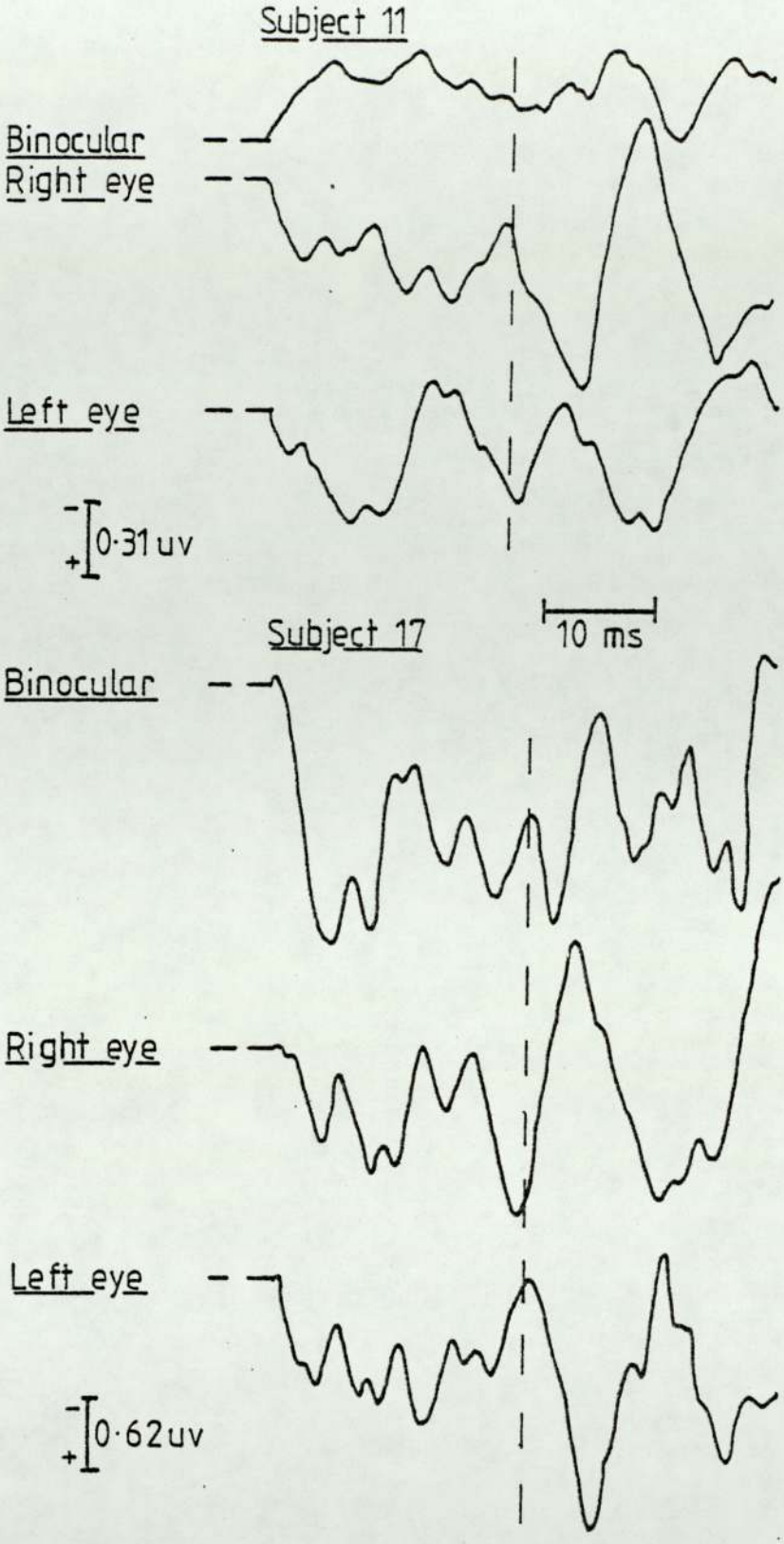

Subject 17
Right eye
F8-Cz
A2-Cz
T6-Cz
O2-Cz
O1-Cz
T5-Cz
A1-Cz
F7-Cz
2·5 uv
10 ms
Left eye
F8-Cz
A2-Cz
T6-Cz
O2-Cz
O1-Cz
T5-Cz
A1-Cz
F7-Cz

Figure 7.22

Bipolar A1-A2 VESPs found in Albinos 11 & 17

The binocular and monocular responses are shown. The two monocular responses of each subject show polarity reversal (dotted line) but in opposite directions such that subjects 11 and 17 show contralateral and ipsilateral lateralisation respectively. (See text for further details).



All channels A1-A2

7.6 The VESPs of albino 20

The binocular and monocular responses recorded from this subject are shown in Figure 7.23. To ensure some independent evaluation, the responses of this subject had been included in those given to the blind scorer (see 7.3.1). The scorer was unaware of this at the time so that any observations made were independent of the fact that the subject was an albino and, in addition, displayed a gross field defect of the right eye. The binocular responses of this subject are poorly formed but the scorer considered the VESP to undergo ipsilateral lateralisation on monocular stimulation; as shown in Figure 7.23 the amplitude of the response is slightly greater over the right hemisphere on right eye stimulation and over the left hemisphere on left eye stimulation particularly with respect to the N28-P34 component. A further comment made by the blind scorer was that the response had a shorter latency on stimulation of the left eye compared to the right. This was the only subject, albino or control, who produced such comments about the latency of the responses from the blind scorer.

7.7 Summary

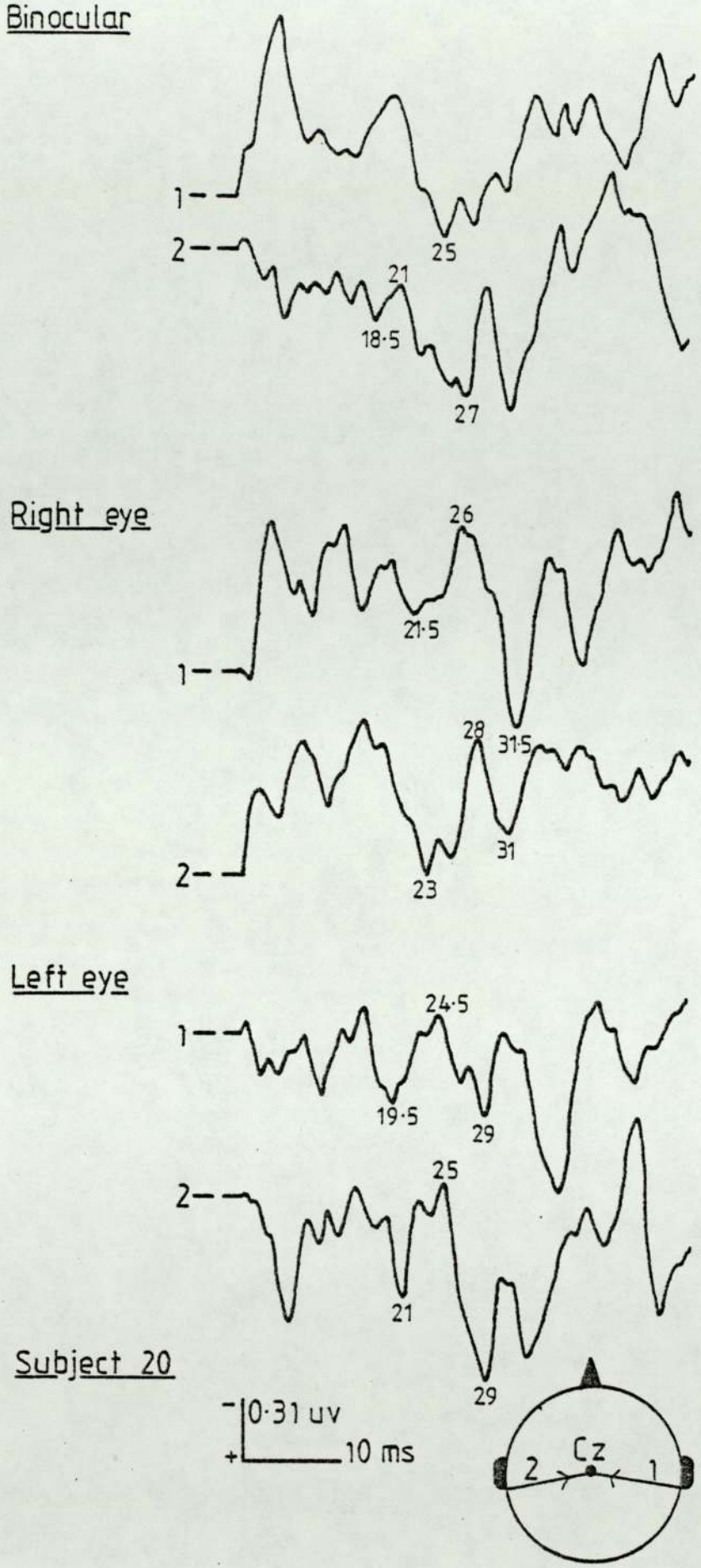
The following observations can be made regarding the VESPs recorded in the albinos and their controls:

1) Both contralateral and ipsilateral lateralisation of the response is found within both the albino and control populations with no obvious statistical significance between

Figure 7.23

The Binocular and Monocular VESPs REcorded in Albino 20

The blind scorer considered the responses to undergo ipsilateral lateralisation on monocular stimulation. In addition the responses from the left eye have a shorter latency than those from the right eye which showed a gross visual field defect. See text for further details. (Flash intensity 8, 5 flashes per second, 750 sweeps).


Binocular
1
2
25
21
18·5
27
Right eye
26
21·5
1
28
31·5
31
2
23
Left eye
24·5
1
19·5
29
25
2
21
29
Subject 20
0·31 uv
10 ms
Cz
2
1

the numbers showing the two patterns in the two groups. However, there is a tendency for the amount of lateralisation, either contralateral or ipsilateral, to be of a slightly greater amount in the albino population.

2) The existence of the two forms of monocular lateralisation can be confirmed by topographical studies and the observation of bipolar derivations.

3) The lateralisation of the VESP is independent of that of the VECP. This can be seen by comparison with the flash VECP P2 latency data and in topographical studies by recordings from occipital sites.

CHAPTER EIGHT

8 RESULTS IV : ALBINO BABY STUDIES

During the course of this study we had the opportunity of examining three albino babies. All were born at full-term and had been diagnosed as possessing oculocutaneous albinism. Each of these subjects is given a number (see Table 8.1), and will be subsequently referred to by this number. No matched control subjects were obtained so that examination of the results obtained from these babies will necessarily be qualitative in nature.

The clinical findings in each subject are shown in Table 8.1. Subjects 24 and 25 were males and 26 a female; and subject 25 was in fact the offspring of subjects 1 and 2 of the previous study.

The flash VECPs and VESPs of each subject were recorded and on each occasion the repeatability of the responses was checked by recording each response at least twice.

8.1 Subject 24

Initially, subject 24, a 7 months old male oculocutaneous albino was examined and from these results it became apparent that misrouting can manifest itself in VEP recordings at an early age.

This subject had slow, wandering nystagmus but no evidence

Table 8.1

Observations Made on each Visit of the Albino Babies

The findings on each visit are given for the albino babies examined. (See text for further details).

NUMBER	1ST VISIT	2ND VISIT	3RD VISIT
24 Male	Age - 7 months No strabismus Slow, wandering nystagmus		
25 Male	Age - 1 month No strabismus No nystagmus	Age - 4½ months No strabismus No nystagmus	Age - 8 months No strabismus Slow, wandering nystagmus
26 Female	Age - 1 month No strabismus No nystagmus	Age - 4½ months No strabismus No nystagmus	Age - 10 months No strabismus No nystagmus

of a squint could be found using the Hirschberg test. The flash VECP responses on binocular and monocular stimulation are shown in Figure 8.1. Binocular responses were dominated by a major positive component at 162-165ms, present over both hemispheres but of greater amplitude over the left compared to the right. On monocular stimulation, as illustrated in Figure 8.1., this major positive component lateralised over the hemisphere contralateral to the eye stimulated with attenuation over the ipsilateral hemisphere. The flash VECP results from this subject therefore followed the pattern of lateralisation expected in albino subjects.

Flash VESPs were easily recorded in this subject and these responses also showed monocular lateralisation of the contralateral type. This is illustrated in Figure 8.2. On binocular stimulation bilateral VESPs were recorded but on monocular stimulation the only consistent responses were those found on the channel contralateral to the eye stimulated. As in the case of the older subjects examined, lateralisation of the VESP was confirmed by superimposition of two or more responses.

Following examination of this subject two further oculocutaneous albino babies were examined initially at one month of age and at intervals after this. As shown in Table 8.1. these were subjects 25 and 26 male and female respectively. The clinical findings in these subjects at each visit are shown in Table 8.1. The VEP findings in

Figure 8.1

The Flash VECPs of Albino 24

The binocular and monocular responses recorded in this baby at 7 months of age are illustrated. The binocular response can be seen to be dominated by a bilateral major positive component at 162-165 ms preceded by an earlier negative. On monocular stimulation the positive component lateralises over the contralateral hemisphere. (Flash intensity 2, 1 flash per second, 50 sweeps).

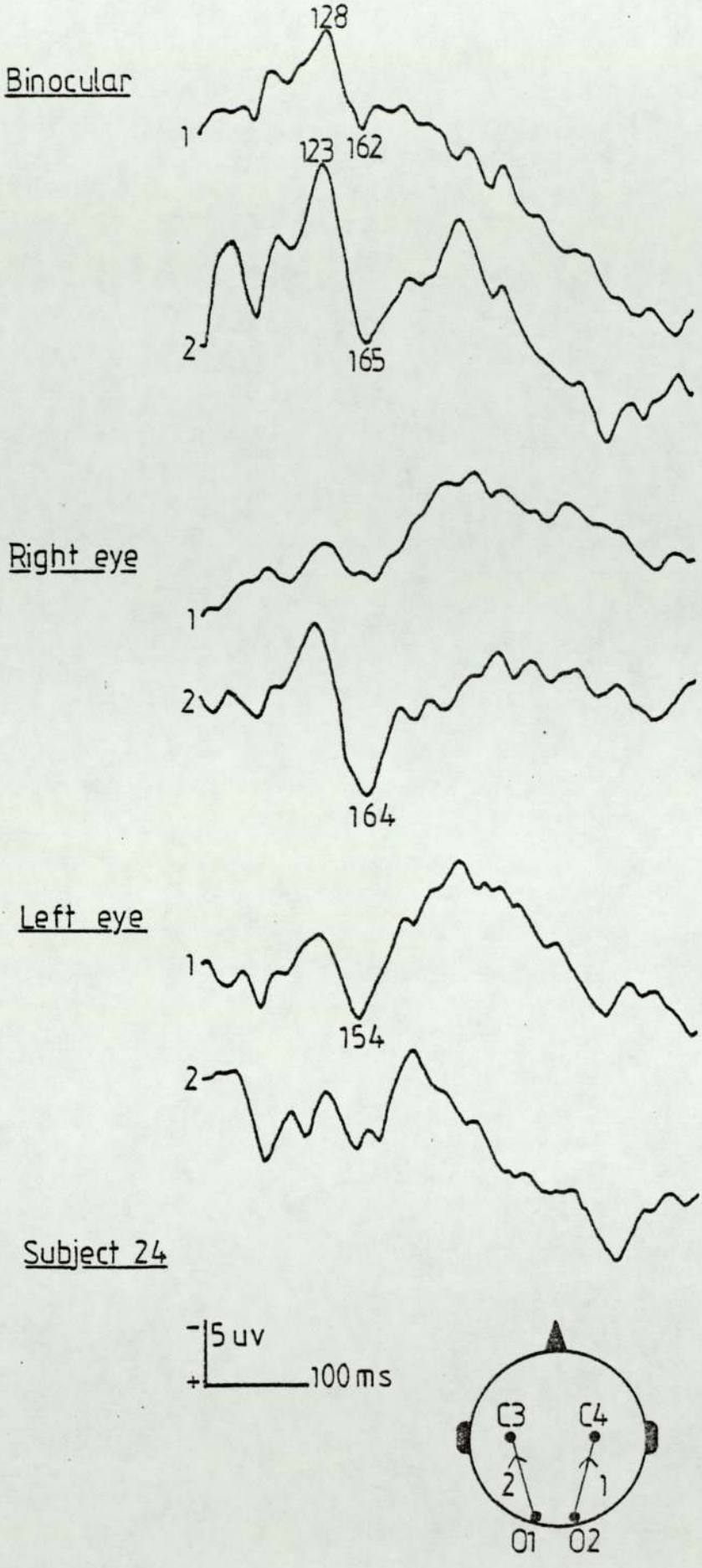
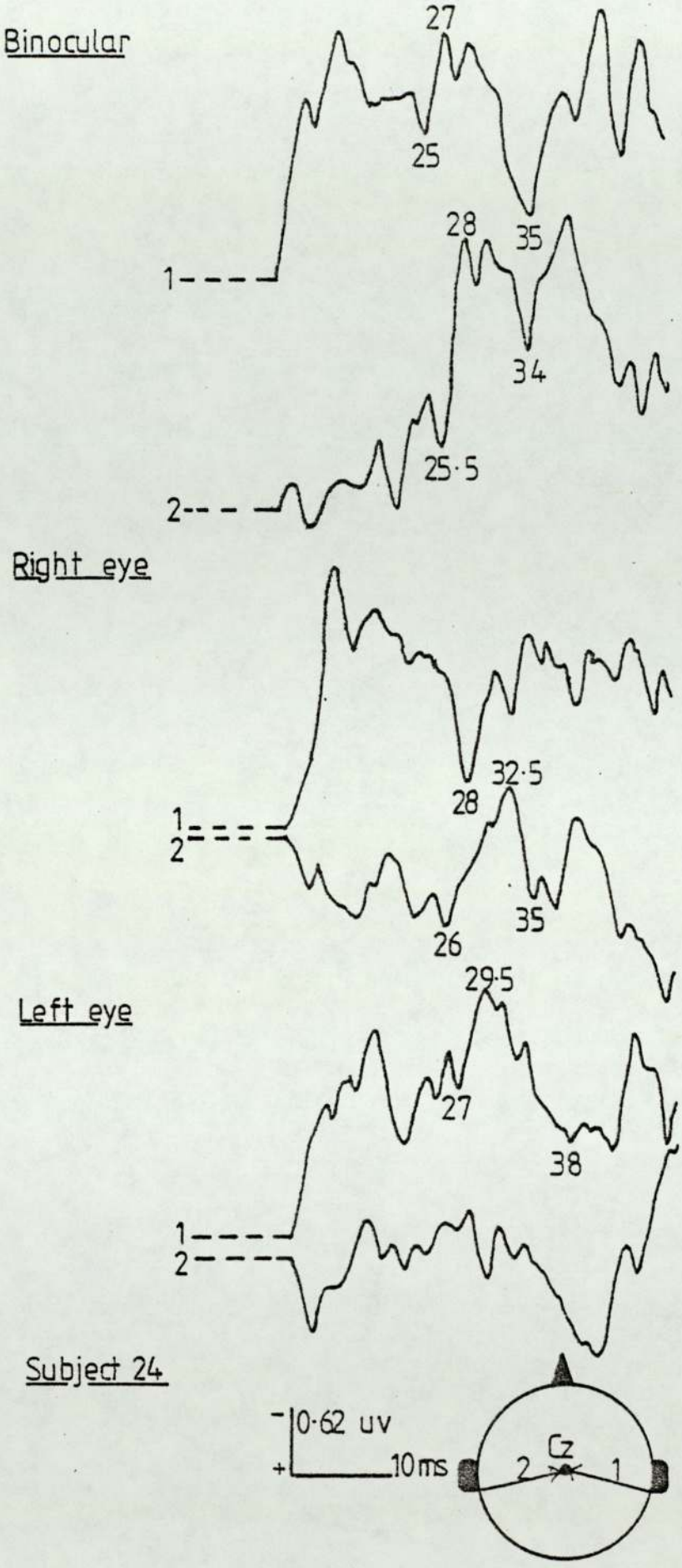

Binocular
128
1
123
162
2
165
Right eye
1
2
164
Left eye
1
154
2
Subject 24
5 uv
100 ms
C3
C4
2
1
O1
O2

Figure 8.2

The Flash VESPs of Albino 24

The binocular and monocular responses are shown. On binocular stimulation bilateral VESPs can be seen; the latencies of the components are labelled. On monocular recording the VESP complex is only clearly present contralateral to the eye stimulated. (Flash intensity 8, 5 flashes per second, 500 sweeps).


