The Effect of the Menstrual Cycle on Visual Performance

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Declaration

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Abstract

The primary purpose of this thesis was to investigate the effect of the normal human menstrual cycle on visual performance.

Optimum experimental design was established for the serial measurement of the peripheral visual field by automated perimetry using program 30/60-2 of the Humphrey Field Analyser (HFA). A proportion of subjects demonstrated learning effects over the first two sessions. In subsequent investigations the first two field plots were discarded from the data set.

A pilot study investigated the effect of the menstrual cycle on central 30-2 and peripheral 30/60-2 fields of the HFA on 11 normally menstruating women. Subjects attended two to three times weekly for 10 weeks. There was much inter- and intra-subject variability. Although mean sensitivity of the visual field decreased over the first cycle, this was not repeated in a second cycle. The large degree of variability and noise inherent in the data may be masking any menstrual cycle fluctuation. Self-reported symptomatology was assessed using the Moos Menstrual Distress Questionnaire (MDQ). Subjects prospectively reported few fluctuations in symptomatology associated with the menstrual cycle.

The main study, using a protocol design taking into account conclusions drawn from the pilot study, investigated the effect of the menstrual cycle on the central 24-2 field of the HFA, contrast sensitivity at five spatial frequencies (0.75, 1.5, 4, 8 and 14cpd), logMAR high and low contrast visual acuity, and pupil diameter. Subject groups comprised 18 normally menstruating women (F), and control groups of eight women taking oral contraceptives (P) and four men (M). Subjects attended two to three times weekly for six to 10 weeks and were unaware of the purpose of the study. Daily self-report questionnaires assessed mood and physical symptomatology. There was a large degree of inter- and intra-subject variability with overall no significant repeatable fluctuation in any visual field performance measure across the menstrual cycle in P or F, or across a randomly allocated 28 day cycle in M. Curve-fitting techniques identified a significant cosine curve in mean sensitivity of the visual field in group F over the three cycles as a whole ($F(1,245)=4.62$, $p=0.03$), suggesting peaks in sensitivity around mid-cycle with low points paramenstrually. However, when repeated on individual cycles, a significant cosine curve was identified in one cycle alone, thus highlighting inter-cycle differences. The extent of fluctuation was 0.5dB and thus not clinically significant. These significant curve fits in the F accounted for less than 10% of the variance in mean sensitivity, with a spurious curve in one 'cycle' of the M control group accounting for about 50% of the variance. Any conclusions must therefore be drawn cautiously.

Abdominal pain and backache were greater paramenstrually in all women, with no repeatable cyclical pattern in symptoms of mood in either group of women. Overall men reported higher scores of both mood swings and positive mood, and similar scores of irritability as women. Visual performance was not found to be dependent upon mood and physical symptomatology.

Fluctuations in visual performance across the menstrual cycle are unlikely to be a contributory factor in reported increases in accident rates paramenstrually.

Key of Abbreviations

ANS	Autonomic nervous system
asb	Apostilb
CAG	Closed angle glaucoma
CCT	Central corneal thickness
CFFT	Critical flicker fusion threshold
CNS	Central nervous system
CPSD	Corrected pattern standard deviation
CRT	Cathode ray tube
CTT	Corneal touch threshold
dB	Decibel
EDA	Electrodermal activity
FL	Fixation losses
FN	False negative errors
FP	False positive errors
FSH	Follicle stimulating hormone
HFA	Humphrey Field Analyser
HR	Heart rate
IOP	Intra-ocular pressure
LF	Long-term fluctuation
LH	Luteinising hormone
MAO	Monoamine oxidase
MD	Mean defect/deviation
OC	Oral contraceptives
PMS	Premenstrual syndrome
POAG	Primary open angle glaucoma
PSD	Pattern standard deviation
SD	Standard deviation
SE	Standard error
SF	Short-term fluctuation
SNK	Student-Newman-Keuls multiple range test
TFFT	Two-flash fusion threshold

CHAPTER 1

Introduction

1.1 The human female menstrual cycle

The normal female human reproductive cycle lasts 28 days (± 4 days) (Franz 1988) and can be described in terms of two cycles; **ovarian** and **uterine** (Marieb 1989). A schematic summary of the hormone levels throughout the menstrual cycle is shown in figure 1.1.

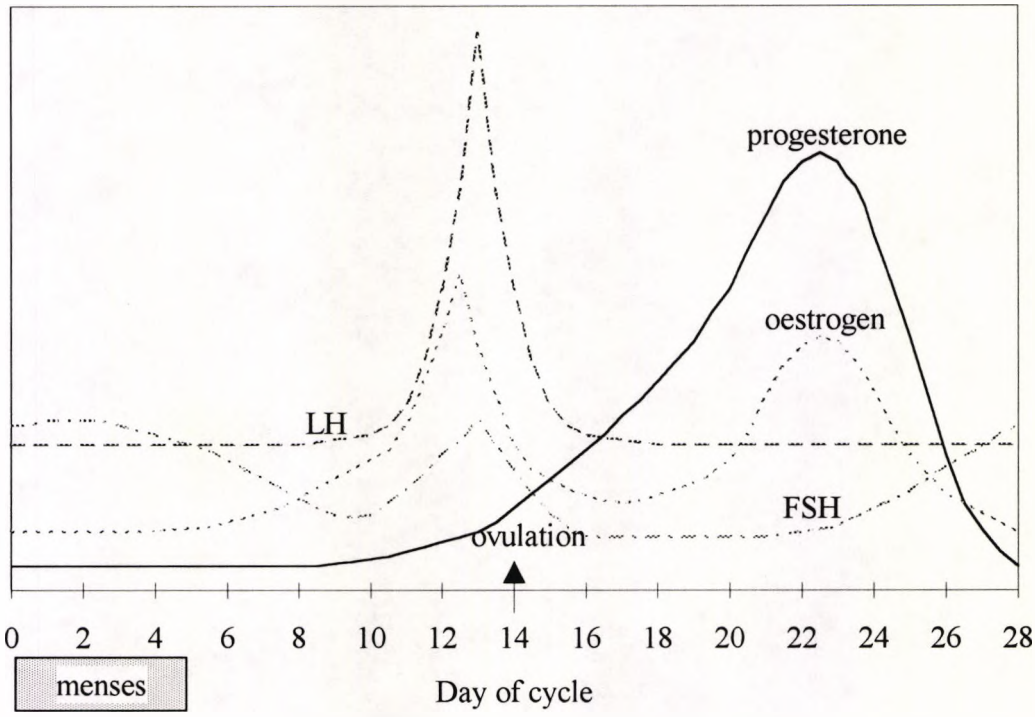

Figure 1.1 Schematic summary of hormone fluctuations throughout the normal human menstrual cycle.