Binocular
27
25
28
35
34
1
2
25·5
Right eye
32·5
28
1
2
26
35
Left eye
29·5
27
38
1
2
Subject 24
0·62 uv
10 ms
Cz
2
1

each subject will be considered first with regard to the flash VECP and secondarily the flash VESP.

8.2 Subjects 25 and 26

8.2.1 The flash VECP

On the initial visit both babies were one month of age; neither subject appeared to display nystagmus or a strabismus. The VECPs recorded at this age in both albinos are illustrated in Figure 8.3. In this diagram, part (a) shows the responses of subject 25. The binocular response of this baby was dominated by a positive component at 265-274ms present over both hemispheres. On monocular stimulation the amplitude of this major component became attenuated over the hemisphere ipsilateral to the eye stimulated. Figure 8.3(b) shows the responses of subject 26. In this case the binocular response was dominated by a positive component at 215ms present primarily over the right hemisphere. On stimulation of the right eye the latency of this component increased to 310ms over the right hemisphere while over the left a positive component at 138ms appeared. Conversely, on left eye stimulation, the latency of the major positive component over the right hemisphere decreased to 231ms while over the left the latency increased.

On the second visit, both babies were 4.5months of age and, again, no nystagmus or strabismus was seen. The responses recorded at these visits are shown in Figure 8.4. In subject 25, as shown in 8.4(a), on binocular stimulation

FIGURE 8.3

The Flash VECPs of Albinos 25 and 26 at one month of age

The binocular and monocular responses of both babies are shown. (a) illustrates the responses of subject 25. In this case the binocular response is dominated by a positive component at 265-274ms. On monocular stimulation the amplitude of this component is attenuated over the ipsilateral hemisphere. The responses of subject 26 are illustrated in (b); in this subject the binocular response is dominated by a positive component at 215ms present primarily over the right hemisphere. On monocular stimulation contralateral lateralisation of the response is found. (Flash intensity 2, 1 flash per second, 50 sweeps)

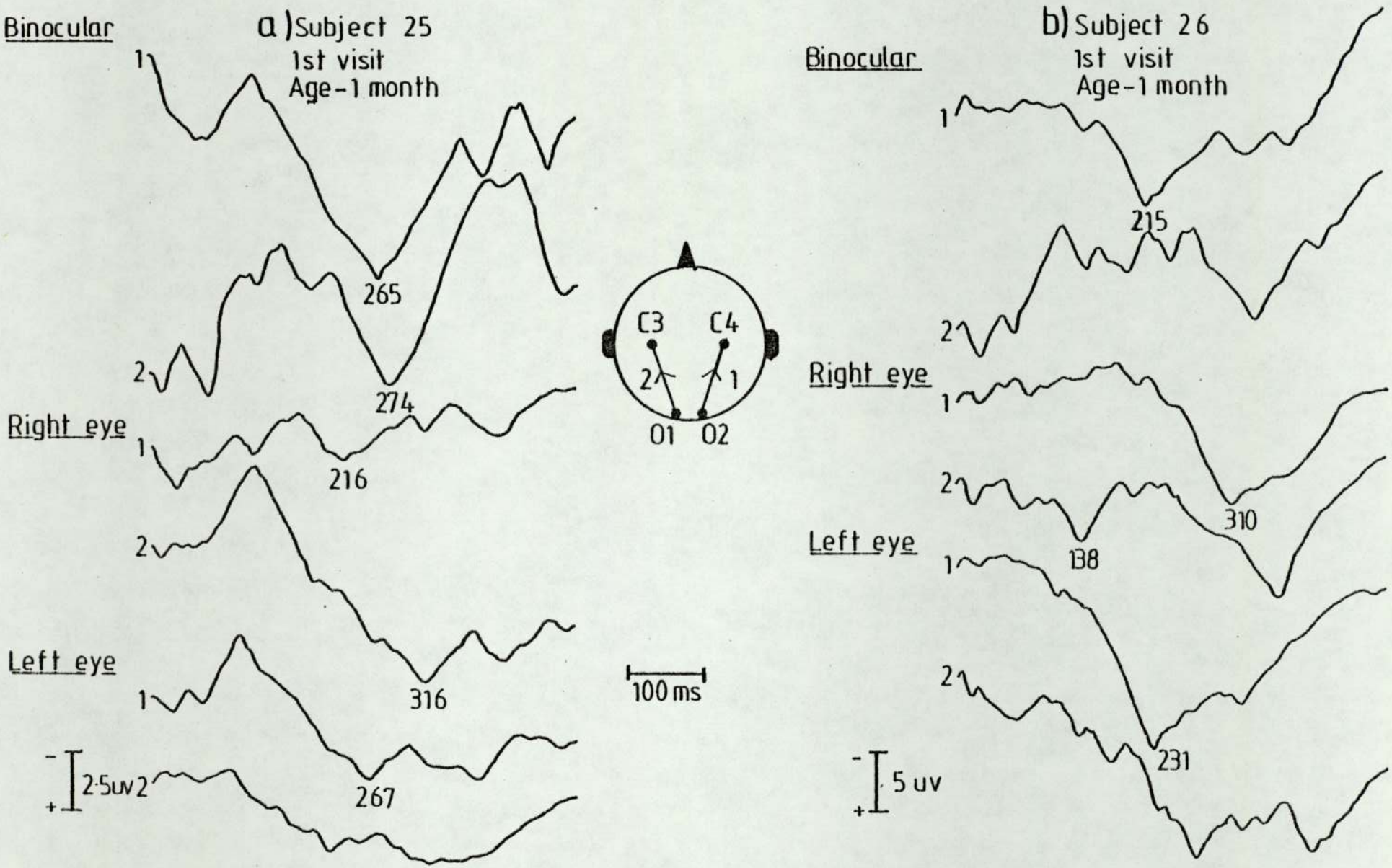
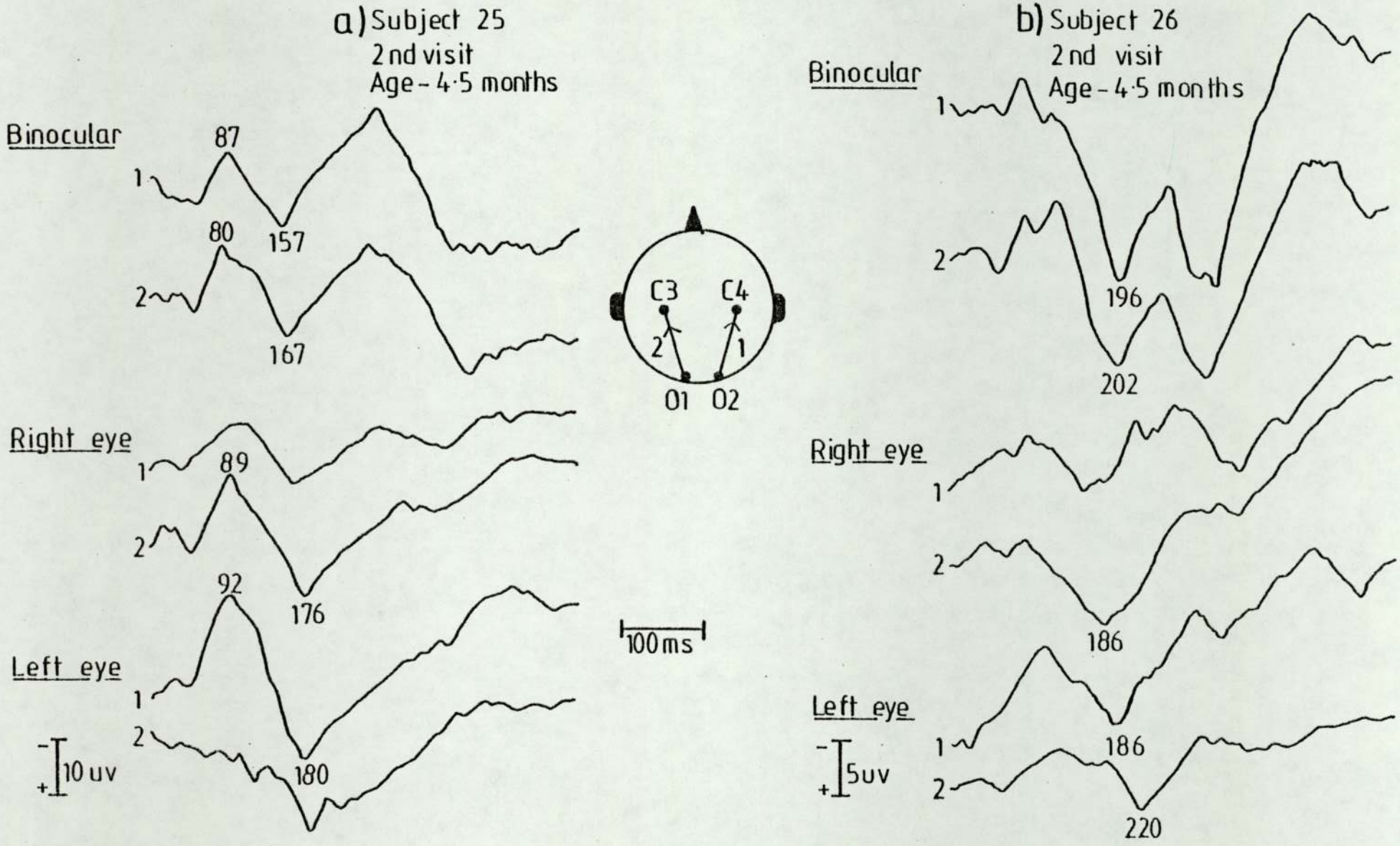

Binocular
a) Subject 25
1st visit
Age-1 month
1
265
2
274
Right eye
1
216
2
Left eye
1
316
267
2·5uv2
C3
C4
2
1
O1
O2
100 ms
b) Subject 26
1st visit
Age-1 month
Binocular
1
215
2
Right eye
1
310
2
138
Left eye
1
2
231
5 uv

Figure 8.4

The Flash VECPs of Albinos 25 and 26 at 4.5 Months of Age

Again (a) shows the responses of baby 25. On binocular stimulation a bilateral positive component at 157-167 ms is found preceded by an earlier clear negative. On monocular stimulation both these components are more clearly formed over the hemisphere contralateral to the eye stimulated. (b) illustrates the responses of baby 26. In this case the binocular response is somewhat triphasic in waveform with an early positive at 196-202 ms followed by a later positive. It is the earlier of the two which lateralises over the contralateral hemisphere on monocular stimulation. (Flash intensity 2, 1 flash per second, 50 sweeps).


a) Subject 25
2nd visit
Age - 4·5 months
Binocular
87
80
157
167
Right eye
89
176
Left eye
92
180
10 uv
C3
C4
2
1
O1
O2
100 ms
b) Subject 26
2nd visit
Age - 4·5 months
Binocular
196
202
Right eye
186
Left eye
186
220
5uv

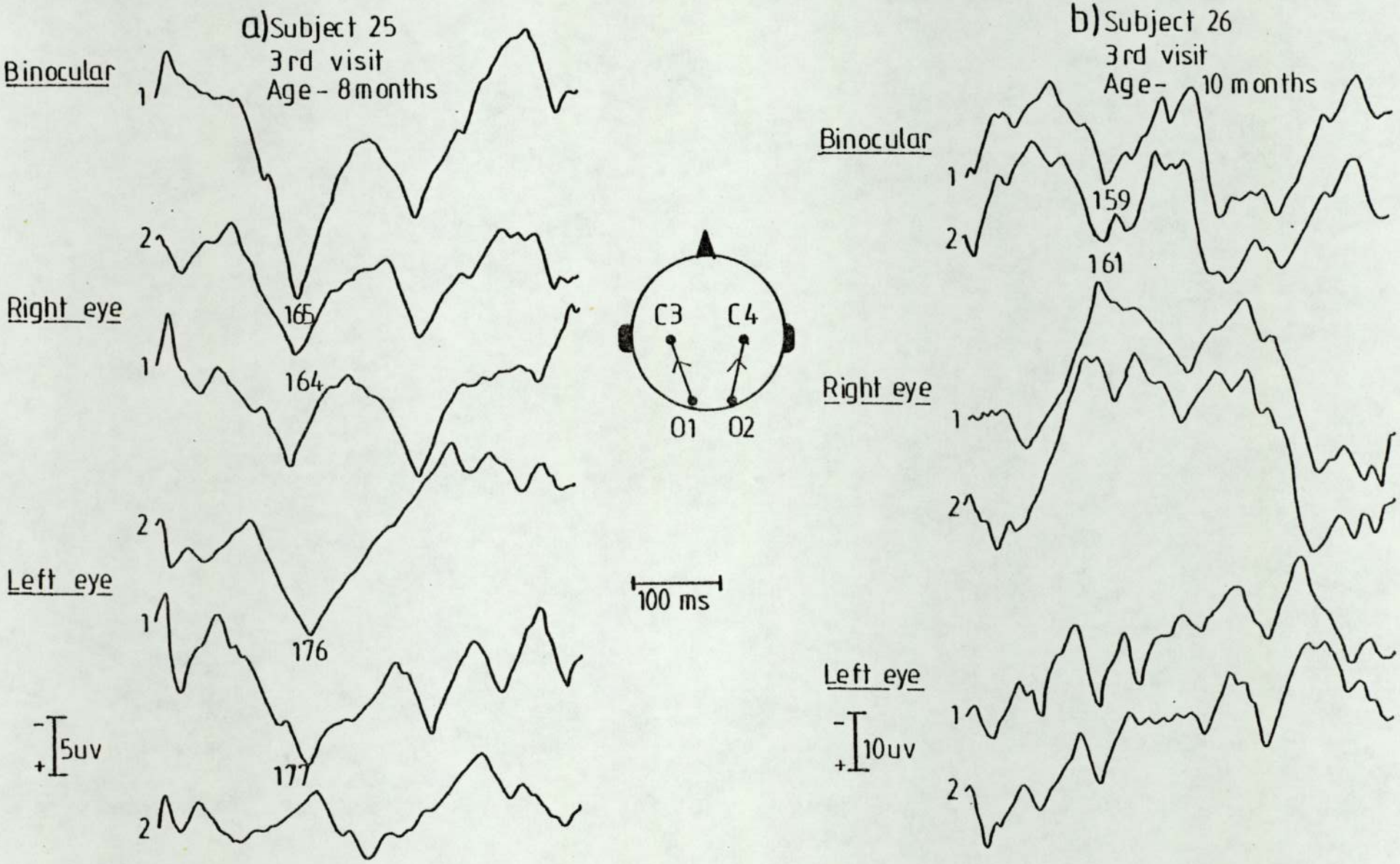
the latency of the major positive component had decreased to 157-167ms preceded by an earlier negative at 80-87ms; such a waveform was present over both hemispheres. In agreement with the findings at one month of age, it can be seen that on monocular stimulation the response became attenuated over the ipsilateral hemisphere. At the same age the binocular response of subject 26 was somewhat triphasic in form with an initial major positive at 196-202ms (see Figure 8.4 part b). This component appears to lateralise over the contralateral hemisphere on monocular stimulation.

On the third and final visits (see Figure 8.5), subject 25 was 8 months of age and subject 26, 10 months (the recordings in the latter had to be delayed due to the baby contracting chickenpox). On these visits neither subject showed a strabismus. Nystagmus was still absent in subject 26 but baby 25 had developed a slow, wondering nystagmus of varying amplitude. In the latter subject the binocular VECP again showed a major positive component at 164-165ms present over both hemispheres; this is seen in Figure 8.5(a). Again this component appeared to lateralise over the contralateral hemisphere on monocular stimulation. In Figure 8.5(b) it can be seen that by 10 months of age the latency of the major positive component recorded in subject 26 had reduced to 159-161ms and was present over both hemispheres on binocular stimulation. Unfortunately, on this visit the baby was extremely active and greatly objected to the covering of either eye. Consequently,

FIGURE 8.5

The Flash VECPs of Albinos 25 and 26
Aged 8 and 10 months respectively

In (a) it can be seen that the binocular response of baby 25 is dominated by a positive component at 164-165ms. On monocular stimulation this lateralises over the contralateral hemisphere. The binocular response of baby 26 are shown in (b); here again the response is dominated by a positive component at 159-161ms. Unfortunately the baby becomes very active during monocular recordings resulting in poorly formed responses with no clear evidence of hemispheric lateralisation. (Flash intensity 2, 1 flash per second, 50 sweeps).


a) Subject 25
3rd visit
Age - 8 months
Binocular
1
2
165
Right eye
1
164
2
Left eye
1
176
177
2
-
+
5uv
C3
C4
O1
O2
100 ms
b) Subject 26
3rd visit
Age - 10 months
Binocular
1
2
159
161
Right eye
1
2
Left eye
1
2
-
+
10uv

monocular responses were not as easily recorded as on previous visits and showed some variability when repeated. No clear monocular lateralisation could, therefore, be demonstrated on this occasion (Figure 8.5 part a).

8.2.2 The flash VESP

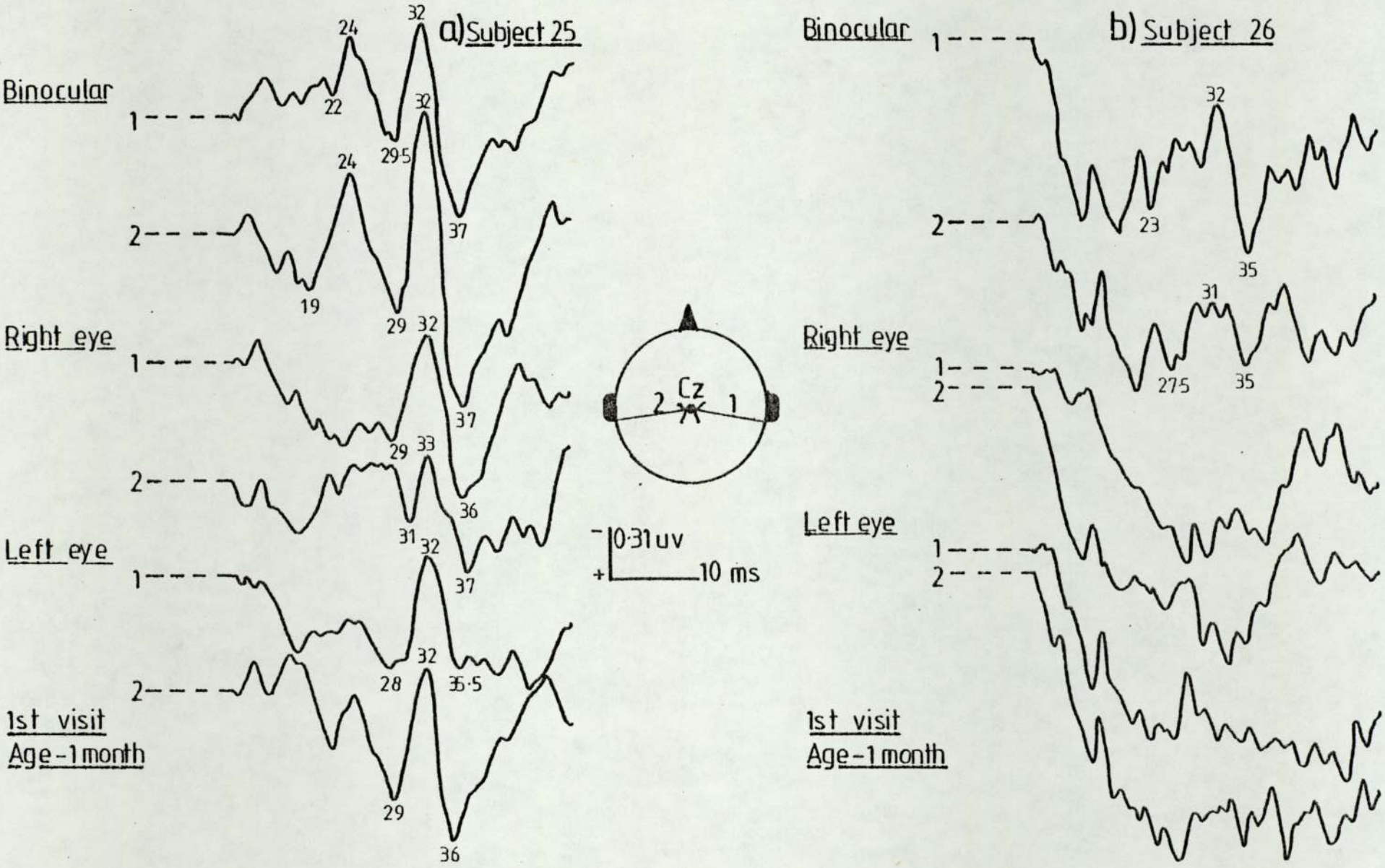
The binocular and monocular responses recorded in the two babies on each visit are illustrated in Figures 8.6, 8.7 and 8.8.

In subject 25, on the first visit at one month of age, bilateral VESPs were recorded on binocular stimulation; see Figure 8.6(a). Two possible configurations representing the VESP were found; an early triphasic wave at around P20, N24, P29 or a second, later configuration at P29, N32, P37. Which of these represents the true VESP is not clear due to the lack of data in babies of this age. The early components are more near the VESP latencies found in older subjects but it is possible that, in accordance with the increased VECP latencies at this age, that the latency of the P-N-P complex of the VESP is also increased. On monocular stimulation the later peaks were those most clearly seen and showed ipsilateral lateralisation on monocular stimulation. Figure 8.6(b) shows the VESPs recorded at one month of age in subject 26. On binocular stimulation a triphasic complex was repeatedly recorded bilaterally. However, on monocular stimulation the VESPs were less clearly seen with the absence of any clear lateralisation.

Figure 8.6

The Flash VESPs of Albinos 25 and 26 at One Month of Age

The responses of baby 25 are shown in (a). Binocular stimulation resulted in a bilateral complex with both early and late components either of which could form the true VESP. However, on monocular stimulation the early complex almost disappears while the later lateralises ipsilaterally. The responses of baby 26 are shown in (b). On binocular stimulation a bilateral VESP complex is seen but monocularly the complex is not clearly seen. (Flash intensity 8, 5 flashes per second, 500 sweeps).


a) Subject 25
Binocular
1
2
24
22
32
29·5
37
24
19
32
29
37
Right eye
1
29
33
31
32
36
37
2
Left eye
1
32
28
32
35·5
37
2
29
36
1st visit
Age-1 month
Cz
2
1
0·31 uv
10 ms
b) Subject 26
Binocular
1
2
23
32
35
31
27·5
35
Right eye
1
2
Left eye
1
2
1st visit
Age-1 month

The VESPs recorded at 4.5 months of age in subjects 25 and 26 are shown in Figure 8.7(a) and 8.7(b) respectively. In subject 25 the VESP was more clearly defined as a single peak. On monocular stimulation the response clearly lateralised ipsilaterally. In subject 26 the binocular responses were again clearly seen. On monocular stimulation, in contrast to the responses shown in 8.6, contralateral lateralisation of the VESP was found although this effect was more prominent on stimulation of the left eye compared to the right.

The responses recorded in subject 25 on the third visit are illustrated in Figure 8.8(a). At this time the baby became more active and as can be seen in the diagram the small VESPs became easily hidden in background noise. Despite repeated recordings and superimposition no true monocular lateralisation could be found. Figure 8.8(b) shows the VESPs recorded at the final visit of subject 26. In contrast to the recordings on subject 25, bilateral, binocular VESPs were easily recorded and again contralateral lateralisation on monocular stimulation was present.

In agreement with the findings in the older albino subjects, when examining the VESPs of the babies studied, the technique of superimposition of repeated responses proved essential not only for the identification of the response but also in the determination of the type of monocular lateralisation found. This lateralisation often manifests itself not only by the presence of a repeatable response

FIGURE 8.7

The Flash VESPs of Albinos 25 and 26 at 4.5 months of age

The responses of baby 25 are illustrated in (a). At this age the binocular VESPs are more clearly seen as a single peak which again lateralises ipsilaterally on monocular stimulation. (b) shows the responses of baby 26. Here, again, bilateral binocular VESPs are seen, and in contrast to the responses recorded at 1 month of age, clear monocular responses are seen. The latter appear to lateralise contralaterally. (Flash intensity 8, 5 flashes per second, 500 sweeps)

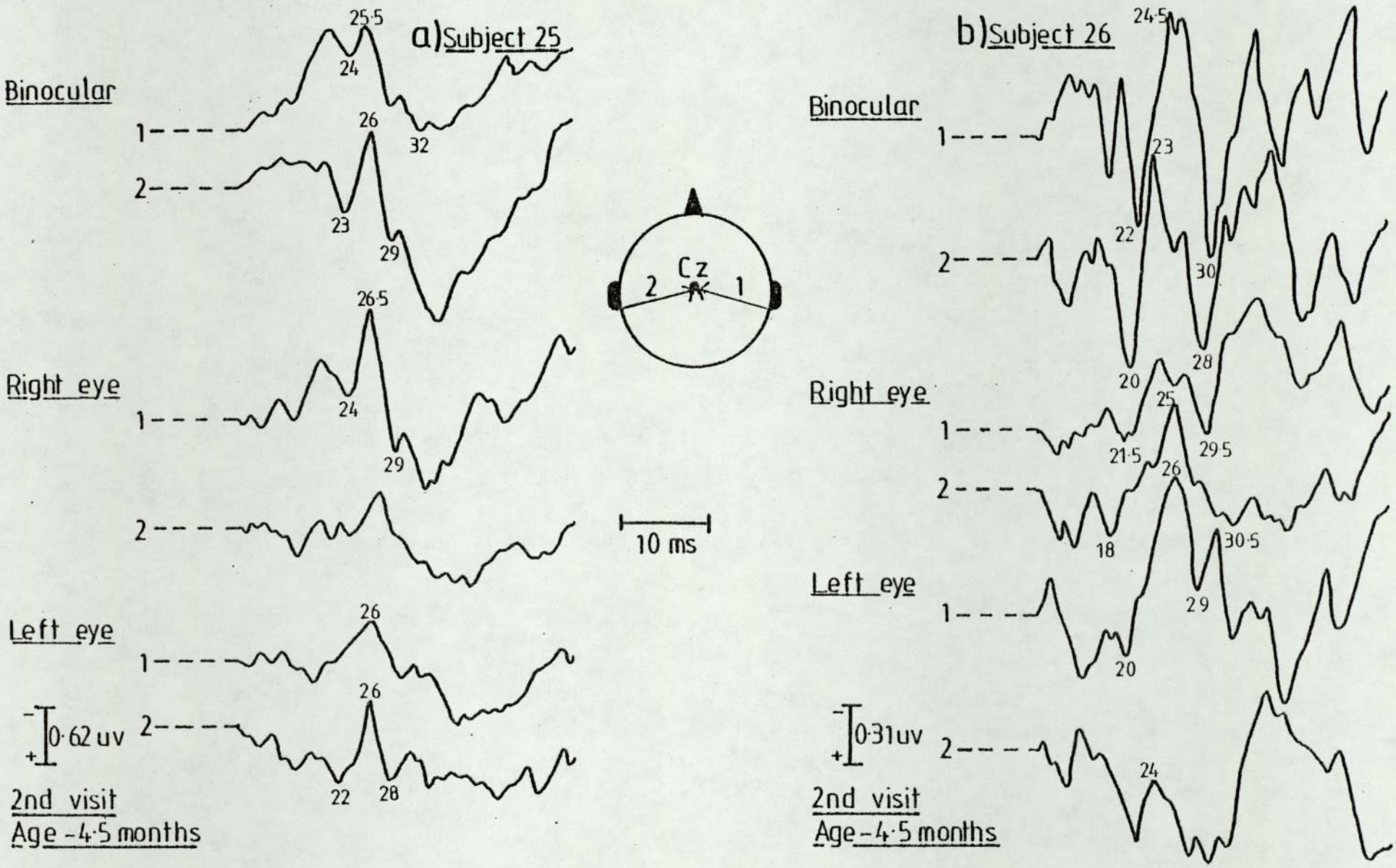

a) Subject 25
Binocular
1
2
25·5
24
26
32
23
29
Right eye
1
2
26·5
24
29
Left eye
1
2
26
26
22
28
0·62 uv
2nd visit
Age - 4·5 months
Cz
2
1
10 ms
b) Subject 26
Binocular
1
2
24·5
22
23
30
20
28
Right eye
1
2
21·5
25
29·5
18
26
30·5
Left eye
1
2
20
29
0·31uv
24
2nd visit
Age - 4·5 months

Figure 8.8

The Flash VESPs of Albinos 25 and 26 Aged 8 and 10 Months Respectively.

In (a) the bilateral, binocular responses of baby 25 are labelled. However, on monocular stimulation the baby became very active and the small VESPs are so hidden in background noise that no clear lateralisation is seen. A clear binocular response was recorded in baby 26; this is shown in (b). On monocular stimulation the VESP complex lateralises contralaterally. (Flash intensity 8, 5 flashes per second, 500 sweeps).

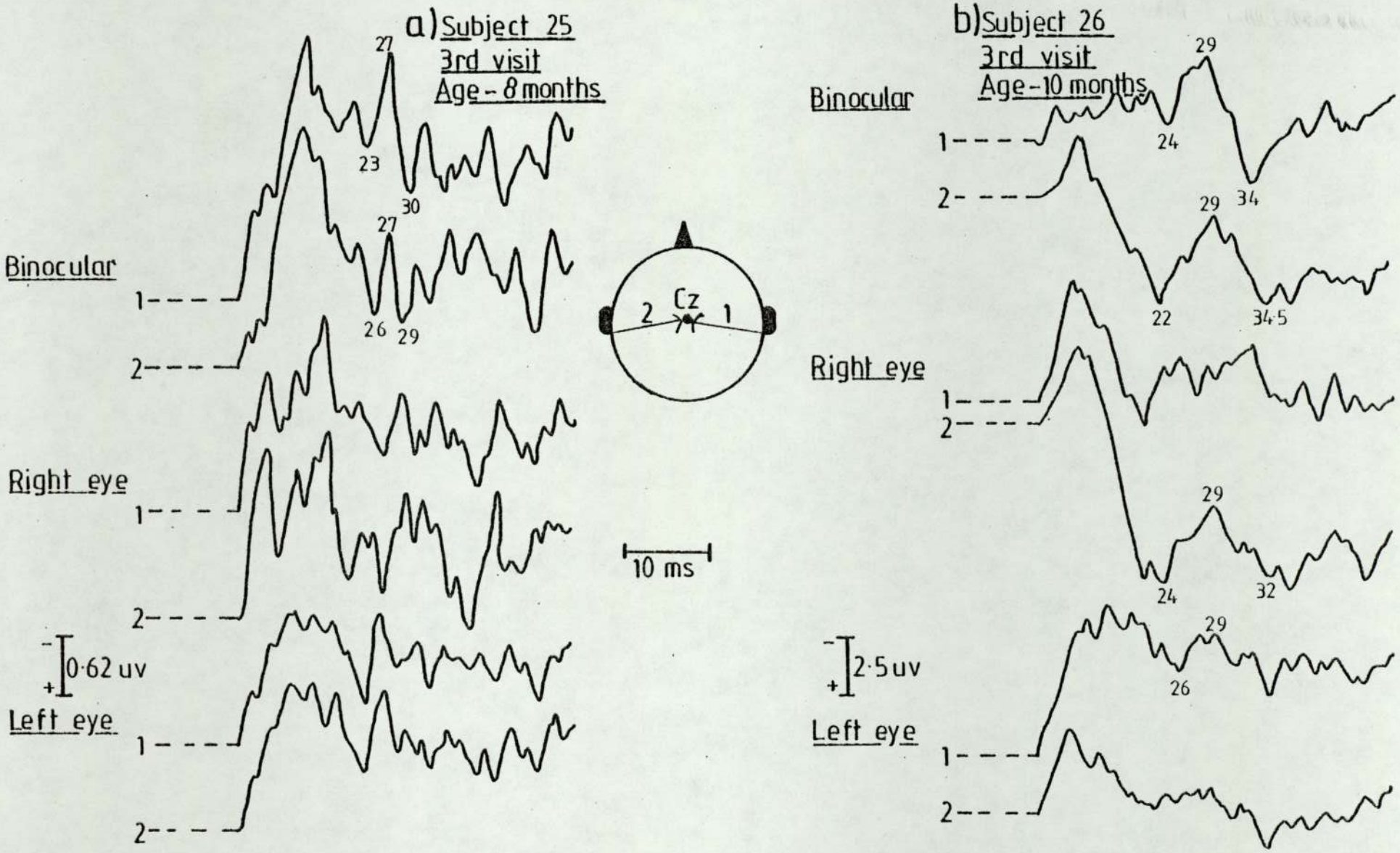
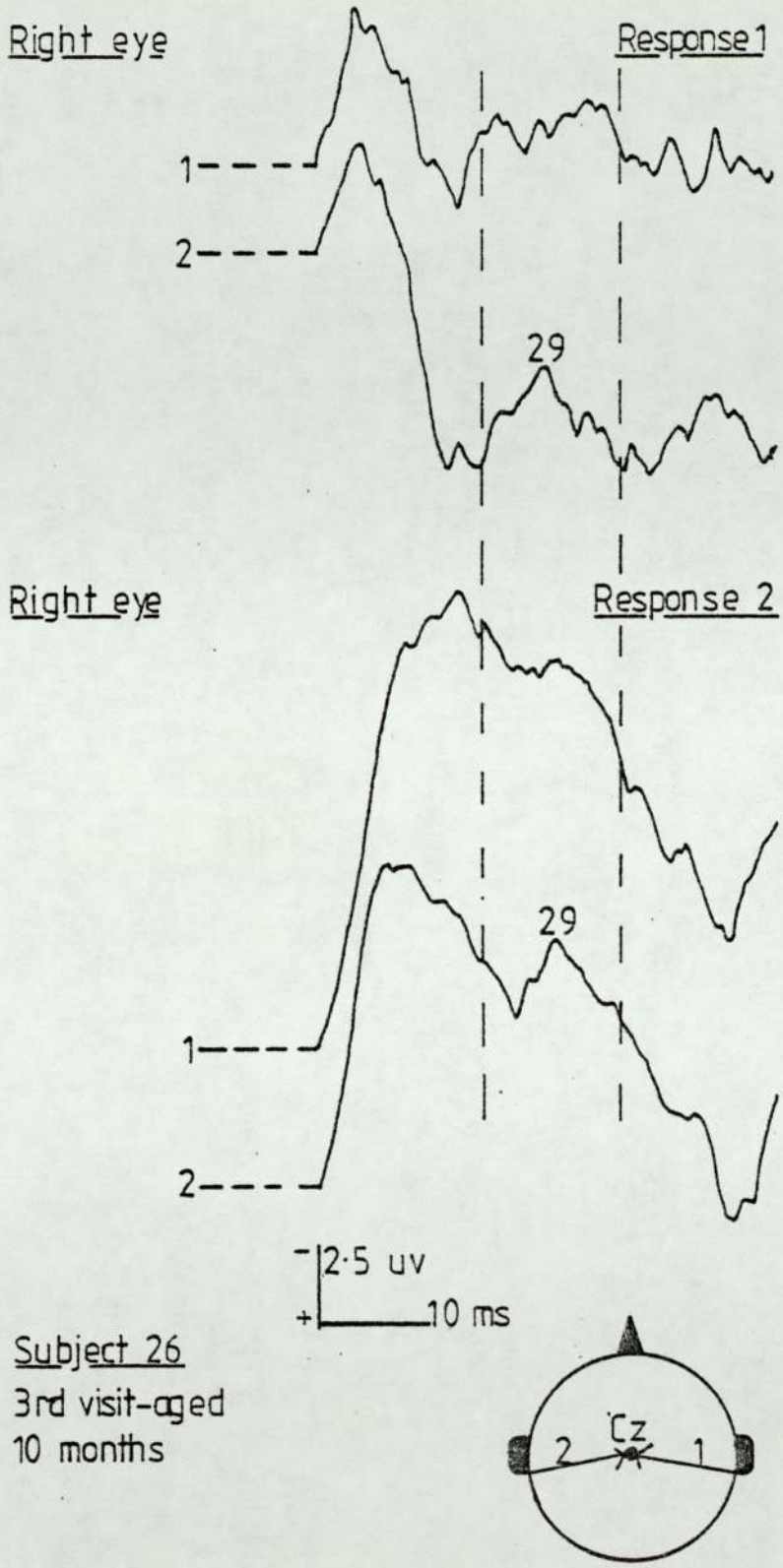

a) Subject 25
3rd visit
Age - 8 months
Binocular
Right eye
Left eye
1
2
27
23
30
27
26
29
Cz
2
1
10 ms
0·62 uv
b) Subject 26
3rd visit
Age - 10 months
Binocular
Right eye
Left eye
29
24
34
29
22
34·5
29
24
32
2·5 uv
29
26

Figure 8.9

Two Repeat Monocular VESPs Recorded From Albino 26 at 10 Months Age

As found in the older albinos examined monocular lateralisation of VESP was usually confirmed by superimposition of repeat responses. Here two right eye responses recorded in baby 26 at 10 months of age are shown. Clearly the only consistent response is present over the left hemisphere. The response over the right is poorly formed and very variable. (Flash intensity 8, 5 flashes per second, 500 sweeps).


Right eye
Response 1
1
2
29
Right eye
Response 2
29
1
2
2·5 uv
10 ms
Subject 26
3rd visit-aged
10 months
Cz
2
1

on one channel but also by the inconsistency and unrepeatability of the waveform on the other channel. An example of this is shown in Figure 8.9. This illustrates two responses from the right eye of subject 26 at 10 months of age. The only consistent response found is that over the left hemisphere; that over the right shows variability between recordings.

8.3 Summary

The responses presented in this Section illustrate that the results found regarding the flash VECP and VESP in the child and adult albinos can be repeated in albino babies. Examination of the three infants showed that:-

1) Monocular contralateral lateralisation of the flash VECP is present; this lateralisation more clearly affects the major positive component of the response

2) Monocular lateralisation of the VESP is also present; both contralateral and ipsilateral patterns are found

CHAPTER NINE

9 DISCUSSION AND CONCLUSIONS

9.1 Discussion

The albinos examined in the presented study displayed the ocular features commonly associated with the condition, notably reduced pigmentation, lowered V.A., nystagmus and strabismus.

The V.A. of all of the albinos was defective to some extent and the range of monocular acuities recorded (6/12 - 2/60) is in general agreement with that of other investigators (Edmunds 1949; Wallner and Rudens 1950; Falls 1951; Gillespie 1961; Johnson et al. 1971; Taylor 1978). Many albinos had V.A.s at the lower end of the range probably reflecting the sources from which they were originally obtained. Subjects attending partially-sighted schools and low vision aid clinics would, by definition, possess particularly low vision. This factor probably also accounts for the fact that few ocular albinos were examined; as a group these subjects tend to have better V.As (Falls 1951; Trevor-Roper 1963; Witkop 1971; Witkop et al. 1973, 1974, 1978; Carr and Siegel 1979) and can, therefore, be educated in schools for the normally sighted. In agreement with other authors many of the albinos had high refractive errors particularly of an astigmatic variety (Edmunds 1949; Wallner and Rudens 1950; Ohrt 1956; Fonda 1962; Gillespie and Covelli 1963; Duke-Elder 1964; Johnson et al. 1971; Taylor 1978). In many cases correction of the error did

not result in any increase in V.A. and as found by Edmunds (1949) many of the children examined preferred not to wear the prescription due to the lack of subjective improvement.