The **ovarian cycle** describes ovulation and its hormonal regulation and consists of three phases; follicular (days 1-10), ovulatory (days 11-14) and luteal (days 15-28).

During the follicular phase, follicle stimulating hormone (FSH) and luteinizing hormone (LH) are released from the anterior pituitary under the influence of increasing gonadotropin releasing hormone (GnRH) from the hypothalamus. Increasing levels of FSH and LH stimulate the growth of several primordial follicles already present in the ovary. One

follicle will undergo complete maturation to become a Graafian follicle containing an ovum, the female gamete. The remaining immature follicles degenerate in the ovary.

As the follicle matures it begins to secrete oestrogen into the blood plasma. Low levels of oestrogen have a negative feedback effect on the hypothalamus, decreasing the output of FSH and LH and thus preventing any further follicle development. As the Graafian follicle further matures the levels of oestrogen increase still further. A threshold level is reached above which oestrogen causes a positive feedback to the hypothalamus and a sudden burst of LH is released. The release of LH induces ovulation, when the ovum is released into the peritoneal cavity and begins its journey along the fallopian tube. A small amount of FSH is also released, but the purpose of this is unclear.

The ruptured follicle collapses to form the corpus luteum which acts as a temporary endocrine organ in the ovary, continuing to secrete mainly progesterone and some oestrogen throughout the early luteal phase. The increasing blood plasma levels of these hormones exert a powerful negative feedback on the anterior pituitary, blocking the release of further LH and FSH, inhibiting development of any further follicles in the ovaries. As the levels of LH decrease in the luteal phase the corpus luteum degenerates after about ten days, and with it levels of oestrogen and progesterone decrease. Decreasing levels of these ovarian hormones ends the blockade of FSH and LH secretion, and the cycle begins again.

The **uterine cycle** describes the changes that occur in the female reproductive organs, particularly the uterus, accompanying changes in the ovary. It can be described in terms of three phases; menstrual (days 1-5), proliferative (days 6-15) and secretory (days 16-28).

During the menstrual phase the functional endometrial layer of the uterus wall detaches, and the tissues and blood pass through the vagina as the menstrual flow. Under the influence of increasing oestrogen from the ovary the endometrium of the uterus wall is repaired. Throughout this proliferative phase the spiral arteries become more numerous and tubular glands are repaired. Ovulation occurs at the end of this phase and the increasing levels of progesterone from the corpus luteum cause further elaboration of the uterus wall throughout the secretory phase. If fertilisation of the ovum fails to occur, levels of progesterone drop, depriving the endometrium of its hormonal support. Endometrial cells begin to die and self-ingest via lysosomes. On day 28 there is a sudden dilatation of the arteries supplying the endometrium, blood rushes into the weakened capillary beds and they fragment and slough off, beginning the menstrual flow.

Although described above in terms of two separate cycles, for ease of understanding, the ovarian and uterine cycles are intimately linked, with changes in the uterus being dependent upon the hormonal fluctuations of the endocrine system. In the majority of research the cycle is thought of as one entity, most often called the menstrual cycle. A summary of cycle phases and corresponding physiological and physical changes is given in table 1.1.

Table 1.1 Summary of events of the normal human menstrual cycle

Day	Ovarian cycle	Uterine cycle	Hormonal fluctuations	Physical changes
1			Increasing levels of FSH and LH from anterior pituitary	Menstrual flow
2				
3		menstrual		Development of primary follicles in ovary
4				
5	follicular		Oestrogen secreted from maturing follicles gives negative feedback to hypothalamus preventing the release of FSH and LH, thus preventing further follicle development.	
6				Repair and proliferation of endometrium
7				
8				
9				Maturation of Graafian follicle in ovary
10		proliferative		
11			High levels of oestrogen lead to positive feedback to anterior pituitary and subsequent surge of LH	
12				Ovulation
13	ovulatory			
14				Corpus luteum formation in the ovary
15			Progesterone and oestrogen secreted by corpus luteum	
16				Further elaboration and maturation of endometrium
17				
18				
19				
20			Decrease in LH and FSH levels results from negative feedback and further follicle development inhibited	
21	luteal	secretory		
22				
23				Breakdown and reabsorption of corpus luteum
24				
25				
26				
27			Decreasing levels of progesterone and oestrogen end the blockade of FSH and LH	Endometrial wall begins to break down
28				

1.2 Accident rates across the menstrual cycle

Although there is no evidence to suggest that women have proportionally more accidents than men (MacDonald 1970), the distribution of accidents across the menstrual cycle may vary.

Whitehead (1934) was the first to suggest the existence of a link between accidents and menstrual cycle phase. On investigation into a number of serious and fatal aeroplane accidents involving females as pilots, he found that, when no other cause for the accident could be determined, 'certain' pilots were in their menstrual phase at the time of the accident. The possibility of this being a coincidence was noted, but the conclusion drawn was that this was not likely to be the case. To support this, three case histories were presented.

In a survey carried out by Balsam in 1954 (cited Liskey 1972) concerning female drivers in automobile accidents, those women who were in their premenstrual phase had more serious accidents compared with those in other phases. A frequently cited study by Dalton (1960a) investigated the relationship between phase of menstrual cycle and admission to four London accident wards in 124 women. She found that 52% were involved in accidents either during menstruation or in the four days prior to menstruation compared with the rest of the cycle ($p=0.001$), and concluded from this that 'menstruation is a significant factor in accident-proneness' (p. 1425). However, Dalton's study has been criticised on several counts (Clare 1985). It is retrospective, with no attempts made to check the accuracy of reported cycle phase at the time of the accident. The results also appear to indicate similar percentages for women described as 'active' (e.g. driver of a vehicle) or 'passive' (e.g. passenger in a vehicle) participants in the accidents. The distributions of these different types of accidents across the cycle are not provided. Furthermore, control groups were not included in the study.

In another hospital based study the time of death in relation to the menstrual cycle was determined by means of endometrial histology (MacKinnon and MacKinnon 1956). Forty-seven successive post-mortem examinations, in which the cause of death was accident, suicide or disease, were analysed over a time period of 2½ years. For all causes separately, death was more likely to occur in the luteal or postovulatory phase of the cycle as compared with the follicular or preovulatory phase. It was concluded by the authors that 'highly strung women and those suffering from chronic disease should be warned of the hazards and advised to take more care and rest' (p. 555) in the luteal phase.