In agreement with the findings of other investigators (Fonda 1962; Duke-Elder 1964) the majority of the albinos displayed some form of nystagmus; in only one subject was it not seen. The severity of the nystagmus varied greatly but the movement was horizontal, rotatory or mixed as reported by Duke-Elder (1964); Johnson et al. (1971) and, in agreement with Edmunds (1949) the size of the movement varied greatly. It was also noted that as reported by Falls (1951) the nystagmoid movement tended to increase on monocular fixation.

A manifest strabismus was thought to be present in 8 (35%) of the albinos examined.

Convergent and divergent squints of varying sizes were seen. However, it must be born in mind that the observation of strabismus in albinos is made difficult by the presence of nystagmus which tends to increase on the monocular fixation necessary to perform the cover test. In addition, the latter test is thought to be only accurate in detecting deviations of 2 prism dioptres or greater (approximately 1^{o}; Romano and Noorden 1971) and, hence, squints may have been present in some albinos but of such small magnitudes as to avoid detection.

Of the subjects who were found to display a strabismus, both

convergent and divergent deviations were evident. In five of the eight the direction was convergent which may indicate the slightly higher incidence of esotropia reported by Fonda (1962); Johnson et al. (1971) but more probably supports the results of Taylor (1978) who found no consistent pattern in the direction of the deviation.

The peripheral visual fields of all but one of the albinos examined by perimetry were found to be normal or only mildly constricted along the horizontal meridian. Similar mild constrictions, both temporal and nasal were reported by Carroll et al. (1980b) and in this and our own case it is possible that the constrictions may have been slightly greater than recorded as the presence of nystagmus, which tends to increase on monocular vision, would itself tend to increase the visual field rather than reduce it (Edmunds 1949). The difficulties encountered in measuring visual fields accurately in the presence of nystagmus may account for the discrepancies reported by other investigators where some report the peripheral fields as full (Falls 1951; Goodman et al. 1965; Creel et al. 1974; Coleman et al. 1979) and others as constricted (Edmunds 1949; Falls 1951; Fonda 1962; Duke-Elder 1964). The gross sensitivities of the nasal and temporal retinae were found to be equal in all of the albinos examined with the exception of one who displayed a gross nasal hemianopia of the right eye. From the information at our disposal it is not possible to confirm that this defect was linked to the presence of albinism or due to some other cause.

The psychophysical findings in the albinos studied will be related to the findings in Siamese cats known to possess the optic nerve fibre misrouting examined in human albinos in the presented study by VEP techniques.

The V.A. of Siamese cats has been poorly investigated but was reported as equal to that of normally-pigmented cats by Packwood and Gordon (1975). However, underdevelopment of the area centralis observed by Shatz (1977a) and Stone et al. (1978a) may indicate the possible existence of a degree of defective central vision in some Siamese cats.

The presence of strabismus in human albinos is in agreement with similar findings in Siamese cats. The variation in the deviation direction reported here is found in Siamese cats (Rengstorff 1976; Shatz 1977a) and is in some conflict with the theory that albinos develop a convergent strabismus in order to favour the nasal retina with its normally routed fibres (Hubel and Wiesel 1971). However, this does not alter the fact that ocular deviations are present and could possibly be due to the existence of optic nerve fibre misrouting.

Nystagmus, a common feature of human albinism is poorly documented in Siamese cats (Creel 1971b; Cool and Crawford 1972; Kaas and Guillery 1973; Zeki and Fries 1980; Loop and Frey 1981) although its presence was reported in an albino sub-primate (Gross and Hickey 1980). Nystagmus is a common feature in humans with poor central vision from birth due to a variety of causes (Cogan 1956) and its presence in albinos may simply be a reflection of the poor foveal

differentiation (Naumann et al, 1976; O'Donnell et al. 1976; Fulton et al. 1978). However, an alternative reason for the presence of nystagmus in albinos has been proposed by Creel, Garber, King and Witkop (1980) and Witkop, Jay, Creel and Guillery (1982). They suggest that the development of the abducens nucleus which controls the lateral rectus muscle, may be anomalous in albinos and from this it was postulated that nystagmus (and possibly strabismus) may be generated by a 'brain component' possibly through this abnormal nucleus development.

Visual field investigation in the albinos presented here did not reveal the high incidence of nasal hemianopias found in some Siamese cats (Elekessy et al. 1973; Guillery et al. 1973; Guillery and Casagrande 1975a and b). The presence of such field defects has been associated with the presence of the Midwestern type abnormality in Siamese cats (Guillery et al. 1974; Guillery and Casagrande 1975a and b) and it has been suggested that measurement of the visual fields may be a simple way of differentiating between Midwestern and Boston types, (Guillery et al. 1974), the latter of which have normal full monocular fields (Simoni and Sprague 1976). On this basis, in the presented study, we were unable to clearly show the existence of the two populations in human albinos; the study by Carroll et al. (1980b) also failed to identify a high incidence of nasal hemianopias among the albinos they examined. It is possible that the one albino presented in this study who displayed a monocular nasal hemianopia may represent an albino of the Midwestern type. However, the defect was only present in one eye, the

visual field of the other being full (see Figure 5.1), and was accompanied by some temporal field constriction. Hence the defect recorded was not a strict nasal hemianopia of both eyes and it is possible that another factor or factors may be contributing to the abnormality rather than simply the presence of albinism.

The results presented in this study with respect to the VEP recordings in human albinos both confirm and conflict with the findings of other investigators.

Our inability to record adequate pattern reversal responses in the two albinos examined using this type of stimulation is in agreement with the findings of Creel et al. (1981a and b). These authors reported that pattern reversal stimulation produced poorly formed VECPs in albinos. In 50% of the subjects they examined the response was absent and in only approximately 20% was a fully developed and reliable negative-positive-negative configuration found. However, even in the latter subjects the responses were of small amplitude and monocular hemispheric asymmetries indicative of albino misrouting were not clearly present.

Our inadequate responses could not be due to lack of subject co-operation; the two albinos examined were the oldest studied (27 and 35 years) and both highly motivated and co-operative. The existence of reduced V.A. did not seem to be an integral factor in causing the poor responses; increasing check size did not improve the pattern reversal waveform and indeed the monocular V.A. of one subject examined was not greatly reduced (6/18). In agreement with

Creel et al. (1981a, b) these factors lead to the conclusion that it is the presence of nystagmus which most likely results in a poorly formed pattern reversal VECP.

These results are in some conflict with the findings of Carroll et al. (1980a and b) and Jay and Carroll (1980) who reported pattern reversal stimulation to show the monocular hemispheric lateralisation expected in albinos and, indeed, from their findings they were able to divide the human albino population into Boston and Midwestern varieties. The recording parameters used in the present study were similar to those used by the above authors; 50' checks and identical electrode placements. One area of discrepancy lies in the number of responses averaged to record an adequate P100 component. Carroll et al. (1980b) reported that in most cases 600 reversals were used for analysis and in some up to 1800 were included in the final average. Even using this method many of the responses recorded were of very small amplitude (1.39 - 1.75uV) and hence the amounts of hemispheric lateralisations found were small in magnitude. In addition the half-field responses of some albinos were inadequate for analysis. The reduced amplitude P100 components were said to be a result of lowered V.A. and a bilateral reduction in the number of functional units in the generator area of the visual cortex with little effect from the nystagmus which was said to diminish considerably during VECP recordings (Carroll et al. 1980a and b).

We achieved greater success in recording pattern responses

in the albinos by the use of appearance-disappearance and, in agreement with Creel et al. (1980a and b), this proved a far superior method of stimulation than pattern reversal. Generally the responses were dominated by a large, early positive CI component with poorly defined CII, CIII and 'OFF' responses. This finding has been previously reported as a characteristic of the albino pattern appearance-disappearance response (Creel et al. 1980a and b; Apkarian et al. 1983) although it does not appear to be a feature restricted to albinos. Both in this study and that of Wright (1983) it has been found that this type of pattern appearance-disappearance response dominated by a large positive component is commonly found in an adolescent population. Spekreijse (1978) and Vries-Khoe and Spekreijse (1982) recorded similar responses in younger children but they believed that the adult type response dominated by a negative, CII, component is acquired by puberty. However, the presented study and that of Wright (1983) suggests the pattern appearance-disappearances response may consist primarily of a large positive, CI, component, beyond this age.

Although we were able to confirm that pattern appearance-disappearance stimuli produce better responses than pattern reversal in albinos, unlike that found by Apkarian et al. (1983) it was evident that in the majority of the subjects simple examination of the reference recordings was insufficient to confirm the expected contralateral lateralisation on monocular stimulation in the albino population.

This finding was in spite of similarities between electrode placements and check sizes in the two investigations.

However, the technique of recording bipolar responses between the two occipital hemispheres (O1-O2) did greatly improve the observation of contralateral monocular lateralisation, in agreement with Creel et al. (1981a,b); Apkarian et al. (1983). Using this method contralateral lateralisation in the form of polarity reversal of the bipolar response was successfully identified in 8 (67%) of the albinos. This result was not present in any of the control subjects and in no albino subject was ipsilateral lateralisation seen. In agreement with Creel et al. (1981b) the bipolar recordings using full-field stimulation in some of the albinos was identical to that found on half-field stimulation of control subjects.

The recording of half-field responses did confirm that in some albinos the full-field response was dominated by that of the temporal half-field although this was not a universal finding. The problem encountered here was the poorly formed half-field response recorded from many of the albinos; in some whose full-field responses were unclear, the half-field responses had undefinable components. This finding may be related to the findings of Creel et al. (1981b) who, using small field stimuli, found the site of decussation in albinos to be shifted by amounts varying from 5 degrees to beyond 20 degrees into the temporal retina. In those albinos in whom a large number of temporal fibres take a

contralateral route one would expect that in view of the fact that these fibres are of central retinal origin the half-field response from this temporal retina (nasal half-field) to tend to lateralise contralaterally, and therefore, be similar to that recorded from the nasal retina (temporal half-field). Hence the two responses may look similar both to each other and to the full-field response. Alternatively, in few temporal fibres lateralise contralaterally the response from this half-field may show lateralisation of a more ipsilateral type and hence any contralateral lateralisation of the full-field response would be more likely to be similar to that seen on temporal half-field (nasal retinal) stimulation.

The calculation of group average responses proved a very suitable method of displaying the results found using pattern appearance-disappearance stimuli. Figure 6.65 shows the full-field responses of the control subjects. They are dominated by a positive wave (CI) preceded by an earlier negative present at all electrode sites. In particular the O1-O2 bipolar responses (Figure 6.67) show that polarity reversal indicating contralateral lateralisation is only present on half-field stimulation; the full field responses have a similar waveform.

The full field group average responses of the albino subjects (Figure 6.68) have a very variable waveform reflecting the variability present between the responses of the individuals and clear contralateral lateralisation

on monocular stimulation is not evident. Similarly, the half-field responses (Figure 6.69) are very poorly formed. Positive results are only seen in the group bipolar (O1-O2) responses (Figure 6.70). In contrast to that found within the control group, the monocular responses show clear polarity reversal indicative of contralateral lateralisation. These findings reflect the results obtained during examination of the individual albino response. Statistical analysis of the individual full-field responses failed to show significant contralateral lateralisation in the albino group while bipolar recordings clearly showed the existence of such lateralisation in 67% and in no case was ipsilateral lateralisation seen (see Table 6.14). However, the two group half-field responses from each eye do not show clear reversal but rather there is a tendency for the two half-field responses to have a similar polarity to that of the full-field response from that eye. Thus the two half-field responses from the right eye show polarity reversal to those from the left eye. This implies that the two half-field responses show contralateral lateralisation and are, therefore, dominated by the contralaterally projecting fibres.

The results found using the flash VECP were in some agreement with those reported by Creel et al. (1974, 1978, 1979b) and Creel (1979). We found this type of stimulus to be particularly effective in demonstrating monocular hemispheric contralateral lateralisation in albino subjects. The superior efficacy of flash in the group of albinos studied

here may be due to the low average age of our subjects and their particularly poor V.As. In some of the young albinos flash was the only suitable stimulus allowing rapid recording of the response without the problems associated with poor fixation associated with pattern responses. The subjects examined by Creel et al. (1981a and b) using pattern appearance-disappearance were of an older age (minimum 16 years) and in many the V.A. of one eye could be corrected to 6/9. Hence, it is not surprising that flash was successful in the albino group studied here as this form of stimulus has been shown to be particularly useful in subjects of a young age (Vaughan and Katzman 1964; Bianchi and Lauri 1974; Borda 1977; Harding 1974, 1980, 1982), in the presence of low V.A. (Spehlmann 1965; Dustman and Beck 1969; Dustman et al. 1977; Harding 1982) and in the presence of nystagmus (Meienberg et al. 1980).

In addition, simple examination of the reference recorded flash responses proved sufficient in detecting contralateral lateralisation on monocular stimulation in 91% of the albinos. It is probable that bipolar recordings between the two hemispheres (as performed during pattern appearance-disappearance stimulation) would have further confirmed contralateral lateralisation using flash. Unfortunately, because initially a common reference electrode had not been used these bipolar responses could not be computed from those stored on floppy discs.

Within the albino group the only component measure showing

statistically significant monocular contralateral lateralisation was P2 latency ($p < 0.001$). No measure in the control group showed statistically significant contralateral lateralisation and in neither group was statistically significant ipsilateral lateralisation of any measure found.

This finding is probably due to the fact that of the flash VECP, P2 is the most consistent component (Spehlmann 1965; Dustman and Beck 1965; Reitveld et al. 1967; Rhodes et al. 1967; Harding 1974) and although contralateral lateralisation of other measures was seen with the albino group there was greater variability present. This is manifest in the P1 data. This component was not consistently present in some albinos; Harmony et al. (1973) found that if any flash VECP components were absent they are more likely to be the early ones such as P1.

Group average responses confirmed the statistical findings. The responses of the control subjects (Figure 6.63) show a clear bilateral P2 component on binocular and monocular stimulation ; P1 is less well defined probably due to its greater variability both in latency and amplitude. Similarly, in the albino subjects (Figure 6.64) P1 is poorly formed but P2 is seen to have a shorter latency and N2P2 a greater amplitude over the contralateral hemisphere on monocular stimulation. Statistically only P2 latency showed significant lateralisation; the absence of a significant result with respect to the N2P2 amplitude is probably due to the fact that of the two measures of the flash VECP,

amplitude is more variable than latency (Schreinemachers and Henkes 1968; Vaughan 1966, 1969; Lewis et al. 1972; Aunon and Cantor 1977).

The observation that the responses of some albinos showed a large P1 component compared to P2 was unexpected and resulted from simple visual examination of the individual responses. The calculation of a P1q showed that in some albinos P1 was much larger than P2 while in others it was of a more normal amplitude considering the age of the subjects examined (Dustman and Beck 1966, 1969; Harding 1974, 1982; Cosi et al. 1982; Wright 1983). The resulting relationship found between the P1q and V.A. showed that particularly low V.A. is associated with an enlarged P1 component although the relationship is not so consistent as to allow a precise prediction of V.A. from measurement of the P1q. In addition, the existence of such a relationship does not necessarily indicate that a large P1 is due to the low V.A. but the possibility of such a relationship can be explored. Enlargement of the P1 component is reported in elderly subjects (Dustman and Beck 1966, 1969; Harding 1974; Cosi et al. 1982; Harding 1982; Wright 1983) and also in the presence of macular disease (Harding 1974, 1977). It is, therefore, possible that although as a group albinos possess foveal malformation (Naumann et al. 1976; O'Donnell et al. 1976; Fulton et al. 1978) the severity of the defect may be greater in some giving a lower V.A. and a large P1 flash VECP component.

Using both pattern appearance-disappearance and flash

stimuli some components showed significant changes in latency and amplitude on binocular vs monocular stimulation with the control group. Using pattern appearance-disappearance stimuli, in agreement with Jeffreys and Axford (1972b); Jeffreys (1977), CI had a greater amplitude binocularly than monocularly ($p < 0.025$) but only at sites O1 and O2. In addition, CI had a shorter latency binocularly than monocularly ($p < 0.05$) but only at O3 and O4. Why this effect is not seen at electrodes O3 and O4 with respect to amplitude and O1 and O2 with regard to latency is evident on consulting the ANOVA graphical results (Figures 6.51 and 6.39 respectively). In both cases the existence of such relationships is evident but variability between the responses of the individual subjects most probably led to a statistically insignificant result.

Similarly, in agreement with Bartlett et al. (1968); Perry et al. (1968); Ciganek (1970) and Borda (1977) the flash VECP had a significantly greater amplitude ($p < 0.01$) and shorter latency ($p < 0.01$) on binocular compared to monocular stimulation. However, this was only true with respect to the N2P2 amplitude and P2 latency and is probably because of the consistency of P2 compared to all other components of the flash VECP (Spehlmann 1965; Dustman and Beck 1965; Reitveld et al. 1967; Rhodes et al. 1967; Harding 1974). Examination of the ANOVA graphs for the other component measures (Figures 6.9, 6.14 and 6.25) shows that such relationships, particularly with respect to N2 latency and P1N2 amplitude are present but, due to interindividual variability, fail to reach statistical significance.

The lack of similar binocular additive findings in the albino subjects may be due to the occurence being hidden by any contralateral lateralisation present particularly in the case of the flash P2 component latency. The existence of a decrease in latency and increase in amplitude on binocular stimulation in the albinos is suggested in the ANOVA graphs for P1 latency (Figure 6.9), P1N2 amplitude (Figure 6.29) and CI amplitude at electrodes O1, O2 and O3, O4 (Figures 6.42 and 6.51 respectively). Here again as in the control subjects inter-individual variability probably accounts for the lack of statistically significant findings. In addition, the incidence of strabismus in some albino subjects may also influence the above findings as under binocular conditions one would expect suppression of the squinting eye.

The VESP results were somewhat unexpected in that although some albinos did show clear contralateral lateralisation on monocular stimulation others showed equally clear ipsilateral lateralisation. The numbers of albinos and control subjects showing contralateral and ipsilateral lateralisation were not significantly different but there is evidence that the amount of lateralisation (in terms of amplitude) is greater within the albino group. In addition, in each albino both P23 N28 and N28 P34 showed consistency in the direction of monocular lateralisation while in some control subjects one measure showed contralateral and the other ipsilateral lateralisation.

The existence of two distinct forms of lateralisation

within the albino group can be confirmed by topographical studies and bipolar techniques. The existence of ipsilateral VESP lateralisation is further evidence for the independence of the VESP and VECP (Harding and Rubinstein 1982). Although in the majority of albino subjects P2 showed contralateral lateralisation, in many of these ipsilateral lateralisation of the VESP occurred; in the two albinos who showed ipsilateral lateralisation of P2 the VESP showed contralaterality (see Table 7.7). In addition, during topographical studies in an albino who showed repeatedly clear ipsilateral VESP lateralisation, simultaneous recordings from the occipital cortex (O1 and O2) showed contralateral lateralisation (Figure 7.21).

The co-existence of opposing forms of VESP and VECP lateralisations indicates the independence of the two responses and presumably reflects their independent sources; Harding and Rubinstein (1980a) suggested the LGN to be the most probable site of VESP production. Evidence for the independence of the two responses was, before the present study was undertaken, quite sparse. Harding and Rubinstein (1982) examined only one patient with a recent head injury to the right occiput. On flash stimulation of either eye the VECP was found to be reduced over the right hemisphere but the VESP remained bilaterally. These indications of 1) VECP and VESP independence and 2) the subcortical origin of the VESP are further supported by the presented albino study.

As found with the flash VECP, in control subjects the flash VESP showed variable amounts of monocular hemispheric lateralisation of both a contralateral and ipsilateral nature (see Tables 7.1; 7.2; 7.4 and 7.6). Similarly, within the albino group both contralateral and ipsilateral lateralisation of the VESP was found. There is some evidence that the mean amounts of contralateral or ipsilateral lateralisation were somewhat greater within the albinos compared to the controls (see Figures 7.10 and 7.14) although it must be stressed that these differences are very small in, the region of 0.13 to 0.33uV (see 7.3.2.).

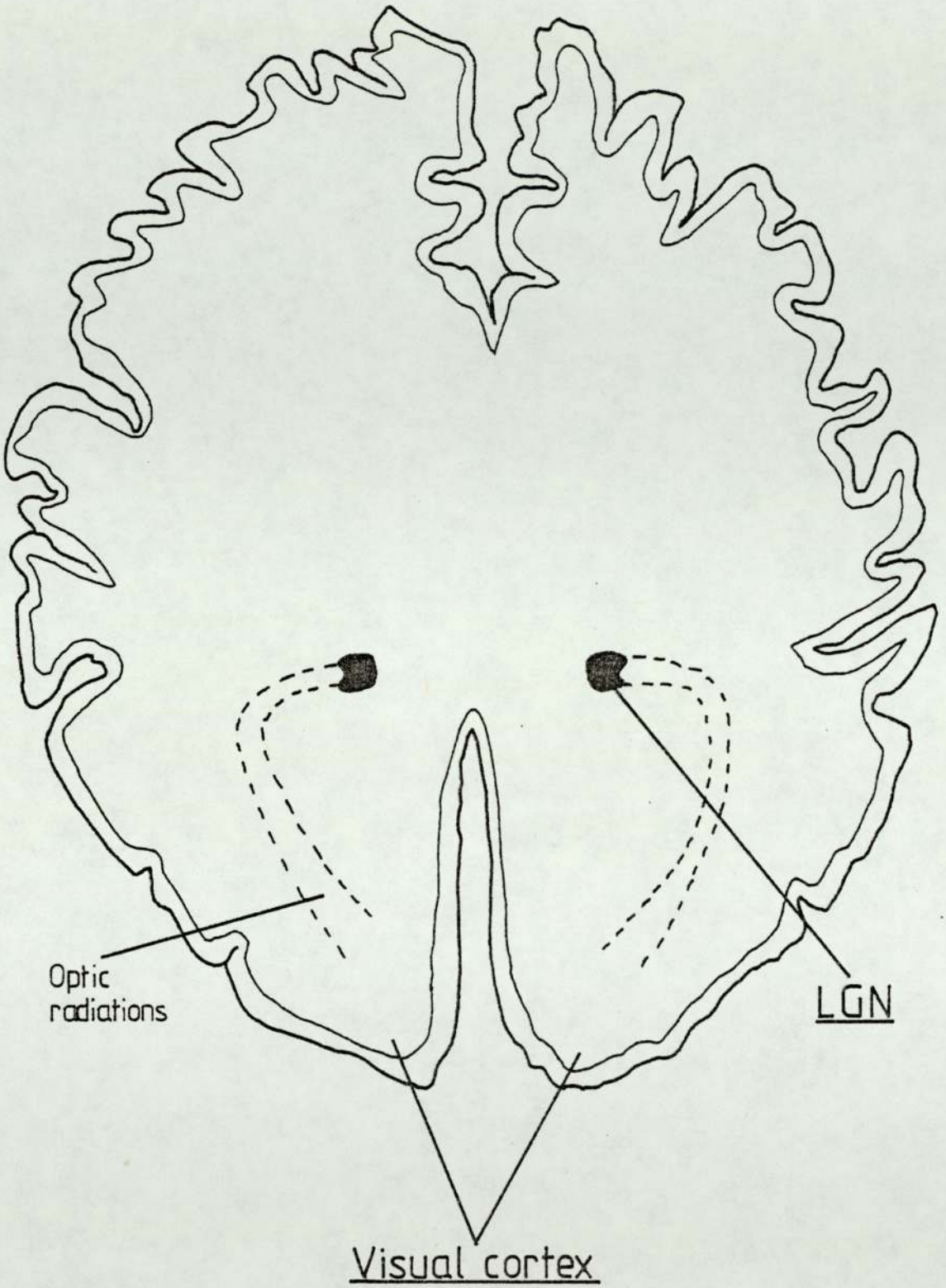
The presence of ipsilateral lateralisation within the albino group is somewhat unexpected. On the basis of anatomical studies there is an increase in contralaterally projecting fibres in albinos and this is reflected in the monocular lateralisation of the P2 component of the flash VECP. The results presented here indicate that analysis of the VESP does not allow albino subjects to be differentiated from pigmented individuals. The reason for this failure most probably lies in the anatomical arrangement of the human visual pathway and in particular the relative positions of the LGN and visual cortex compared to the positions of electrodes used for scalp recordings of potentials generated by these structures.

Figure 9.1 shows the positions of the lateral geniculate nuclei and visual cortex in humans drawn as actual size.

FIGURE 9.1

Anatomical Positions of LGN and Visual Cortex in Man

A horizontal brain section (actual size) is shown with the LGN, optic radiations and visual cortex labelled. (Adapted from DeArmond, Fusco and Dewey, 1976).


Optic
radiations
LGN
Visual cortex

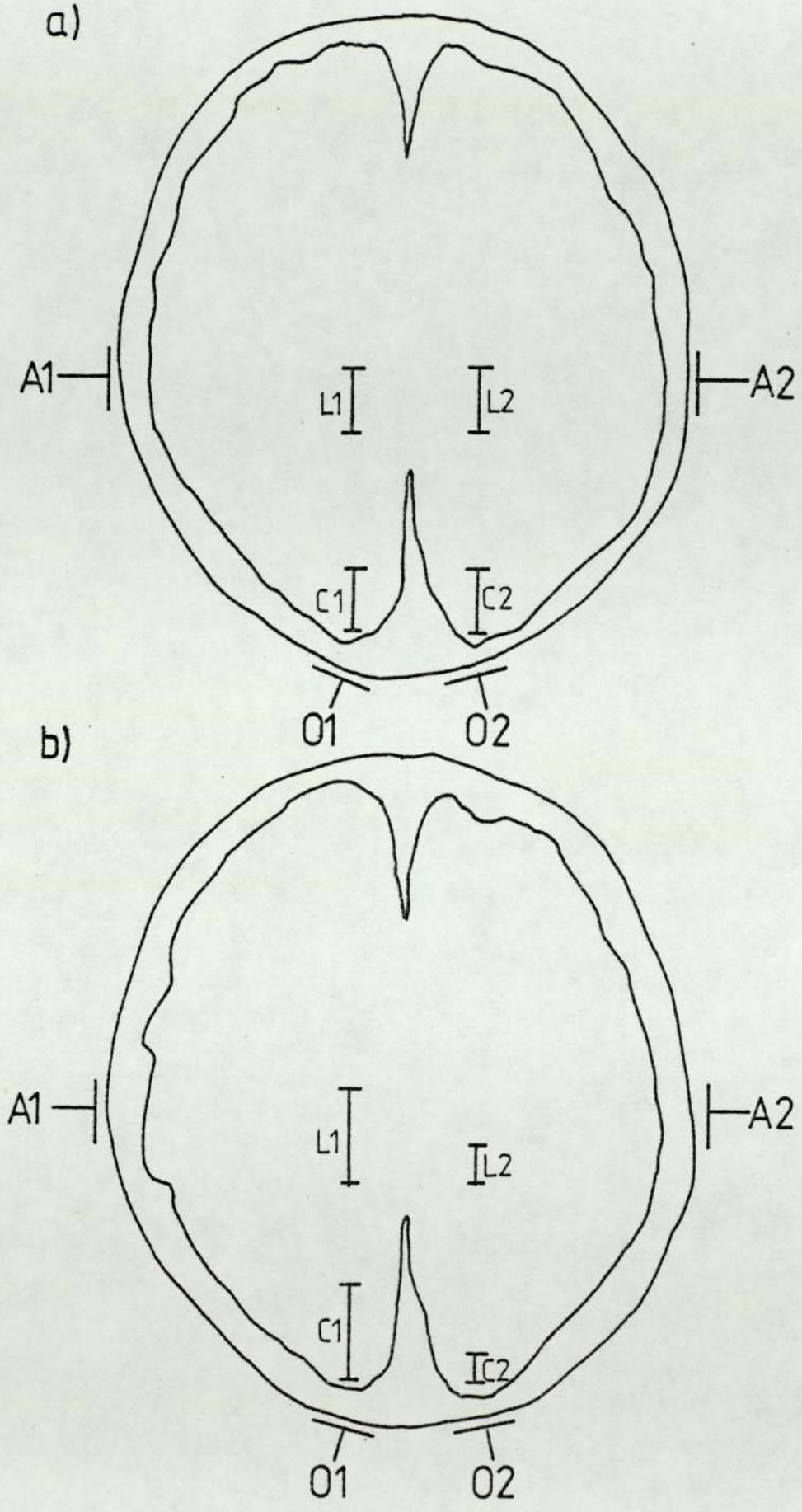
It is apparent that the visual cortex is located on the posterior, occipital, pole of the brain while the two nuclei are more centrally positioned. In addition, the nuclei lie in fairly close proximity to each other (approximately 30mm apart; see Figure 9.1) and are both some distance from the lateral surfaces of the head (approximately 60mm from Figure 9.1 allowing for skull and scalp thicknesses). Figure 9.2a shows, schematically, the positions of the generator units within the two LGNs and the visual cortex and the sites of the scalp electrodes used to record the VESP and VECP. Clearly the occipital electrodes, O1 and O2, are located directly over the site of the VECP generation and are ideally positioned for the recording of hemispheric lateralisation on monocular stimulation of albinos (see Figure 9.2b). However, electrodes A1 and A2 are both a great distance from the closely spaced, bilateral VESP generators. On monocular stimulation of albinos it is, therefore, not surprising that contralateral lateralisation is not always found. The VESP generators are close to each other and a large distance from the recording electrodes. Consequently, if, for instance, the VESP is generated primarily in the left LGN (i.e. on right eye stimulation of an albino; Figure 9.2b), both electrodes A1 and A2 are almost equally likely to record the potential. This will also be true on left eye stimulation. On this basis, the VESP results from an albino population would not necessarily differ significantly from those of a pigmented group.

The evoked potential recordings from albino 20 who showed

FIGURE 9.2

Schematic Diagrams Showing the Relative Positions of the VECP and VESP Generator Sites and the Recording Electrodes

These schematic diagrams illustrate the relative positions of generators located in the lateral geniculate nuclei (L1 and L2) and the visual cortices (C1 and C2). The sites of the scalp electrodes A1, A2, O1 and O2 are shown. The electrodes for scalp recordings of the VECP are located close to the generator sites; those for VESP recording are some distance from the generators, the latter of which (L1 and L2) lie in fairly close proximity. (a) shows the situation on binocular or monocular stimulation of a pigmented individual and binocular stimulation of an albino. Approximately equal potentials are produced at C1 and C2 resulting in symmetrical and synchronous responses at O1 and O2. This is also true for generators L1 and L2 but due to their close proximity the responses may be recorded at either electrodes A1 and A2. (b) shows the situation on monocular (right eye) stimulation of an albino; due to the misrouting the potential shows contralateral lateralisation. At a cortical level this is reflected in scalp recordings from O1 and O2, such that the response from O1 has a greater amplitude and/or shorter latency than that at O2. At the level of LGN the potential produced contralaterally is also greater than that ipsilaterally. However, due to the close proximity of the two generator sites (L1 and L2) and their distance from the scalp electrodes, the potential produced primarily in L1 may be recorded approximately equally by A1 and A2 such that monocular contralateral lateralisation of the VESP is not necessarily produced.


a)
A1
A2
L1
L2
C1
C2
O1
O2
b)
A1
A2
L1
L2
C1
C2
O1
O2

a nasal hemianopia of the right eye were not included in analysis of the results from the albino population as a whole due to the probable effects on the responses by the presence of such a field defect. This precaution proved essential when the results from this albino were examined. The flash VECP indicated the presence of such a field defect; the response from the right eye was reduced in amplitude compared to the left and particularly reduced over the right occiput, i.e. over the hemisphere contralateral to the recorded field defect (see Figure 6.30). The pattern appearance-disappearance responses recorded on full-field stimulation were not indicative of the presence of such a field defect (see Figure 6.59). The response recorded from the right eye was grossly abnormal compared to that of the left with a large reduction in amplitude such that individual components could not be seen. However, hemispheric asymmetry was not present. Similarly, a gross amplitude reduction was present in the half-field and bipolar responses from the right eye. The VESPs recorded suggested an abnormality of the right eye. Figure 7.23 shows that there is some evidence of ipsilateral monocular lateralisation but, in addition, the response from the left eye have a shorter latency to those from the right. However, gross interocular or hemispheric asymmetries suggestive of a hemianopic field defect were not present. This is in contrast to the findings of Harding and Rubinstein (1981) who studied two patients, one with a right homonymous hemianopia and the other with a bitemporal hemianopia. In both cases, on monocular

stimulation, the VESP was reduced contralateral to the field defect. Of these two patients examined, the CAT scan showed that one had global atrophy and the other a large supra-sellar cystic space occupying lesion. However, in the case of albino 20 the presence of two features which may contribute to the lateralisation of the VESP probably complicates the situation. In addition to the presence of albino misrouting, which has been shown to be reflected as both contralateral and ipsilateralisation of the VESP, a gross field defect is present. The interaction of both of these features probably accounts for the lack of clear lateralisation results when the VESPs are examined. This indicates that further studies of patients should be undertaken in order to assess the clinical accuracy of VESPs in the presence of hemianopic defects of differing aetiologies particularly in view of the problems encountered in VESP lateralisation due to the anatomical positions of the two nuclei discussed previously.

The albino baby studies were necessarily preliminary in nature; only three infants were studied using flash stimuli and this was the first investigation in which VESPs have been recorded in albinos.

The flash VECPs recorded from the albino babies were, on the whole, somewhat delayed for the age compared to the data of Hrbek and Mares (1964); Ellingson (1966); Ferriss et al. (1973); Harden (1982); Vries-Khoe and Spekreijse (1982) but did show the typical reduction in latency of the major positive wave with age (Ellingson 1960, 1966;

Ferriss et al. 1967; Marcus 1977; Harden 1982). The delayed flash responses of albino babies may indicate an underdevelopment of the visual pathway at birth compared to normally pigmented infants; the more normal component latencies recorded in the older albinos shows that this feature does not appear to persist. As reported by other authors (Ellingson 1966; Hrbek and Mares 1964; Groth et al. 1973; Marcus 1977) some variability of the responses was present but contralateral hemispheric lateralisation on monocular stimulation indicative of albino misrouting, was evident even at the age of only one month. This finding implies that the visual pathway anomaly of albinos is most probably congenital in nature.

The VESPs recorded were also somewhat variable but results did indicate that these small potentials can be evoked in young babies and, under ideal conditions, are seen as a clear positive-negative-positive complex. The fact that one can record VESPs at a young age is not surprising if one considers post-natal development of the most probable site of VESP generation, namely the LGN. Hickey (1977) found that in the normally pigmented human infant the geniculate cells are, on average, 60% of their adult size. Cell growth nears completion by one year of age but is not totally over until 24 months. This pattern of growth may affect the morphology of the infant VESP and may account for the changes seen during follow-up studies of the albinos presented here (see Figures 8.6, 8.7 and 8.8). Both contralateral and ipsilateral lateralisation of the

VESP was found indicating that the two forms of VESP lateralisation seen in the older albinos are also seen in infants. As in these older subjects the anatomical position of the LGN compared to the recording electrodes probably accounts for the lack of consistent contralateral lateralisation of the VESP.

9.2 Conclusions

From the work described and discussed previously several points may be concluded:

1) Optic nerve fibre misrouting in human albinos can be identified using VEP recording techniques. Using the flash VECP the abnormality is reflected in the latency of the P2 component recorded over the two hemispheres on monocular stimulation. Using reference recording the latency of P2 is shorter over the hemisphere contralateral to the eye stimulated.

2) Pattern appearance-disappearance stimuli also reflect the albino misrouting but the monocular hemispheric lateralisation is more clearly seen on bipolar recordings between the two hemispheres.

3) Pattern reversal is a poor stimulus for evoking responses in albino subjects; this is most likely due to the presence of nystagmus. Thus, if VECPs are to be recorded in any subject the use of pattern reversal stimuli is contraindicated if nystagmus is present. Both flash and

appearance-disappearance can be substituted successfully.

4) Shorter peak latency and larger peak to peak amplitude measures of some VECP components on binocular compared to monocular stimulation is present within control subjects but not within the albino population.

5) There is a trend within the albino population for an enlarged P1 flash VECP component to be associated with very reduced V.A. This does not necessarily imply a causative link and the trend is not so clear that the measure of a P1q could be used as a precise predictor of the Snellen V.A.

6) Flash VESPs do lateralise on monocular stimulation in albinos but the pattern of lateralisation is not easily predicted on the basis of anatomical and VECP data. Both contralateral and ipsilateral lateralisations are present within albino and control populations and although there is a tendency for the lateralisation to be of a greater magnitude in albino subjects the VESP does not easily differentiate between albino and pigmented subjects.

7) The VESP has been shown to be independent of the VECP. This is indicated by the fact that although in the majority of albinos the flash VECP P2 component latency shows contralateral lateralisation, some of these subjects showed ipsilateral lateralisation of the VESP. In addition, two subjects who showed ipsilateral lateralisation of P2 displayed contralateral lateralisation of the VESP. This

independence is also evident from topographical VESP studies where monocular ipsilateral lateralisation of the VESP was recorded in conjunction with contralateral lateralisation of recordings from occipital sites.

8) Misrouting can be identified in albino ~~subjects~~ babies using the flash VECP. The responses show increased latency from accepted normality which may reflect immaturity of the albino babies' visual pathway.

9.3 Proposals for further work

1) Future recordings of the flash VECP in human albinos should include a bipolar O1-O2 channel to verify that the polarity reversal of the two monocular responses seen using pattern appearance-disappearance stimuli is present on flash stimulation.

2) Continued recording in albino babies. Follow-up recordings should examine the development of the evoked potential waveform in these infants. A gradual reduction to normal flash VECP latencies should be evident and measurement of the Plq with advancing age will show how accurately this measure reflects Snellen V.A. In view of the success in recording VESPs in albino babies further studies should be undertaken to investigate the clinical utility of the response in investigating babies with visual pathway abnormalities of varying aetiologies.

3) In view of the findings of Creel et al. (1980),

Garber, Turner, Creel and Witkop (1982) and Creel, Conlee and Parks (1983), brainstem auditory evoked potentials (BAEP) should be studied in human albinos. The above authors found evidence of hemispheric asymmetries of the albino auditory system, possibly even at the level of the cochlear. To further this work BAEP recordings should be included in electrophysiological investigations of human albinos; this is a simple task as VESP electrode placements can be utilised.

APPENDIX - PUBLICATIONS

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INVESTIGATION OF VISUAL PATHWAY ABNORMALITIES IN HUMAN ALBINOS

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Abstract—Flash visual-evoked cortical and subcortical potentials are studied in human albinos for evidence of optic nerve fibre misrouting. The relationships between the results obtained and the visual problems associated with albinism are discussed.