In contradiction to these previous studies, Weist (1966) found that a greater percentage of accidents occurred in the post-menstrual phase in a sample of 300 German women, with an age range of 14-90 years. He suggested that a possible explanation for the differences may be that German women were physically and psychologically stronger than British females!

Additional evidence in support of a cycle phase related increase in accident rates is provided by Liskey (1972), who examined accident rates in high school and college women in the U.S.A. In the high school females 43 of the 92 accidents recorded occurred during the menstrual flow or premenstrual phase of the cycle ($p<0.02$). Among women in college, 65 of 201 accidents recorded took place in the premenstrual and menstrual phases. The premenstrual increase alone was not found to be significant, but the menstrual increase in accident rates was significant at the 0.1% level.

One study has disputed any pattern in the distribution of accidents across the menstrual cycle. In a prospective three year study Friedmann and co-workers (1978) noted all illnesses and accidents occurring in 94 student nurses. Throughout this time no evidence of a cycle phase related increase in either accidents or illnesses was found.

The weight of evidence from the small body of work to date does suggest a cycle phase related increase in accident rates, most commonly found in the premenstrual and menstrual phases. Possible causes for this increase have not been fully discussed in most of the above literature. Dalton (1960a) has suggested that increased lethargy premenstrually and during menstrual flow is responsible for both an impaired judgement and slower reaction time, leading to an increase in accident-proneness in these phases.

Variations in some measures of perceptual-motor performance across the menstrual cycle have been investigated (see section 1.6.1). The most frequent of these is simple reaction time, which has repeatedly shown no significant change with menstrual cycle phase (Pierson and Lockhart 1963; Kopell et al 1969; Zimmerman and Parlee 1973; Hutt et al 1980; Slade and Jenner 1980; Jenson 1982; Kluck et al 1992). Thus it appears unlikely that any increase in accident-proneness is attributable to changes in reaction time. Performance in a pursuit tracking task has been found to be at its worst premenstrually (Jenson 1982) and this may be a contributing factor in accidents.

The possibility of a correlation between accident rate distribution across the menstrual cycle and visual field changes has been proposed (Lanfair and Smith 1974). Recent work using automated perimetry has identified increased traffic accident rates in individuals with visual field loss (Keltner and Johnson 1992). It has also been reported that

individuals with normal visual acuity, but cognitive or perceptual deficits in processing or interpreting visual information, may also have impaired driving performance (Hills 1980).

1.3 Sensory changes across the menstrual cycle

Fluctuations in sensory thresholds of taste, audition, pain, smell and vision across the menstrual cycle have all been investigated (for review see Gandleman 1983; Parlee 1983). Indeed, Parlee (1982) suggests that 'sensory processes, as complex as they are, seem to be more amenable to study ... than are moods, affects, cognitions and actions' (p. 93). Kopell et al (1969) have argued for a theory of general arousal around ovulation such that enhanced sensitivity at this fertile stage may increase the females' chances of mating and thus aid procreation of the species. Visual cues may be of importance in this state of general arousal to aid the chances of copulation!

As in much menstrual cycle research, individual studies on visual changes across the menstrual cycle are often difficult to compare due to differences in methodology, visual modality under examination, menstrual cycle phase designation and statistical analyses used. However, some observations can be made, although often no firm conclusions drawn.

1.4 Visual changes across the menstrual cycle

Some women may specifically report changes in vision and in ocular symptoms across the menstrual cycle (Bergin 1952). A summary of studies investigating visual changes across the menstrual cycle is given in table 1.2.

1.4.1 Two Flash Fusion

Two flash fusion threshold (TFFT) is the point at which a subject perceives two successive flashes of light as one. A lower TFFT indicates an increased sensitivity, as the time between the two flashes, the inter-flash interval, is less. The greater the inter-flash interval, the greater the TFFT, and hence, the lower the sensitivity. TFFT has been identified as a measure of cortical arousal (Kopell et al 1969) and as such it has been used in research on visual changes in an attempt to measure the degree of arousal by any fluctuations in visual sensitivity.

TFFT has been found to increase premenstrually (DeMarchi and Tong 1972; Braier and Asso 1980; Asso and Braier 1982) and menstrually (Wong and Tong 1974), indicating a

loss of sensitivity. Increases in sensitivity have been identified in the late follicular and ovulatory phases of the menstrual cycle (Wong and Tong 1974; Friedman and Meares 1978; Becker et al 1982; Asso 1986). One study (Clare et al 1976) failed to find any significant phase effects. Those studies including oral contraceptive (OC) users as controls failed to find any variations in TFFT associated with menstrual cycle phase in these subjects (Wong and Tong 1974; Friedman and Meares 1978; Becker et al 1982).

The fluctuations found may be caused by changes in visual sensitivity or by a change in the individuals' criterion level across the menstrual cycle. For example a subject may be more cautious in a particular cycle phase, and this would give a greater TFFT, suggesting a lower sensitivity. Signal-detection techniques of presenting stimuli allow control of criterion effects. Criterion changes have been found across the menstrual cycle (DeMarchi and Tong 1970; Wong and Tong 1974), questioning the validity of describing the change in TFFT as a sensitivity change. At variance to this, Braier and Asso (1980) controlled for criterion changes and still found an increase in threshold premenstrually compared with intermenstrually in a between-subjects study design, suggesting an actual change in sensitivity.

1.4.2 Critical Flicker Fusion

Critical flicker fusion threshold (CFFT) is the point at which a flashing light of increasing flash frequency is perceived as continuous. In contrast to TFFT, the higher the threshold, the higher the flash frequency and the greater the visual information processing capacity.

Dye (1989, 1991) measured CFFT in 34 normally cycling women and 11 women taking OCs using a within-subjects study design. Threshold, and hence visual sensitivity, increased in the premenstrual phase of the cycle in both subject groups. A significant positive linear regression ($p<0.005$) indicated a trend of increasing threshold throughout the menstrual cycle, with significant cubic regression ($p<0.025$) implying that there were two turning points in the data, showing the periodic nature of CFFT during the menstrual cycle. In an additional study of 12 known sufferers of premenstrual symptoms, the same cyclical variation was identified, but higher CFFTs were found in all phases. This apparent increase in visual sensitivity in the premenstruum does not support the results of TFFT studies, perhaps due to differences in methodology, or to the fact that TFFT and CFFT may measure different visual processes.