INTRODUCTION

Sheridan (1965) orginally suggested that differences may exist between the visual systems of albino and normally pigmented animals. Following his work on rats he proposed that in the albino there could be a reduction in the number of uncrossed optic nerve fibres. Subsequent studies have confirmed that in a wide range of albino animals some of the fibres from the temporal retina which normally pass to the ipsilateral side of the brain are misrouted at the optic chiasma and terminate in the contralateral hemisphere [see Guillery (1974, 1978) for reviews]. This defect appears to be associated with a reduction of melanin in the retinal pigment epithelium (Sanderson *et al.*, 1974). Creel and Giolli (1972) hypothesised that this anomaly could be a trans-species phenomenon and thus possibly be present in human albinos.

In the visual system of man, fibres from the temporal retina pass to the ipsilateral hemisphere while nasal fibres cross over at the chiasma to the opposite hemisphere. The ratio of crossed to uncrossed fibres is 53:47 (Kupfer *et al.*, 1967). This routing results in each half of the visual field being represented in the opposite side of the brain. If the typical misrouting were present in human albinos then some of the fibres from the temporal retina would also cross over at the chiasma, resulting in a grossly unequal number of fibres from each eye passing to each side of the brain. This would disrupt the normal representation of visual space such that some parts of the visual field would be represented in the wrong cortical hemisphere.

Human albinism is usually associated with reduced visual acuity which is thought to be due to malformation of the fovea (O'Donnell *et al.*, 1976; Fulton *et al.*, 1978). Nystagmus is frequently present and a high incidence of strabismus has been reported (Witkop, 1971).

Anatomical evidence of such misrouting occurring in human albinos is sparse. Guillery *et al.* (1975) examined the brain of one oculocutaneous albino. The lateral geniculate nucleus was found to be smaller than normal and rotated from its usual position. Extensive abnormal fusions between geniculate layers were also present. They concluded that the retinogeniculate pathway in this individual was abnormal and possibly indicative of misrouting.

A simple and non-invasive technique of demonstrating the presence of misrouting is the use of visual-evoked potentials (VEP). By recording the VEP over each hemisphere during monocular stimulation, the relative proportion of fibres travelling to each hemisphere should be reflected in the recorded potential. In the albino subject, owing to the

preponderance of contralateral fibres, one would expect that the evoked potential recorded over the hemisphere ipsilateral to the eye stimulated to be of a smaller amplitude or longer latency or somehow changed in waveform compared to that recorded over the contralateral hemisphere. This hemisphere should retain a more normal or even supranormal waveform. Moreover this lateralization effect should reverse as one changes eyes. With right-eye stimulation the response will lateralize over the left hemisphere and with left-eye stimulation it will be maximal over the right hemisphere.

Such techniques have successfully identified misrouting in the albino rat (Creel *et al.*, 1970), guinea pig (Creel and Giolli, 1972) and Siamese cat (Creel, 1971a, b). The latter animal has been used extensively in studies; it possesses a temperature-sensitive variant of the gene responsible for albinism, accounting for its pale colouration apart from its cooler and hence darker extremities. Genetically, therefore, it is considered an albino (Peltz, 1967).

Carroll *et al.* (1980a, b) and Jay and Carroll (1980) have claimed that pattern-reversal, visual-evoked cortical potentials are successful in demonstrating misrouting in human albinos while other investigators favour pattern appearance – disappearance stimuli (Creel *et al.*, 1981a, b). However, in accordance with other investigators (Creel *et al.*, 1974, 1978) we have found the flash stimulus to be effective in such subjects. This has been utilized to record the flash visual-evoked cortical potential (VECP) and the flash visual-evoked subcortical potential (VESP). The latter is a new technique which records a signal from early in the visual pathway which has been isolated from both the electroretinogram and the cortical potential (Harding and Rubinstein, 1982). It is thought to be of superior colliculus or, more likely, lateral geniculate nucleus origin (Harding and Rubinstein, 1980).

METHODS

Subjects

Nineteen male and six female albinos (22 oculocutaneous; three ocular), have been examined. This includes three babies; one aged 7 months and two aged 4 weeks currently undergoing developmental studies. The age range of the remaining 22 was 5 – 35 (mean 13.6) years.

Initial examination

Where possible, binocular and monocular visual acuities were measured and all subjects were examined for evidence of strabismus, using either the cover test and/or Hirschberg method (Cashell and Durran, 1974). The presence of any nystagmus was noted along with an approximate evaluation of its direction, speed and size. Peripheral visual fields were measured in 15 subjects using a Zeiss Jena bowl perimeter.

Evoked potential recording

Silver – silver chloride electrodes were attached to the scalp using collodion. These were filled with electrode jelly and the scalp was abraded to maintain an electrode resistance below 5 kΩ. The VECP was recorded from two electrodes, one over each occipital hemisphere; O1 over left hemisphere and O2 over right hemisphere. These were referred to C3 and C4 respectively [10/20 System (Jasper, 1958)]. The VESP was recorded from two electrodes, one behind each ear, both referred to the vertex electrode CZ. Subjects were seated comfortably and flash stimuli delivered by a Grass PS22 photostimulator 50 cm

from the eye at intensity 2 for the VECP (flash rate 1.8 per second) and intensity 8 for the VESP (flash rate 5 per second). Both binocular and monocular responses were recorded. All responses were averaged by a Nicolet Pathfinder II. The bandpass for the VECP recording was 0.5 – 30 Hz; for the VESP 30 – 500 Hz. Sweep time was 500 ms for the VECP; 50 ms for the VESP. A total of 50 responses were averaged for the VECP and 750 for the VESP. All amplitudes and latencies were measured using the averager's internal cursor.

RESULTS

Initial examination

The preliminary studies of the two 4-week-old babies are not included in the results.

Monocular visual acuities ranged from 2/60 to 6/12. Seven were thought to exhibit strabismus. In four this was convergent (one alternating) and three were divergent. The size of the strabismus ranged from approximately 5 to 25°. Only one albino showed no nystagmus. The visual fields of 10 albinos were slightly constricted but only one subject, an ocular albino, had a major field defect in the form of a right nasal hemianopia with macula sparing. These results are illustrated in Table 1.

Evoked potentials

The flash VECP from a normally-pigmented individual is shown in Fig. 1. The main peaks are labelled P1, N2, P2 and N3; the most consistent component is P2 occurring at about 100 – 120 ms latency (Harding, 1974). The normal VECP may show slight asymmetries or asynchronies but the important feature is that any such asymmetry or asynchrony is present both binocularly and monocularly. Fig. 1 illustrates this. Here the P2 component has almost the same latency over the two hemispheres while the N2P2 amplitude is consistently larger over the right hemisphere compared to the left.

Fig. 2 illustrates a typical VECP of an albino subject. P2 is present over each hemisphere on binocular stimulation. On monocular stimulation of the right eye this component remains over the left hemisphere but becomes reduced in amplitude over the right. The situation reverses on left-eye stimulation; P2 disappears from the left hemisphere and returns, although of small amplitude, over the right hemisphere.

Lateralization of the VECP by latency has been seen in some subjects. Fig. 3 illustrates such a case. In this subject P2 has very similar latencies over the two hemispheres on binocular stimulation while monocularly its latency becomes delayed over the hemisphere ipsilateral to the eye stimulated.

Seven albino subjects showed a distinctly different VECP waveform. In these individuals P1 proved to be the major component; P2 was present but of greatly reduced amplitude. Fig. 4 shows that in such a case P1 (65 ms) behaves similarly to the P2 component seen in Fig. 2. It is present over each hemisphere binocularly but lateralizes over the contralateral hemisphere on monocular stimulation. Such a VECP waveform with a reduction of P2 relative to P1 tended to occur in subjects whose visual acuity was 6/60 or less.

A summary of the VECP findings in individual subjects can be found in Table 1.

The VESP of a normally pigmented subject is illustrated in Fig. 5. (The initial part of the VESP response is not shown in any of the traces as this is contaminated by a flash artifact.) The VESP is a small-amplitude (< 2 μV), positive – negative – positive wave of latency approximately P22, N27, P35 (Harding and Rubinstein, 1980). This small response is recorded on both right and left channels with binocular and monocular stimulation. This is not, however, the case in albino subjects.

Table 1. Details of the patients studied

TYPE	AGE (YEARS)	V.A.		STRABISMUS (SIZE°)	P1 ENLARGED	P2 AMPLITUDE	P2 LATENCY	VESP
		R	L					
OC	20	6/60	6/60	NIL SEEN	C	=	C	I
OC	21	6/60	6/60	NIL SEEN	C	I	C	=
OC	9	6/36	6/36	NIL SEEN	=	=	C	I
OC	11	5/60	5/60	LCS(20)	=	=	C	=
OC	16	6/60	6/60	NIL SEEN	C	I/C	I	C
OC	6	6/36	6/18	RDS(5)	=	I/C	C	I
OC	8	6/18	6/18	NIL SEEN	=	=	=	C
OC	12	6/18	6/18	NIL SEEN	=	=	C	C
OC	16	6/36	6/24	NIL SEEN	=	=	C	I
O*	14	6/36	6/12	NIL SEEN	=	C	C	=
OC	0.6	-	-	NIL SEEN	=	C	=	C
O	14	6/18	6/18	ACS(15)	=	C	C	C
OC	11	6/60	6/60	LDS(25)	C	=	C	I
OC	27	6/36	6/36	RCS(5)	=	I	C	C
OC	9	6/36	6/36	LCS(15)	=	=	C	I
OC	5	6/24	6/36	NIL SEEN	=	C	C	I
OC	9	6/36	6/36	RDS(10)	=	C	=	I
OC	8	6/24	6/60	NIL SEEN	=	C	=	=
O**	6	-	-	NIL SEEN	=	C	C	-
OC	21	6/60	6/60	NIL SEEN	C	C	C	I
OC	20	5/60	4/60	NIL SEEN	C	=	C	I
OC	5	2/60	2/60	NIL SEEN	C	=	=	C
O	35	6/24	6/18	NIL SEEN	=	C	C	=

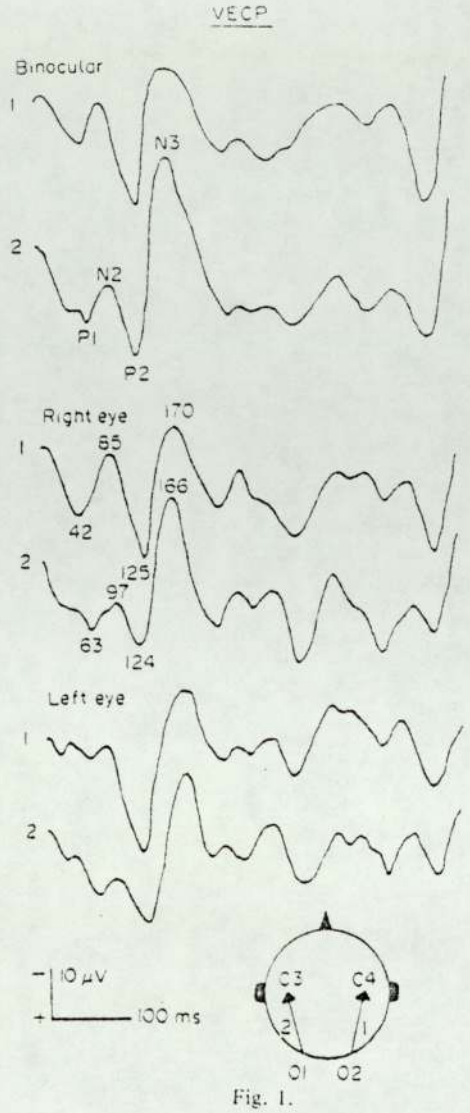

Fig. 1.

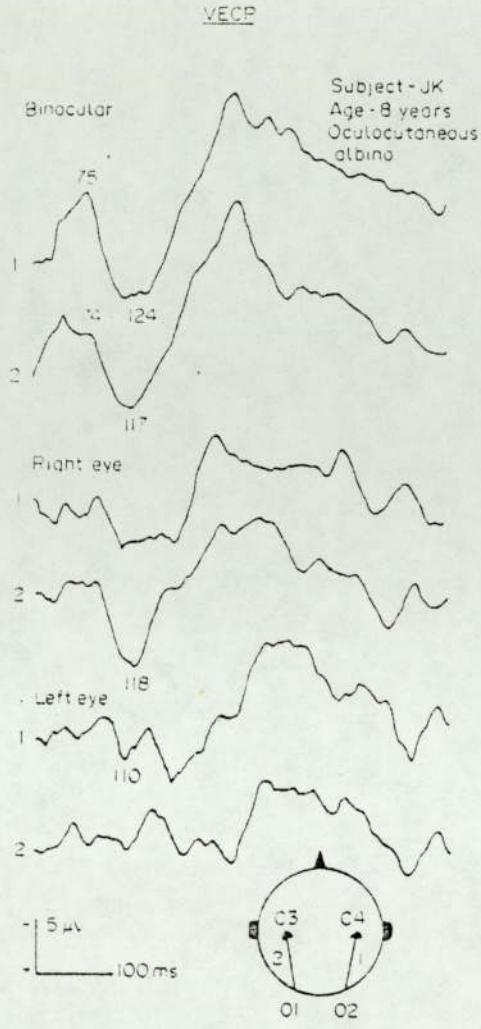

Fig. 2.

Fig. 1. Typical flash VECP in a normally-pigmented individual. The major peaks (P1, N2, P2 and N3) are labelled. The P2 component has almost the same latency over the two hemispheres. The N2P2 amplitude is consistently larger over the right hemisphere compared to the left.

Fig. 2. VECP in an albino showing monocular hemispheric asymmetry. The amplitude of the N2P2 configuration is reduced over the hemisphere ipsilateral to the eye stimulated.

One typical pattern of VESP lateralization seen in albinos is shown in Fig. 6. In this case, as in the normally pigmented individual, the response is recorded on both channels with binocular stimulation but only on the contralateral channel when one eye alone is

Key for Table 1: OC, oculocutaneous albino; O, ocular albino; VA, visual acuity; ACS, alternating convergent strabismus; LCS, left convergent strabismus; RCS, right convergent strabismus; LDS, left divergent strabismus; RDS, right divergent strabismus; *, right nasal hemianopia with macular sparing; **, no nystagmus present; –, test not performed; C, contralateral lateralization on monocular stimulation; I, ipsilateral lateralization on monocular stimulation; =, no lateralization on monocular stimulation.

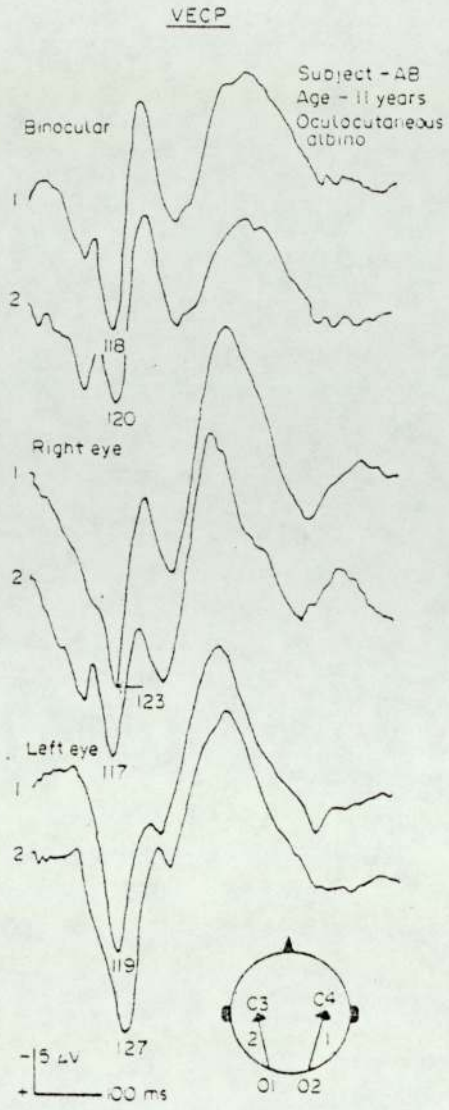

Fig. 3.

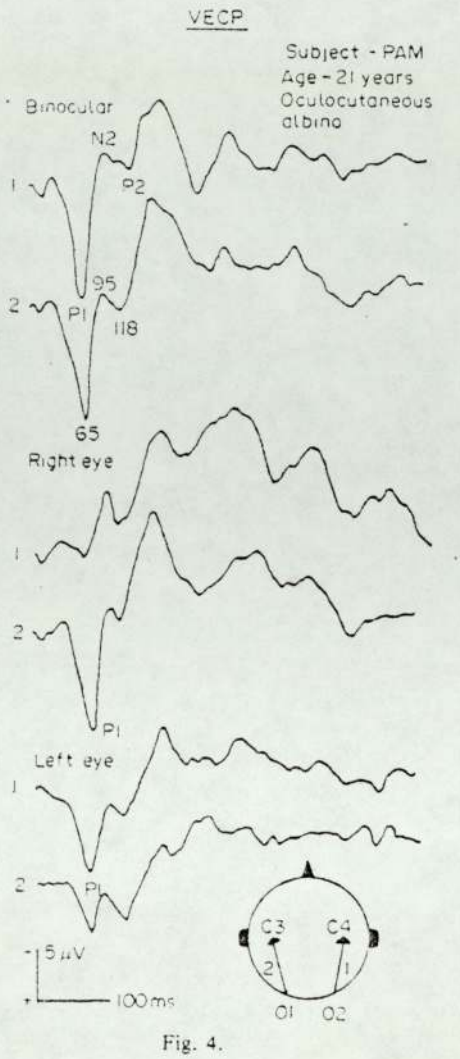

Fig. 4.

Fig. 3. VECP in an albino showing monocular hemispheric asynchrony. The latency of the P2 component is delayed over the hemisphere ipsilateral to the eye stimulated.

Fig. 4. VECP in an albino; P1 is the major component. Monocular responses show hemispheric asymmetry; P1 is present over the hemisphere contralateral to the eye stimulated.

stimulated. Such a pattern of lateralization has been found in seven albino subjects (see Table 1). However, this pattern of lateralization was not the only one which was found in albinos. In Fig. 7 the VESP is seen to lateralize over the ipsilateral channel to the eye stimulated on monocular stimulation. This pattern has been recorded in ten albino subjects all of whom showed the opposite (contralateral) lateralization of the VECP (see Table 1).

It appears possible to demonstrate misrouting in a baby as young as 7 months of age. Fig. 8 shows that in this subject both the VECP and the VESP lateralize over the contralateral hemisphere on monocular stimulation.

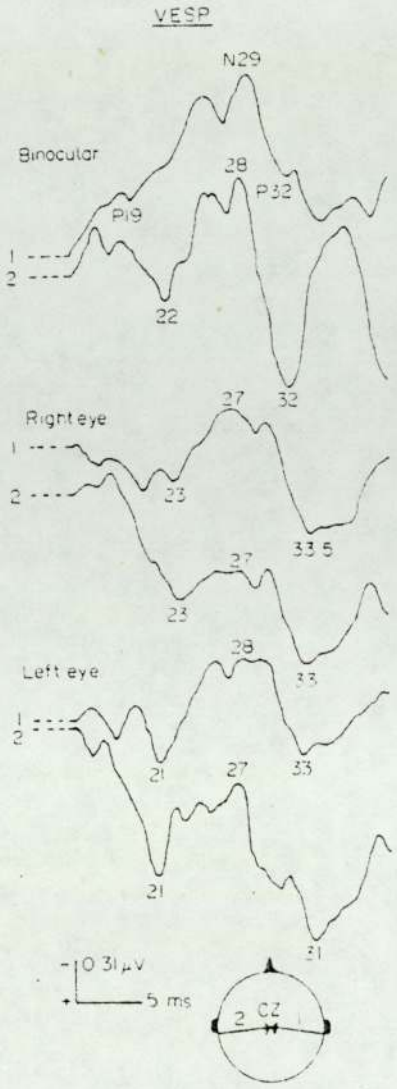

Fig. 5.