1.4.3 Tilt aftereffect

The tilt aftereffect (TAE) is a suprathreshold visual phenomenon observed after looking at a tilted grating, when a vertical grating will appear to be slightly tilted in the opposite direction (Symons et al 1990-91). At different contrasts and test durations it may reflect activity at both retinal and cortical levels of the visual pathway. Using a within-subjects repeated measures study design with a two-alternative forced-choice technique, Symons and co-workers investigated TAE at two phases in the menstrual cycle; preovulatory (days 5-13) and premenstrual (days 26-28). When low contrast gratings and short test durations are used TAE is increased in the preovulatory compared to the premenstrual phase, suggesting a lowering of threshold around ovulation. The authors suggest that this may be due to changes at the retinal level. The results found using high contrast gratings were more difficult to explain, with increases in TAE in the preovulatory as compared to the premenstrual phase with longer test durations possibly reflecting changes in adaptation levels in the cortical orientation channels. The authors suggest that these changes in TAE across the menstrual cycle are due to changes in the neural visual system, rather than physical changes, and may be due to alterations in dopamine activity.

1.4.4 Visual Detection and Discrimination

Visual sensitivity as measured by dark-adapted detection of a flash of light has been shown to increase in the midcycle or ovulatory phase (Diamond et al 1972; Barris et al 1980; Scher et al 1981), and to decrease in the premenstrual phase, with a small increase during menstruation (Ward et al 1978). In control groups of men and women taking OCs no phase variation was found (Diamond et al 1972). Signal detection techniques used in some of these studies (Ward et al 1978; Barris et al 1980) have shown that the changes in the detection ability of a subject at different stages in the cycle are due to real changes in sensitivity, rather than to a shift in criterion level. Barris and co-workers (1980) suggested that the increase in visual sensitivity at ovulation was located in the 'afferent neural components of the visual system' (p. 299) as pupil size remained constant across four consecutive days around ovulation.

Ward and co-workers (1978) found menstrual cycle fluctuations in dark-adapted tasks of the detection of stimuli under different levels of illumination and pattern discrimination. Performance in the pattern discrimination task improved, whilst that of detection was impaired in the premenstrual phase. Oedema of the cornea was implicated by Ward and co-workers as a possible explanation for both the decrease in visual detection and the improvement in visual discrimination in the premenstrual phase. They suggested that the thickening of the cornea due to the oedema reduced sensitivity to environmental

stimulation, thus impairing visual detection, whilst also acting as a filter to irrelevant information such that suprathreshold stimuli in visual discrimination tasks are perceived more accurately.

Light-adapted detection does not fluctuate over the menstrual cycle (Scher et al 1981). However, these results were taken from the same four women in whom changes in dark-adapted detection were found, but over different menstrual cycles. No measure of ovulation was taken in either study and it is possible that anovulatory cycles may have occurred which may have influenced the data.

In a recent study the recognition of visual stimuli belonging to three categories: sex, babies and stimuli related to body care was assessed across the menstrual cycle (Krug et al 1994). Although there was no generalised change (independent from stimulus meaning) in visual perceptual functions across the normal menstrual cycle, performance across the cycle was dependent on the significance of the stimuli. In particular, sex stimuli were better recognised around ovulation. The authors tentatively suggest that increased sexual motivation during this phase may bias recognition performance.

1.4.5 Letter Identification and Visual Acuity

In 1985, Scher and co-workers proposed that even if Kopell et al (1969) were correct in their suggestion of general increases in arousal around ovulation, and if visual sensitivity does increase, it may well be task specific in its response. They found letter identification in the dark-adapted eye was worse in the ovulatory as compared with the menstrual phase over one cycle of four normally menstruating women. This finding is apparently paradoxical if visual sensitivity increases at ovulation, but was explained by Scher et al in terms of retinal saturation. An increase in sensitivity at ovulation would mean a greater potential for saturation of the retina in response to a bright stimulus, leading to a reduction in the contrast of any given target, for example, a letter. Hence, although there is an apparent decrement in visual performance in the dark-adapted eye, there may still be overall increased visual sensitivity. The authors stress the importance of careful consideration in drawing conclusions about sensitivity changes and the direction of visual performance change, and in the comparison of studies using different adaptation levels and tasks.

In a study assessing visual acuity (Jordan and Jaschinski-Kruza 1986), five emmetropic women with normal menstrual cycles were tested monocularly three times a week over a six week period. Visual acuity, as measured with Landolt rings, was found to be significantly better after ovulation than before by about 10%.

1.4.6 Contrast Sensitivity

There has been little study of the effects on contrast sensitivity across the menstrual cycle. Dunn and Ross (1985) measured contrast sensitivity at 9, 18 and 26 cycles per degree (cpd) and found both a sex difference and a relationship with menstrual cycle phase. Males were found to have the highest contrast sensitivity followed by non-cycling women and lastly by women with normal cycles. Contrast sensitivity increased in the postovulatory phase, compared with the rest of the cycle, in 10 women with normal cycles.

In a more recent study (Johnson and Petersik 1987), daily measurements of contrast sensitivity at three different spatial frequencies (2, 4, and 16 cpd) were recorded in two normally cycling women and in two control subjects (one man and one lactating woman). Monitor-based stationary and moving gratings were presented and subjects 'ramped up' the contrast until they became aware of the grating. In both women with normal cycles, cyclical changes were greatest for the lower spatial frequencies, particularly for 4cpd, i.e. nearest the peak of the normal contrast sensitivity function. Time-series analysis showed several peaks of sensitivity across the menstrual cycle suggesting a complex relationship between vision and the underlying physiological events in the menstrual cycle. Control subjects did not appear to show any cyclical fluctuations.

Variations in contrast sensitivity may be due to hormonal shifts across the menstrual cycle or changes in ocular parameters, for example pupil size and lens shape. However, it is difficult to draw any conclusions when the number of subjects and controls is so small. The changes in this study may also be due to alterations in subjects' criterion levels. A method of forced-choice threshold determination would differentiate between this and a true sensitivity change.

1.4.7 Visual Fields and Colour Vision

Small fluctuations in the visual field across the menstrual cycle may not be clinically significant in terms of increased risk in daily life, but would be important in the management of patients requiring repeated visual field examinations e.g. glaucoma patients and suspects. A temporary fluctuation in the visual field caused by menstrual cycle phase may confound interpretation of the results.

In 1887 Finkelstein reported a concentric narrowing of the visual field as measured by a Forster perimeter during the premenstrual and menstrual phases of the cycle in 20 healthy women. The extent of the narrowing was found to be at its greatest on the fourth or fifth day of menstruation, gradually disappearing by the seventh or eighth day.

Colour fields also demonstrated this change, although refraction appeared unchanged. The results for colour fields were supported by the work of Lorenzetti (1926, cited Lanfair and Smith 1974). There was a slight but significant narrowing of red and green fields in the premenstrual phase, returning to normal by the end of menstruation.

Lorenzetti also observed colour vision across the cycle and found an increased difficulty in colour perception (measured in terms of the greatest distance at which a colour was still recognisable) of yellow and green in the premenstrual phase which disappeared during menstruation. The results obtained may be due to a change in criterion level by the subject at a particular time during the cycle rather than a true sensitivity change. Central colour vision as tested by the Holmgren Worsted test was unaffected by the cycle.

Lanfair and Smith (1974) carried out a preliminary study using the Ferree-Rand manual arc perimeter to measure the visual field across the menstrual cycle in three normally menstruating women and two women taking OC preparations. Tentative conclusions of narrowing of the peripheral field in the cycling women support previous work (Finkelstein 1887).

Anomaloscope colour matches have been investigated across the menstrual cycle. Although an initial pilot study (Astell et al 1989) appeared to demonstrate a menstrual cycle variation, subsequent work by the same group has failed to provide a reliable effect and no positive conclusions can be drawn from this work to date (Mollon 1993).

1.4.8 Refraction

Fluctuations in refraction across the menstrual cycle have been implicated as a possible cause of change in visual performance. Finkelstein in his 1887 study on twenty women found no refractive changes, whilst Bergin (1952) found a shift of less than 0.25DS in the myopic direction at around the time of menstruation. In the seven subjects studied there were no significant consistent variations that would enable prediction of the effect of menstruation on refraction. Thus, from the evidence to date, changes in refraction are minimal or negligible, and unlikely to substantially alter visual performance.

1.4.9 Accommodation

Very little data has been collected on variations in accommodation across the menstrual cycle. In an unpublished study, Hogan (1985) investigated the effect of the menstrual cycle on the stability of measures of tonic accommodation and tonic vergence. Daily measurements were taken over one cycle, 28 days, in three normally menstruating young

women. Variability of the measurements was greatest in the premenstrual and menstrual phases and least in the preovulatory phase. Overall, females were found to be slightly more variable observers than males. At no phase in the cycle was there a significant difference in the effect on tonic accommodation to that on tonic vergence.

Jordan and Jaschinski-Kruza (1986) investigated the accommodative state of the eyes in complete darkness with a laser optometer in five normal emmetropic women. The so-called dark focus shifted significantly outwards by about 0.25D at ovulation, whilst a smaller, non-significant outward shift was also observed at menstruation. The variations of the dark focus were found to be greater in the near-dark-focus subjects than in the far-dark-focus subjects.

Table 1.2 Summary of visual changes across the menstrual cycle.

NC = women with normal menstrual cycles, OC = women oral contraceptives, M = men, P = pregnant women and BF = breast-feeding women.

Visual task	Results	Author	Subjects	Days/phases examined
Two flash fusion threshold	Decrease in sensitivity premenstrually	Kopell et al (1969)	8NC	Days 3,14,24,26,28 of 2 cycles, averaged into 1 cycle
		Demarchi and Tong (1972)	20NC	3x over 1 cycle, in premenstrual, menstrual and postmenstrual phases
		Braier & Asso (1980)	36NC	Between subjects design: 18S premenstrually, 18S intermenstrually
		Asso & Braier (1982)	36NC	As above
	Increase in sensitivity in late follicular & ovulatory phases	Wong & Tong (1974)	8NC, 2OC	Days 1,5,10,15,26 of 1 or 2 cycles (only 1 cycle reported)
		Friedman & Meares (1978)	21NC,7OC	3-4x over 2 or more cycles (only 1 cycle reported)
		Becker et al (1982)	14NC/OC	Every other day over 1 cycle
		Asso (1986)	30NC	2x over 1 cycle, in mid-cycle and premenstrually
	No phase difference	Clare et al (1976)	8NC	Days 14 and 27 of 2 cycles (only 1 cycle reported)
Critical flicker fusion threshold	Increase in sensitivity premenstrually	Dye (1989, 1991)	34NC,11OC	1-3x weekly for 4-7 weeks
Tilt after effect	Increased preovulatory with low contrast (short test duration) and high contrast (long test duration)	Symons et al (1990-91)	17NC	2x over 1 cycle, in preovulatory (days 5-13) and premenstrual (26-28)
Visual detection	Dark adapted: increased mid-cycle (ovulatory)	Diamond et al (1972)	4NC, 4OC, 4M	1x weekly for 5-6 weeks
		Barris et al (1980)	5NC	7 consecutive days over ovulation in 1 cycle for 6S, 3 cycles for 1S
		Scher et al (1981)	4NC	Days 1,7,14,21,28 of 1 cycle

Table 1.2 contd

Visual detection	Dark adapted: decrease premenstrually, small menstrual increase	Ward et al (1978)	12NC	4x over 1 cycle, in menstrual (days 2-4), preovulatory (10-14), luteal (19-23 and premenstrual (21-30)
	Light adapted: no sig. difference	Scher et al (1981)	4NC	as before
Visual pattern discrimination	Improved premenstrually	Ward et al (1978)	12NC	as before
Visual recognition	No generalised effect, better recognition of sex stimuli around ovulation	Krug et al (1994)	16NC, 16OC	3x - menstrual, preovulatory and midluteal
Letter identification and visual acuity	Dark adapted: worse in ovulatory than menstrual phase	Scher et al (1985)	4NC	2x over 1 cycle, on 1st day of menses and on day of BBT rise
	Landolt rings: acuity better after ovulation	Jordan & Jaschinski-Kruza (1986)	5NC	3x weekly for 6 weeks
Contrast sensitivity	Increase in sensitivity in post-ovulatory phase	Dunn & Ross (1985)	10NC, 10OC, 11M	12x over 5 weeks
	Complex relationship with menstrual cycle, with several peaks in sensitivity	Johnson & Petersik (1987)	2NC, 1M, 1BF	Daily for 32 days
Visual fields	Constriction of fields premenstrually and menstrually	Finkelstein (1887)	20NC	not stated
		Lanfair & Smith (1974)	3NC, 2OC, 1P	3x weekly for 6 weeks
	Constriction of red and green fields premenstrually	Lorenzetti (1926, cited Lanfair & Smith 1974)	unknown	unknown
Colour vision	Perception of yellow & green more difficult premenstrually	Lorenzetti (1926, cited Lanfair & Smith 1974)	unknown	unknown
	Anomaloscope: No reliable results	Mollon (1993)	unknown	unknown
Refraction	No change	Finkelstein (1887)	20NC	not stated
	<0.25DS myopic shift menstrually	Bergin (1952)	7NC	3x weekly over 5 weeks
Tonic accommodation	Variability greatest premenstrually & menstrually, least in ovulatory phase	Hogan (1985)	3NC	Daily over 28 days (different cycles combined)

1.5 Ocular Physiological Changes

1.5.1 Corneal parameters

It has been suggested that changes in visual performance across the menstrual cycle may be due to increased water retention or corneal oedema (Ward et al 1978). Corneal hydration and oedema can be assessed by the measurement of corneal thickness and corneal curvature.