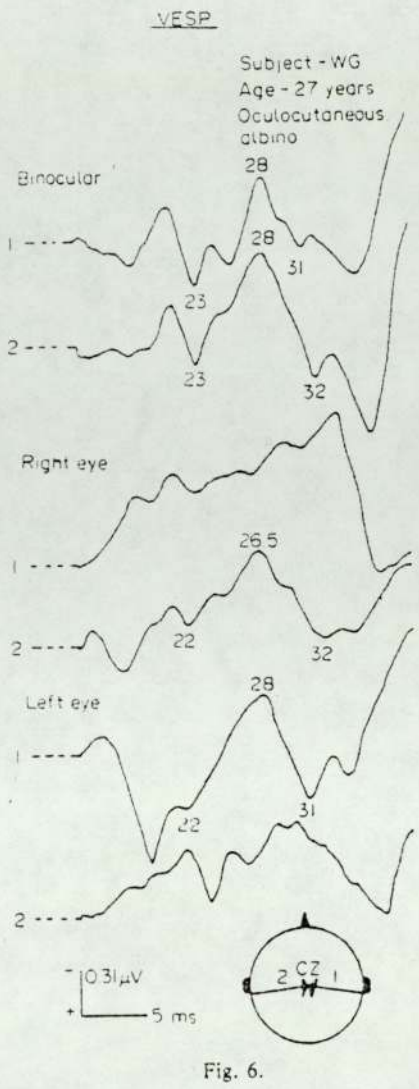

Fig. 6.

Fig. 5. VESP in a normally pigmented individual showing the typical PNP configuration.

Fig. 6. VESP in an albino showing contralateral lateralization with monocular stimulation.

DISCUSSION

Optic nerve fibre misrouting can be identified successfully in human albinos using visual-evoked potential techniques. The major component of the VECP may be P1 or P2; whichever peak dominates appears related to the visual acuity. It is not known whether low visual acuity itself produces an enlarged P1 component or if an enlarged P1 can be said to be indicative of poor visual acuity. That the flash stimulus is more useful than pattern in albino subjects with reduced visual acuity and nystagmus is not surprising. Other authors have reported pattern reversal to be a poor stimulus in albinos (Creel *et al.*, 1981a) and indeed much of the published data using this technique have shown monocular lateralization of the order of less than 1 μV (Jay and Carroll, 1980). That flash is useful in

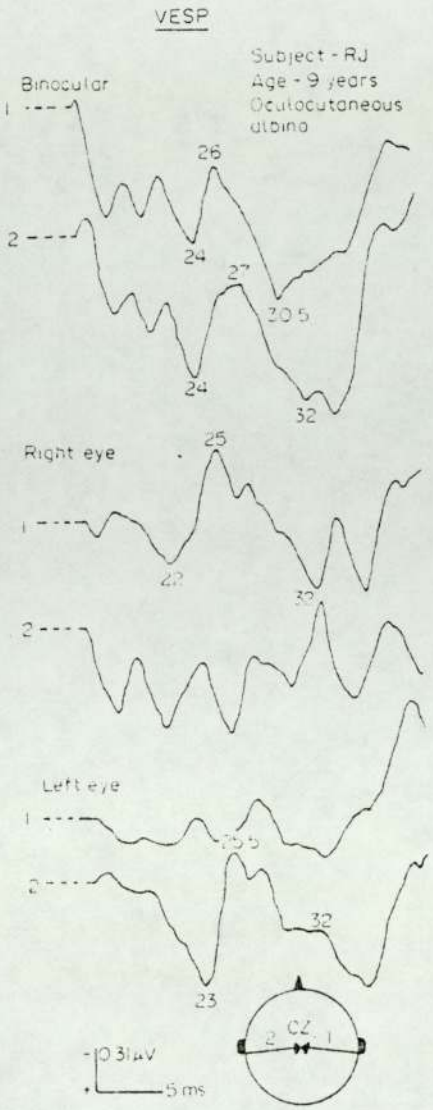

Fig. 7. VESP in an albino showing ipsilateral lateralization with monocular stimulation.

this situation also correlates well with the efficacy of this technique in another condition characterized by reduced visual acuity, namely hereditary optic atrophy (Harding and Crews, 1982). The results presented in this report show that contralateral lateralization on monocular stimulation characterizes the VECP and, in some subjects, the VESP. The unexpected (ipsilateral) lateralization of the latter response in some subjects is currently under investigation. At the moment the only explanation we can offer for such a result is related to the anatomical studies by Guillery *et al.* (1975) on the human albino brain. The lateral geniculate nucleus in some albinos may be rotated to such an extent that the dipole orientation is altered. In this case it may be possible for the VESP to be generated on one side, but recorded more efficiently by the electrodes on the opposite side of the head. Such a model has been proposed for the pattern reversal evoked cortical potential (Blumhardt and Halliday, 1979).

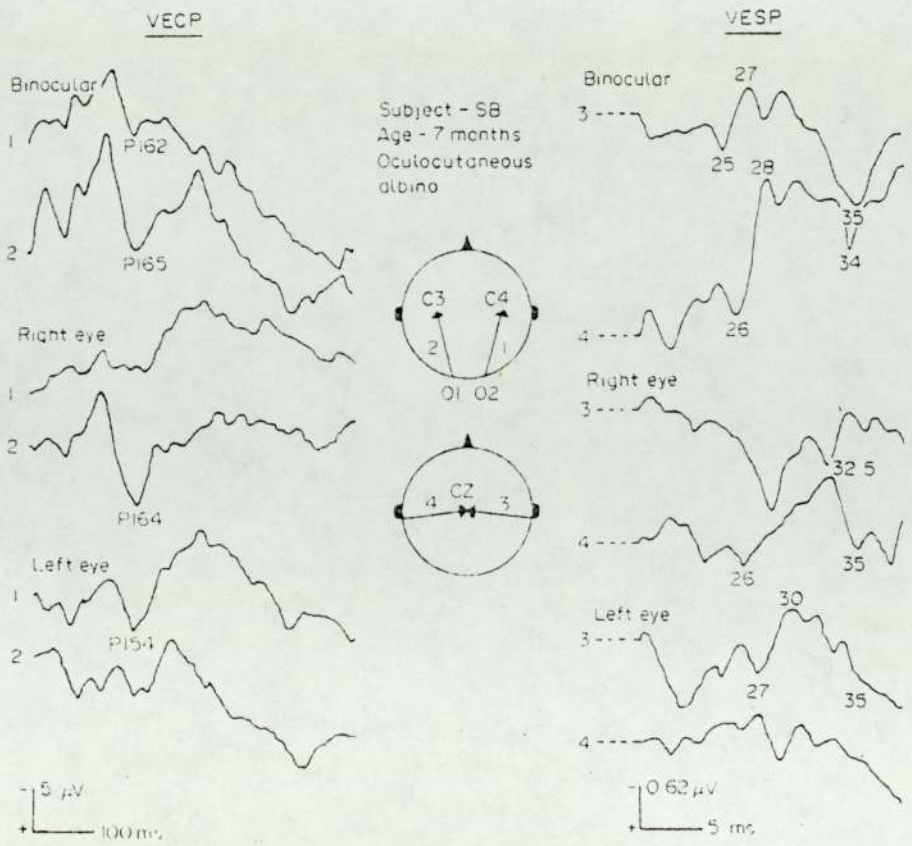

Fig. 8. VECP and VESP of a 7-month-old albino. Contralateral lateralization of both responses is present.

Now that it has been ascertained that misrouting does occur in human albinos the question arises as to how this may relate to the other visual problems commonly associated with the condition, namely reduced visual acuity, strabismus and nystagmus.

Reduced visual acuity

The major causative factor of reduced visual acuity in human albinos appear to be malformation of the fovea. The foveal reflex is absent (Vogt, 1924) and anatomical studies by O'Donnell *et al.* (1976) and Fulton *et al.* (1978) have failed to show foveal differentiation in either ocular or oculocutaneous albinos. The latter authors reported the fovea to be absent, the ganglion cell layer being present throughout the retina. The central cones resembled those found normally in the parafoveal area.

Packwood and Gordon (1975) reported Siamese cats to have the same visual acuity as normal pigmented animals while Blake and Antoinetti (1976) found abnormal contrast sensitivity in these animals. Chino *et al.* (1978) reported that the Siamese cat retina is dominated by X-cells, the number of Y-cells being significantly reduced compared to normal. This would support the finding of normal visual acuity in these animals as X-cells have been closely associated with visual acuity (Enroth-Cugell and Robson, 1966). However, Shatz (1977) found some Siamese cats with poorly defined area centrales and more detailed anatomical studies by Stone *et al.* (1978) found this region to be "underdeveloped" with a low peak ganglion cell count. Throughout the retina there was a

reduction in the incidence of cells of possibly the X-type. These results lend support to but do not confirm the findings of Blake and Antoinetti (1976).

Consequently, relating animal studies to those in humans in this area is very difficult. Visual acuity measurement in man is a relatively easy procedure compared to the methods which have to be employed in animal work. There is a definite anatomical basis for the reduced visual acuity in humans and it is probable that the main cause of defective acuity is not the misrouting but more the reduced pigment formation. It is thought that melanin may possibly influence the development of the fovea (Carr and Siegel, 1979). This theory is supported by the observation that the more pigmented an albino the greater usually is his visual acuity (Carr and Siegel, 1979).

Strabismus

Strabismus can be a feature of human albinism as shown in this and other studies (Carroll *et al.*, 1980b). However, it is often difficult to assess and measure accurately due to the variable nystagmus usually present in these subjects. Albinos also appear to have no stereopsis (Coleman *et al.*, 1979; Creel *et al.*, 1981a, b).

The presence of misrouting in the Siamese cat aroused interest as these animals were said to show a high incidence of convergent strabismus; it was thought that the two could possibly be linked (Guillery, 1969). The development of a convergent strabismus would be advantageous in that the nasal retina would be favoured over the temporal retina which gives rise to the misrouted fibres. The squint was thought to be secondary to the misrouting (Hubel and Wiesel, 1971; Guillery and Kaas, 1971) and its presence and size dependent on the number of misrouted fibres (Guillery, 1969; Guillery and Kass, 1971).

Berman and Cynader (1972) found abnormal retinotectal pathways in Siamese cats. They concluded that the convergent strabismus exhibited by the animals was an adaptive response to these abnormal projections.

Packwood and Gordon (1975) found no stereopsis in the Siamese cats and studies by Cool and Crawford (1972) showed a total lack of binocular cells in the striate cortex of these animals. Of these cats at least two were thought to be orthophoric the rest displayed varying degrees of esotropia. Cool and Crawford commented that, if the strabismus was secondary, resulting from a lack of central mechanisms for coding binocular fusion and stereopsis, then all of the cats in their study should have exhibited a strabismus. Consequently, they considered the squint to be primary and not dependent on binocular innervation of the cortex.

However, one must bear in mind that different methods of measuring ocular alignment in cats have been used by different investigators. Some consider only the gross appearance (Blake and Antoinetti, 1976; Kaas and Guillery, 1973); here problems of eye movement and anatomical factors such as prominent canthi may effect results. If electrophysiological investigations are to be carried out measurement is often made under anaesthesia (Hubel and Wiesel, 1971; Shatz, 1977). Corneal reflex photography is another technique and Rengstorff (1976) utilized this to study a large number of Siamese cats. This work showed that these animals may be orthophoric or possess varying degrees of intermittent or constant esotropia or exotropia. This agrees with our findings that human albinos may show either a convergent of divergent strabismus.

Clearly, although a link may exist between the misrouting and the strabismus in albinos the relationship does not appear to be a simple one. We do not as yet know whether misrouting affects the retinotectal pathway in humans; it has been thought that this may contribute to the strabismus in such subjects (Creel *et al.*, 1979). It seems that both animal

and human albinos can exhibit varying degrees of strabismus. When viewing results experimental methods must be considered in the former case of animals while in humans factors such as high refractive errors often seen in such subjects (Edmunds, 1949; Taylor, 1978) become important.

Nystagmus

Nystagmus is a common feature of human albinism and is thought to be due to the lack of foveal differentiation (Duke-Elder, 1964). In animal studies its occurrence is poorly documented. Gross and Hickey (1980) reported its presence in an albino monkey and it has been occasionally reported in Siamese cats (Creel, 1971a; Cool and Crawford, 1972; Loop and Frey, 1981). Abnormal pathways to the midbrain have been thought to contribute to nystagmus in animals (Creel *et al.*, 1979) but as yet we are not aware if this may be the case in human albinos. Hence, as in the case of strabismus, there may be a link between nystagmus and misrouting or it may simply be a feature of human albinism arising from poor central fixation.

CONCLUSIONS

Misrouting of optic nerve fibres is present in human albinos and may in some way be related to the concomitant visual problems associated with the condition. From the evidence available at the moment it seems that the reduced visual acuity and nystagmus seen in human albinos may not be directly related to the misrouting but more a feature of the condition arising from reduced melanin formation in the retinal pigment epithelium (Carr and Siegel, 1979). There may, however, be a more intimate relationship between the abnormal projections and the development of strabismus.

From the findings of the present study it can be concluded that the most reliable indicator of misrouting is the latency of the P2 component to flash stimulation. If visual acuity is grossly reduced the most reliable indicator is the amplitude of the P1 component. With regard to the VESP, although the response becomes asymmetric on monocular stimulation, the lateralization does not appear to follow a simple model of misrouting.

Although the cause of the misrouting is unknown, the albinos do form an interesting group for study. This is an ideal area in which work on animals and humans can unite. Such studies will help make us more aware of the problems and pitfalls involved in each area. The Siamese cat visual system is not totally suitable for direct comparison to that of humans but further work on primates, such as that by Gross and Hickey (1980) on the monkey may be of more direct relevance. Developmental studies on albino babies such as we are currently undertaking may also provide results. Together these investigations may help not only in our understanding of the condition of albinism but also widen our knowledge about the visual pathway and its development.

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MISROUTING OF THE VISUAL PATHWAY IN HUMAN ALBINOS STUDIED USING VISUALLY EVOKED CORTICAL AND SUBCORTICAL POTENTIALS.

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In recent years it has become apparent that the visual pathway of albino animals differs from that of their normally pigmented counterparts. Sheridan (1965) originally suggested that in albino animals there could be a reduction in the number of uncrossed optic nerve fibres and subsequent studies have revealed that in a wide range of albinos some of the fibres from the temporal retina, which normally pass to the ipsilateral side of the brain, are misrouted at the optic chiasma and terminate in the contralateral hemisphere (see Guillery 1974, 1978, for reviews).

Anatomical evidence for such misrouting in human albinos is very sparse. Guillery, Okoro and Witkop (1975) examined the brain of one oculocutaneous albino. The lateral geniculate nucleus (LGN) was found to be smaller than normal and rotated from its usual position. In addition, extensive, abnormal fusions between geniculate layers were also present and it was concluded that the retinogeniculate pathway in this individual was abnormal and possibly indicative of albino-type misrouting.

A simple, non-invasive technique of examining the visual pathway of human albinos is by the use of visually evoked potentials. If the evoked potential is recorded over each hemisphere on monocular stimulation, due to the preponderance of crossed optic nerve fibres, one would expect the response to lateralise over the contralateral hemisphere. Hence, on right eye stimulation the response should have a shorter latency and/or a greater amplitude over the left hemisphere compared to the right. The reverse should be found on left eye stimulation.

This technique has been found to be successful in identifying misrouting in human albinos when recording the visually evoked cortical potential (VECP) to flash (Creel, Witkop and King, 1974; Creel, O'Donnell and Witkop, 1978), pattern reversal (Carroll, Jay, McDonald and Halliday, 1980a,b; Jay and Carroll, 1980) and pattern appearance-disappearance stimulation (Creel, Spekreijse and Reits 1981a,b). The presented study investigates the use of all the above stimulation techniques in albinos and in addition utilises the relatively new method of recording the visually evoked subcortical potential (VESP) to a flash stimulus. The latter potential is recorded from early in the visual pathway from a post-chiasmal but pre-cortical site and is most probably of LGN origin (Harding and Rubinstein 1980, 1982). This technique offers the possibility of detecting albino misrouting at a site in the visual pathway before the visual cortex is reached.

METHODS

Twenty-two human albinos (20 oculocutaneous; 2 ocular) were examined; age range 5-35 years. The binocular and monocular visual acuities were measured and the presence of strabismus and nystagmus noted. In addition, a group of age and sex matched normally pigmented control subjects were examined under identical conditions.

Silver-silver chloride electrodes were attached to the scalp using collodion. These were filled with electrode jelly and the scalp abraded to maintain an electrode resistance of 5 KOhms. Electrode positioning varied dependent upon the stimulus type. For pattern reversal identical sites were used to those of Carroll et al. (1980a,b) and Jay and Carroll (1980). A midline electrode was placed 5 cm above the inion with additional electrodes 5 and 10 cm laterally. Pattern appearance-disappearance was recorded from electrodes Oz,O1,O2,O3 and O4 (10/20 system: Jasper 1958). In the above two cases a common reference, Fz, was used. Flash VECPs were recorded from O1 and O2 referred to C3 and C4 respectively and VESPs from bilateral high mastoid sites (A1 and A2) referred to Cz.

Pattern reversal stimulation was provided by a Nicolet T.V. system, field size 11 x 14 degrees. Routinely 50' checks were used (contrast 93%) with a stimulation rate of 2 reversals per second. Pattern appearance-disappearance was provided by an S.C. Electronics grating generator T221

linked to a Hitachi Video monitor subtending 14 x 18 degrees. A Research Machine 380Z computer was used to trigger the stimulator to produce checks of approximately 80% contrast appearing for 100 ms followed by a blank field of the same mean luminance (100 candelas per square metre) for 400 ms. Flash stimulation was delivered by a Grass PS22 photostimulator 50 cm from the eye at intensity 2 for the VECP (flash rate 1.8 per second) and intensity 8 for the VESP (flash rate 5 per second). Fifty responses were averaged for all VECP recordings and 500-750 for the VESP. In all cases binocular and monocular responses were recorded.

Averaging was performed by a Nicolet Pathfinder II. Bandpass for the VECP was 0.5-30 Hz and 30-500 Hz for the VESP. All amplitudes and latencies were measured using the averager's internal cursor.

RESULTS I - VECP

Initially, 2 subjects were examined using pattern reversal. However, this form of stimulation proved unsuitable for evoking responses in albinos. This is shown in Figure 1. As can be seen in the pattern reversal response of both subjects there is little or no evidence of a P100 component. Pattern appearance disappearance stimulation evokes responses with more easily recognisable components (see Figure 1.) but statistically significant contralateral

lateralisation on monocular stimulation of albinos was only found using a flash stimulus.

The most consistent finding was one of clear contralateral monocular lateralisation with respect to the latency of the P2 component such that P2 has a shorter latency over the hemisphere contralateral to the eye stimulated (Figure 2).

The flash VECP usually contains three early components; P1, N2 and P2, the latter being the largest and most consistent component (Harding, 1974). For statistical analysis of the results the responses of each albino and control subject were measured in terms of the P1, N2, P2 latencies and P1N2, N2P2 amplitudes. Measures were made over each hemisphere on binocular and monocular stimulation and the data subjected to two-way analysis of variance. None of the component measures showed statistically significant contralateral monocular lateralisations in the control group. In the albinos only the P2 latency showed statistically significant contralateral lateralisation ($p < 0.001$). The mean amount of contralateral lateralisation with the albinos was 6.21 ms (standard error 2.0ms) compared to only 0.36 ms (standard error 0.52) for the controls.

RESULTS II - VESP

The VESP results obtained within the albino group were somewhat unexpected. In the control group bilateral VESPs

characterised by small amplitude positive-negative-positive configurations at 22-35 ms were usually recorded on binocular and monocular stimulation (Figure 3.). Within the albino group 9 subjects showed the expected contralateral lateralisation (Figure 4) but 13 showed equally clear ipsilateral monocular lateralisation (Figure 5). On the basis of monocular lateralisation of the VESP it was thus impossible to differentiate with certainty between albino and control subjects.