1.5.1(i) Corneal thickness

In 1970 Manchester observed hydration of the cornea across the menstrual cycle in six normally menstruating women. Measurements of central corneal thickness (CCT) using a Haag-Streit pachometer and corneal curvature by keratometry were taken, and slit-lamp appearances noted twice daily for one month. Although there were individual variations, the average corneal thickness and curvature did not change appreciably throughout the menstrual cycle. Other studies measuring CCT only (Feldman et al 1978) and the thickness of both central and peripheral cornea (El Hage and Beaulne 1973; Hirji and Larke 1978), have been in general agreement with Manchester, with no significant changes across the menstrual cycle.

However, there are some reports of fluctuations in corneal thickness across the menstrual cycle have been found. Leach et al (1971) measured CCT, using the Donaldson pachometer, over one menstrual cycle in the right eye of six women with normal menstrual cycles. CCT was found to increase in parallel with increasing plasma oestrogen levels, being thicker prior to ovulation and in the luteal phase. These results are supported by more recent work (Kiely et al 1983). During one cycle of six women Keily and co-workers found that central and peripheral corneal thickness, as measured with the Haag-Strait pachometer, increased on the second day of the cycle and around ovulation, then thinned before another slight thickening on day 21. To further investigate the timing of corneal thickness changes throughout any cycle, they measured the CCT of both eyes of two normally menstruating women over three cycles. Increases in CCT appeared to occur at times of increasing oestrogen levels, with a slight decrease in thickness at the end of menses, an increase at ovulation and four days after ovulation. Considering the normal changes in urine levels of oestrogen, increases in thickness were concurrent with increased oestrogen levels, suggesting that the cornea is an oestrogen sensitive tissue. The percentage increase in thickness for one subject was 5.6% from day 15 to day 16. This is greater than the average overnight corneal swelling of 4.5% observed by Mertz (1980) in nine subjects, and may be sufficient to cause changes in visual performance. These changes may lead to significant problems if combined with

any corneal swelling induced by contact lens wear. Keily and co-workers (1983) suggest the differences between their results and those of previous authors may be due to different statistical techniques and menstrual cycle phase designations used.

Soni (1980) has also reported cyclical variation in CCT in eight normally menstruating women. Over a period of three months, the central cornea appeared to be at its thinnest just prior to an assumed ovulation point, when oestrogen levels are high. This change was absent in 15 women taking the oral contraceptive pill. Soni suggests that oestrogen alone may not have such a marked effect on the cornea as it does when combined with progesterone, as in the luteal phase when the corneal thickness increased.

The conclusions in these studies of changes in corneal thickness across the menstrual cycle are controversial, and it is difficult to compare individual studies, due to differences in methodology and instrumentation. It is also difficult to draw conclusions when the subject sample sizes are small. Hirji and Larke (1978) calculated that 122 subjects would be required for statistical significance to be reached, if corneal thickness does change with menstrual cycle phase.

1.5.1(ii) Corneal curvature

Changes in corneal curvature across the menstrual cycle have been studied alongside CCT in the assessment of corneal hydration.

Manchester (1970) and Leach et al (1971) found no significant alterations in central keratometry readings over the menstrual cycle. However, Keily et al (1983) using a Bausch and Lomb keratometer, found steepening central curvatures in both horizontal and vertical meridians at the beginning of the cycle with flattening occurring after ovulation.

Changes in corneal thickness and curvature are intimately linked. Irregular changes in thickness cross the cornea may lead to changes in curvature, whilst uniform change may show less curvature changes. Further studies using topographical keratometry and pachometry are needed before firm conclusions can be drawn about the state of corneal hydration throughout the menstrual cycle.

1.5.1(iii) Corneal sensitivity

Sensitivity of the cornea has been studied in relation to menstrual cycle phase (Millodot and Lamont 1974). An increase in corneal touch threshold (CTT), or decrease in sensitivity, with the Cochet-Bonnet aesthesiometer was found during the premenstrual

phase in nine normally menstruating women. This was not reproduced in five women taking the OC pill and eight men. Millodot and Lamont (1974) suggest that the change in corneal sensitivity during the premenstruum may be due to a generalised increase in water retention at this time, and/or to increases in intraocular pressure (IOP).

With the advent of the electromagnetic aesthesiometer of Dräger, Riss and co-workers (1982) claimed they were able to determine more accurate and reproducible daily CTT measurements. In three normally menstruating subjects with ovulatory cycles, as proven by serial determinations of urinary LH levels, CTT rises occurred just prior to, or on the day of, ovulation. However, they were unable to reproduce the lowering of corneal sensitivity premenstrually found by Millodot and Lamont (1974), and suggested that this may be due to the different instrumentation used. Some evidence of a relationship between levels of oestrogen and corneal sensitivity is presented by Riss et al, but further studies are needed to fully investigate this possibility.

An increase in IOP also leads to a decrease in corneal sensitivity (Boberg-Ans 1955). Changes in IOP throughout the menstrual cycle may have a causal relationship to changes in corneal sensitivity.

1.5.2 Intraocular pressure, aqueous output facility and glaucoma

The prevalence of chronic simple open-angle glaucoma (POAG) in the under 50 age group is greater in men than in women (Armaly 1965). After the age of 50 however, the prevalence in men and women is much the same. Most women have reached menopause by this age, when sex hormone levels change dramatically. The influence of female sex hormones has been implicated as a possible cause of this difference in the prevalence of POAG between men and premenopausal women (Meyer et al 1966).

Fluctuations in IOP and outflow facility have been observed in normally cycling, non-glaucomatous women. Using the Schiotz tonometer to measure IOP in both eyes of nine women, Salvati (1923) found an increase in IOP during the menstrual phase as compared with the two days pre- and post-menstrually. Other work has shown increases in outflow facility, with associated decreases in IOP, in phases of the cycle when levels of oestrogen alone, or together with progesterone, are high (Paterson and Miller 1963) or when progesterone levels alone are high (Becker and Friedwald 1953).

With the advent of accurate radioimmunoassay techniques of measuring blood plasma hormone levels, Feldman and co-workers (1978) attempted to correlate anterior chamber (AC) depth and IOP fluctuations across the menstrual cycle with hormonal fluctuations. No significant changes in IOP or AC depth were found across different phases of the

cycle. However, IOP did appear to be at its lowest around ovulation, when oestrogen levels are high. More recent studies have also failed to demonstrate any significant correlations between serum progesterone levels and IOP and aqueous outflow rate across the menstrual cycle (Green et al 1984; Gharagozloo and Brubaker 1991).

IOP fluctuations across the menstrual cycle may differ in glaucoma sufferers. Dalton (1967) found simultaneous rises in IOP, as measured by applanation tonometry, blood pressure and body weight in the premenstrual or menstrual phase in 14 women with glaucoma. In 34 premenopausal women with different types of glaucoma, the timing of so-called 'ocular symptoms', comprising blurred vision, pain, and headaches, were recorded across several menstrual cycles. In women with closed-angle glaucoma (CAG), and it is unclear as to whether these were treated or untreated cases, ocular symptoms were much greater in the premenstrual and menstrual phases as compared to the remainder of the cycle. This time relationship was absent in POAG sufferers. Dalton also found a high prevalence of 'premenstrual syndrome', being reported in 70% of all the women in the study, rising to 89% in the CAG group, and falling to 50% in the POAG sufferers. However, it is unclear as to how premenstrual syndrome was diagnosed in this study (see section 1.7), and there is no discussion as to the cause or relevance of the apparent increase in prevalence in the CAG patient group.

IOP response to various sex hormone treatments may vary between glaucomatous patients and normal subjects. The potential therapeutic value of sex hormone treatment in glaucoma has been considered by several authors. Obal in 1950 reported improvement in most of his 37 patients, both male and female, following the administration of progesterone. Posthumus (1952) reported successfully treating 13 glaucomatous patients, six of whom were males, with progesterone. Other studies have reported varying degrees of success. These range from no improvement in glaucomatous patients (Treumer 1952) to a drop in IOP in post-menopausal females with glaucoma following progesterone injections, but little or no effect in males and pre-menopausal females (Becker and Friedwald 1953; Avasthi and Luthra 1967).

Combinations of progesterone and oestrogen, oestrogen alone and relaxin, a hormone found predominantly in pregnant women, have also been shown to decrease IOP in normals and glaucoma sufferers (Paterson and Miller 1963). Meyer and co-workers (1966) carried out a controlled double-blind study with patients suffering from POAG to investigate the effect on IOP of a widely used OC preparation containing progesterone and oestrogen. Before administration of the drug, the average IOP of both test and control groups were the same. After treatment the average IOP of the test group was 4.2 mmHg lower than that of the control group. This study gave no indication of the usefulness, if any, of this preparation in the long term management of POAG. Treister

and Mannor (1970) found a decrease in IOP and increased outflow facility in normal women taking either an oestrogen only, or a combined oestrogen and progesterone preparation. The decrease in IOP was thought to be caused by the action of these drugs on the trabecular meshwork, facilitating the outflow of aqueous.

Despite publications suggesting a potential therapeutic use of female sex hormones in the management of glaucoma, none are in use today as a standard form of treatment. This is not surprising as consistent improvements with a particular hormone have yet to be found. This may be due to the different responses seen in individuals, particularly between glaucomatous patients and normals, between males and females, and pre- and post-menopausal women. Many of the earlier studies also fail to give the type of glaucoma under study, or have investigated responses in POAG subjects only (Meyer et al 1966). Further study of response differences with different glaucoma types may prove more informative.

Female sex hormones in premenopausal women may contribute to the reduced prevalence of POAG in this group, but this remains unproven. In normally cycling women a delicate and constantly changing balance of hormones is maintained. This may be impossible to accurately reproduce by the administration of hormone treatments to non-cycling individuals. With the increasing use of hormone replacement therapies in postmenopausal women, studies of the incidence of glaucoma in these women compared with those not undergoing treatment may supply more information on this interesting topic.

1.5.3 Conjunctiva

Dry eye conditions have a greater prevalence in postmenopausal women (Terry 1994), suggesting female hormone deficiency as a possible aetiology.

A recent study (Kramer et al 1990) examined the conjunctiva in nine premenopausal, seven postmenopausal, two oestrogen deficient females and one male. By examining conjunctival smears taken over 28 days, or one complete cycle in normally menstruating women, they found that oestrogen levels correlated with the maturity of the conjunctival cells. The conjunctiva was at its most mature around ovulation, when oestrogen levels are high, identifying the conjunctival epithelium as an oestrogen sensitive tissue. In men and postmenopausal women there was no apparent peak in maturity. Kramer and co-workers suggest that conjunctiva not undergoing maturational change may be more susceptible to aqueous deficiency of the tear film, and thus to subsequent dry eye conditions. This may also be a factor in reports of contact lens intolerance in pregnancy (Ruben 1966), when oestrogen levels are low and progesterone high. These results may

prove important in the pathogenesis and management of keratoconjunctivitis sicca. It is not clear why men, who do not have cyclical oestrogen level fluctuations, have a lower incidence of dry eye. It is probable that there are other factors in postmenopausal women, for example changes in the tear make-up, that contribute towards dry eye problems. The possibility of treatment with hormone therapy has yet to be fully investigated.

1.5.4 Tear production and consistency

Changes in comfort and vision reported by some female contact lens wearers on becoming pregnant or starting OCs may be due to changes in tear make-up. If these changes are as a result of hormonal variations, it is likely that alterations in tear make-up also take place across the menstrual cycle.

Feldman et al (1978) attempted to record tear production throughout the menstrual cycle in 10 females, using the Schirmer tear test. However, the results were so variable that the only conclusion they could draw was that the test itself was unreliable for assessing tear production.

A recent unpublished study (Cooke 1991) has reported preliminary findings of higher wetting angles, indicating poorer contact lens surface wetting, on female rigid contact lens wearers during a presumed ovulatory phase. It has been suggested that the high levels of oestrogen at this time may be a cause of this variation, but further studies of greater subject numbers are required before firm conclusions can be drawn.