DISCUSSION

That flash is the most successful form of stimulation for identifying optic nerve fibre misrouting in albinos is not surprising if one considers the major ocular feature of the condition, notably reduced visual acuity (Taylor 1978). The flash VECP is particularly useful in the presence of low vision due to a variety of causes where pattern stimulation is impossible (Harding 1974, Thompson and Harding 1978, Harding and Crews, 1982).
The fact that it is only the P2 component latency which shows statistically significant contralateral lateralisation is probably due to the fact that this is the largest and most consistent component of the response (Spehlmann 1965, Dustman and Beck 1965, Harding, 1974) and in addition, of the two, latency is a more reliable measure than amplitude (Vaughan 1966, 1969, Lewis, Dustman and Beck, 1972, Aunon and Cantor, 1977).

The absence of consistent contralateral lateralisation of the VESP is probably due to the anatomical arrangement of the human visual pathway. The visual cortex is situated on the occipital pole (see Figure 6.). The recording electrodes (O1 and O2) are placed directly over the generator sites and are ideally positioned for recordings from each hemisphere leading to contralateral lateralisation of the response on monocular stimulation. However, the two LGNs lie in fairly close proximity near the centre of the brain. The recording electrodes are situated some distance from the generator sites (Figure 6) and it is possible that although a potential may be generated primarily by one LGN, it may be recorded almost equally by either electrode A1 or A2. Thus, both contralateral and ipsilateral lateralisations may be found within the albino group with no predominant pattern.

FIGURE LEGENDS

FIGURE 1.

Illustration of the pattern reversal and pattern appearance-disappearance responses of two albino subjects. The pattern reversal responses are poorly formed with little or no evidence of a P100 component. The pattern appearance-disappearance responses are also not fully developed but tend to show more easily identifiable components.

FIGURE 2.

The binocular and monocular VECPs of an albino subject. These responses illustrate the most consistent finding within the albino group. The P2 component (labelled with latency values) shows contralateral lateralisation on monocular stimulation; the component has a shorter latency over the hemisphere contralateral to the eye stimulated.

FIGURE 3.

The binocular and monocular VESPs of a normally-pigmented control subject. A clear positive-negative-positive configuration is recorded bilaterally on both binocular and monocular stimulation.

FIGURE 4.

The binocular and monocular VESPs of one albino subject. The binocular responses are not clearly seen but the expected contralateral lateralisation on monocular stimulation is found.

FIGURE 5.

The binocular and monocular VESPs of one albino subject. The binocular responses are clearly seen as a bilateral positive-negative-positive configuration. The monocular responses show clear ipsilateral lateralisation.

FIGURE 6.

Shows the anatomical arrangement of the human visual pathway illustrating the sites of the lateral geniculate nuclei and the visual cortex. The relative positions of these structures to the recording electrodes are shown (see text for further details).

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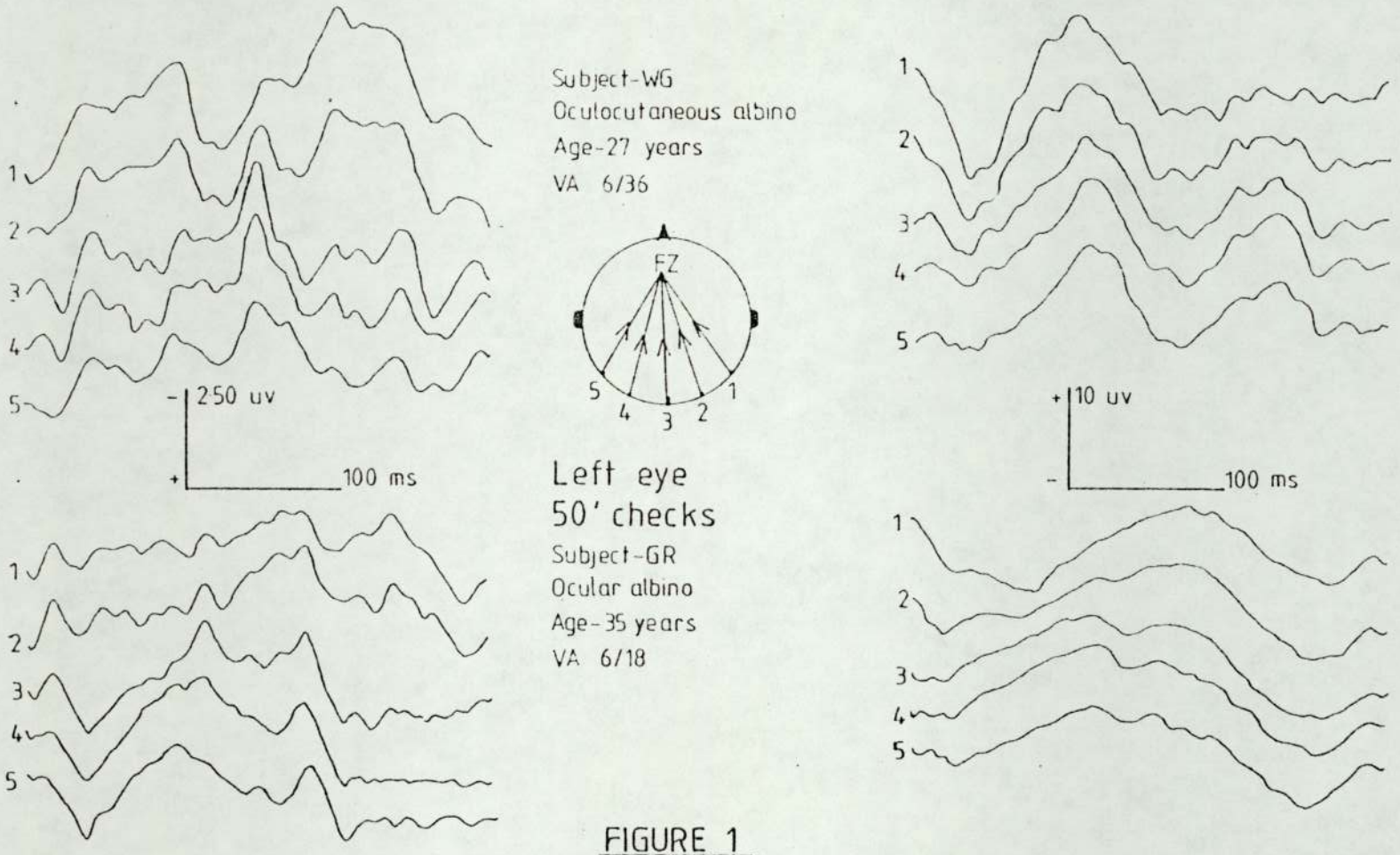
PATTERN REVERSAL
PATTERN APP/DISAPP
Subject-WG
Oculocutaneous albino
Age-27 years
VA 6/36
FZ
5
4
3
2
1
250 uv
100 ms
10 uv
100 ms
Left eye
50' checks
Subject-GR
Ocular albino
Age-35 years
VA 6/18

FIGURE 1

FLASH VECP

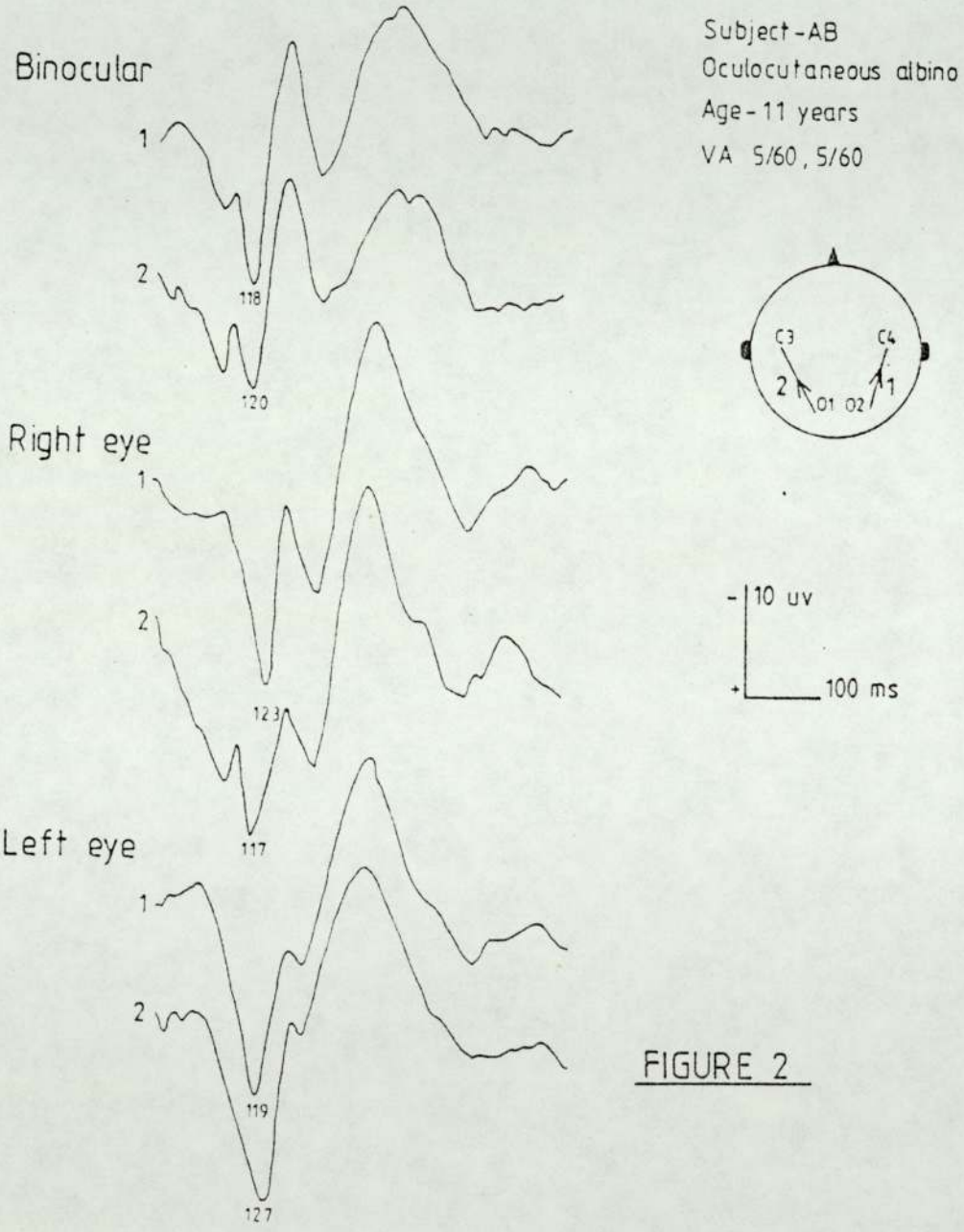

FIGURE 2

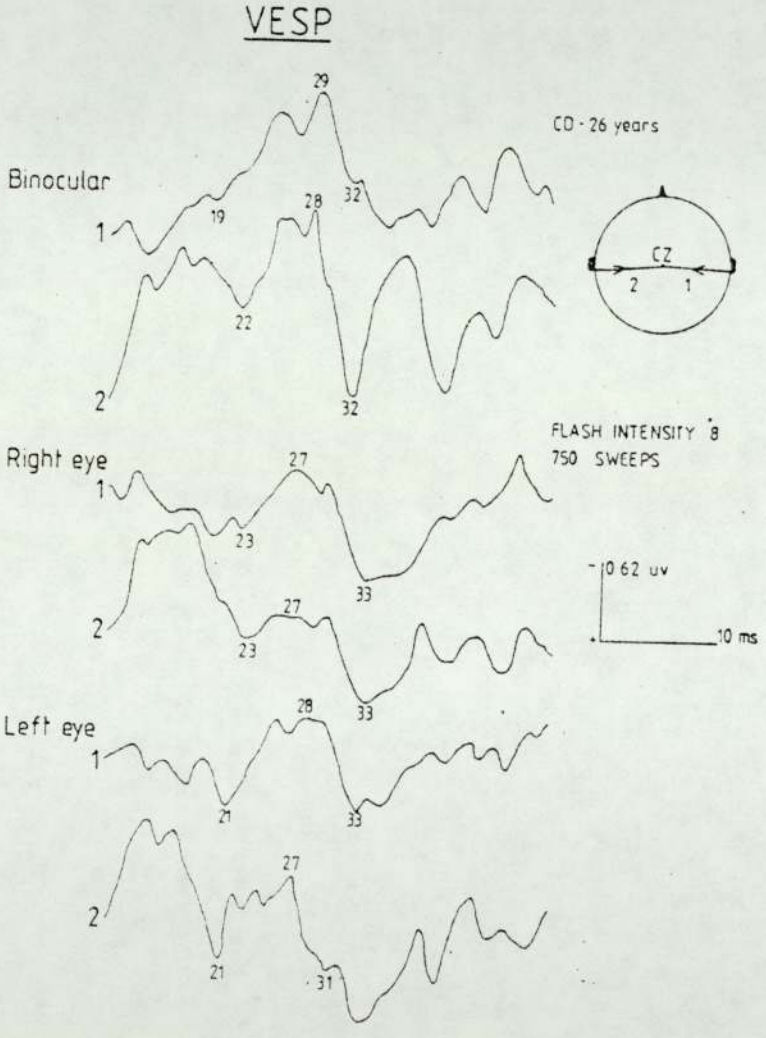
VESP
CO - 26 years
Binocular
1
2
29
19
28
32
22
32
CZ
2
1
FLASH INTENSITY 8
750 SWEEPS
Right eye
1
2
27
23
33
23
27
33
0 62 uv
10 ms
Left eye
1
2
28
21
33
27
21
31

FIGURE 3

VESP

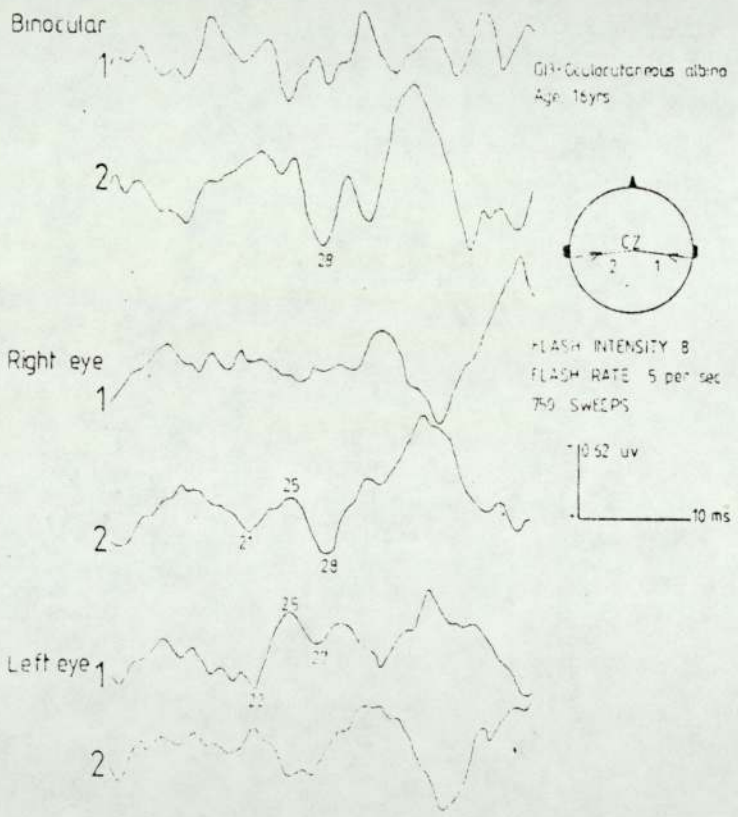

FIGURE 4

VESP

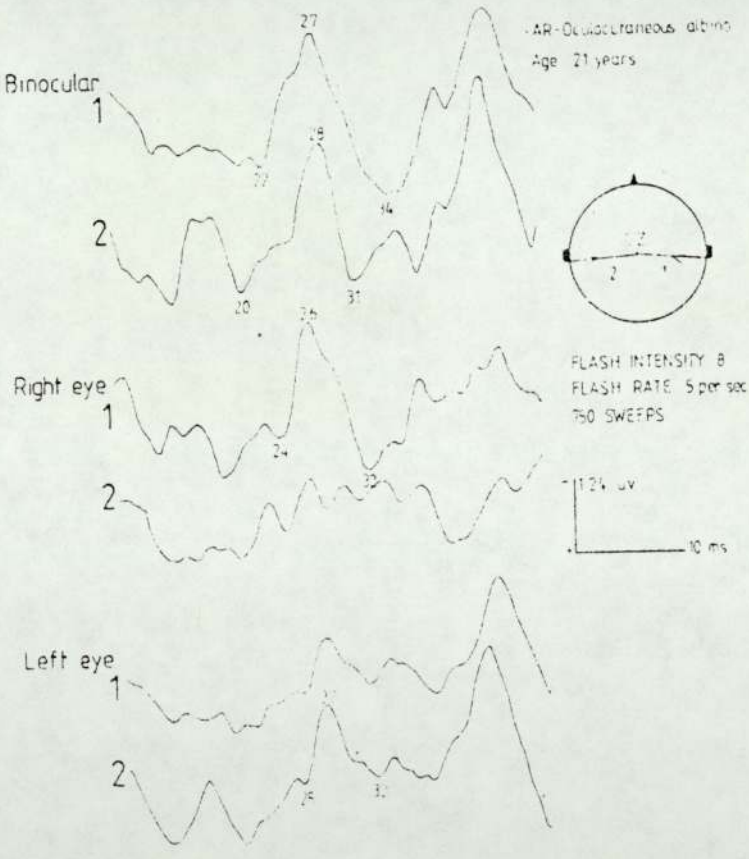

FIGURE 5

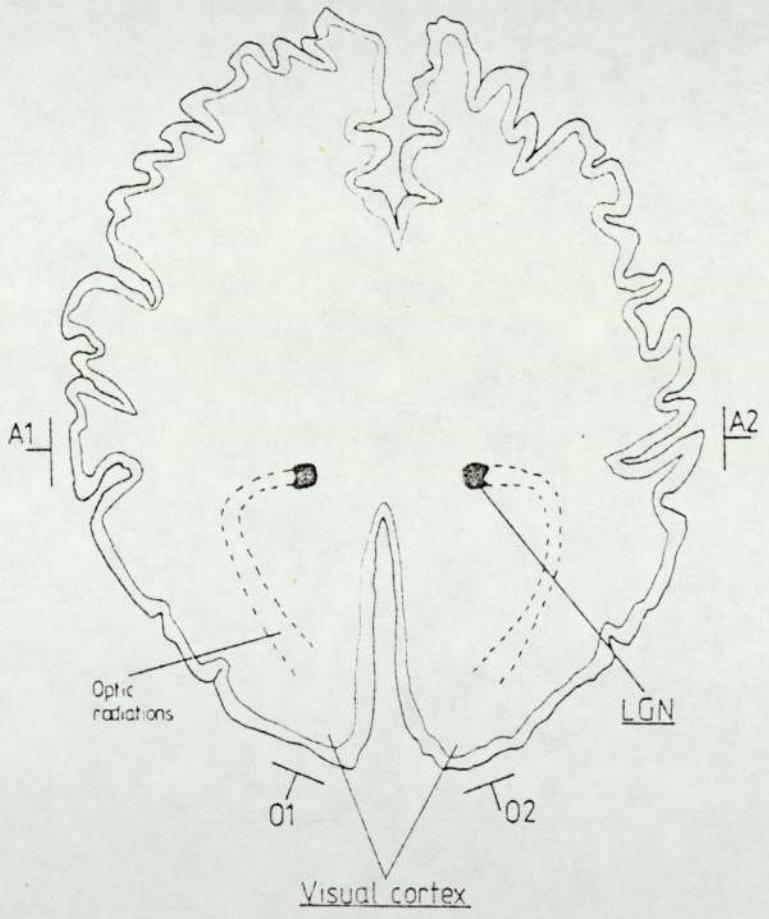

FIGURE 6

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