1.5.5 Pupil diameter

In their study on visual detection Barris and co-workers (1980) also assessed the size of the dark-adapted pupil across four consecutive days around ovulation in one menstrual cycle of three normally menstruating women. No significant change in the pupil diameter was found across these days.

1.5.6 Lens opacities

Recent evidence suggests that there may be a link between oestrogen and age-related lens opacities. Klein et al (1994) found that the current use of postmenopausal oestrogens and an earlier age at menarche, were associated with a decreased risk of nuclear sclerosis. Older age at menopause was found to be associated with a decreased risk of cortical opacities. The authors suggest that although oestrogen appears to

provide a modest protective role against age-related lens opacities, other factors may be involved and further work is being conducted.

1.5.7 Ocular vicarious menstruation

Vicarious menstruation is a rare condition where cyclical bleeding occurs in extragenital organs during menstruation. The most common site for this bleeding is the nasal mucosa, but there have been reports of bleeding from other sites including the lungs, stomach, lips and eyes (Israel 1963). Ocular vicarious menstruation was first described by Dodoneaus in 1581 (cited Duke-Elder 1965) and has been reported sporadically in the literature since then. It has been reported that only 1% of women suffering extragenital bleeding have ocular involvement (Roth 1920). Sikorski et al (1978 cited by Barat and Kwedar 1988) gave case histories of two patients with bilateral vitreous haemorrhage during menstruation. Neither had hormonal deficiencies and both were treated successfully with oestrogen preparations. Barat and Kwedar (1988) presented a case report of a 17-year-old female who experienced intermittent bleeding in one eye during menstruation. Ophthalmalogical examination revealed bleeding from the fornix, medial canthus and lacrimal gland area. Treatment was successful with Enovid, an OC preparation of oestrogen and progesterone.

Haemolacria is specifically the presence of blood in the tears, and has been described in association with the menstrual cycle and the menopause (for review see Ottovay and Norn 1991). In a recent study (Ottovay and Norn 1991), the incidence of haemolacria was found to be significantly greater in the menstrual phase of the cycle in 64 normally cycling females than in any other phase. Additionally haemolacria was found to occur much less frequently in pregnant women, menopausal women and men.

The cause of bleeding is obscure but may be related to vascular changes induced by hormonal stimuli. Oestrogen and progesterone are known to increase the permeability of capillaries in extragenital tissues that may lead to congestion, hyperaemia and secondary bleeding. Bleeding in an extragenital organ may also be due to the presence of endometrial tissue, similar to that of the uterus, in the organ. Vicarious menstruation is more common in the third and fourth decades of life and usually occurs within 48 hours of the onset of menstrual flow (Barat and Kwedar 1988). Treatment is most effective with hormonal suppression of ovulation using OCs, or suppression or resection of endometrial tissue.

1.5.8 Other ocular changes

The menstrual cycle has been implicated as a potential factor in the timing of onset of other ocular conditions and symptoms eg uveitis (Bell 1989), glaucoma (Dalton 1967) and systemic conditions with associated ocular changes eg migraine (Lehtonen et al 1979), epilepsy (Logothetis et al 1959).

1.6 Nervous system activity throughout the menstrual cycle

1.6.1 Central nervous system (CNS)

Fluctuations in behaviour or performance across the menstrual cycle may be due to changing levels of activation in the central nervous system (CNS) mediated by fluctuating concentrations of gonadal steroids. Increases in arousal in the ovulatory phase have been reported by women (e.g. Hartley et al 1987). Alterations in cortical responsiveness with menstrual cycle phase are evident from studies of menstrual migraine (Lehtonen et al 1979) and epilepsy (Logothetis et al 1959; Bäckström et al 1986). Fluctuations in EEG (Vogel et al 1971; Wuttke et al 1975; Creutzfeldt et al 1976; Becker et al 1982) and evoked potentials (Abramovitz and Dubrovsky 1980) across the menstrual cycle in normal women provide additional evidence of hormonal influences on the CNS.

Other measures of cortical responsiveness studied include the visual performance measures of two-flash fusion threshold and critical flicker fusion threshold (see sections 1.4.1 and 1.4.2), and reaction time. These studies are summarised in table 1.3. Although the results show considerable variability, and several studies (particularly those assessing reaction time) fail to find any phase effects, the general observation is that cortical responsiveness is enhanced in the preovulatory phase, and at its lowest premenstrually.

The general view is that oestrogens have an activating effect on CNS functioning, whilst progesterone may block or oppose this action (Abramovitz and Dubrovsky 1980; Klaiber et al 1982). The mechanism by which these changes take place is still unclear (Asso 1988). Some authors (Vogel et al 1971; Broverman et al 1981) have suggested that oestrogen inhibits monoamine oxidase (MAO) activity, thus prolonging the action of neurotransmitters, and hence increasing CNS activation. Broverman and co-workers (1968) have further speculated that oestrogen facilitates the performance of highly practised 'automatized' tests and impairs performance on 'perceptual-restructuring' tasks, whilst progesterone counteracts the effects of oestrogen. These theories have been criticised for lack of direct evidence (Parlee 1973), and although Richardson (1991b) has

suggested that it remains the only articulated analysis of the potential effects of reproductive hormones upon cognitive function, he found no evidence in its favour in his study on long-term memory across the menstrual cycle.

In summary, differences in CNS activation in different phases of the menstrual cycle have been observed, with general arousal appearing to increase mid-cycle (Becker et al 1982), whilst the direct effects of gonadal hormones on the CNS remain unclear.

Table 1.3 Studies investigating cortical arousal across the menstrual cycle

Task	Author(s)	Results
Two-flash fusion threshold	Kopell et al (1969)	lower premenstrually
	DeMarchi and Tong (1972)	lower premenstrually (due to criterion changes)
	Wong and Tong (1974)	lowest menstrually and highest ovulatory (due in part to criterion changes)
	Clare et al (1976)	no phase effects
	Friedman and Meares (1978)	higher in late follicular phase
	Braier and Asso (1980)	lower premenstrually
	Asso and Braier (1982)	lower premenstrually
	Becker et al (1982)	ascending - higher in luteal phase than menstrual descending - no phase effects
	Asso (1986)	higher mid-cycle than premenstrually
Critical flicker fusion threshold	Dye (1989, 1991)	higher premenstrually
Reaction time	Kopell et al (1969)	no phase effect
	Pierson and Lockhart (1963)	no phase effect
	Baisden and Gibson (1975)	no phase effect
	Wuttke et al (1975)	faster in luteal phase than follicular
	Zimmerman and Parlee (1973)	no phase effect
	Hutt et al (1980)	no phase effect
	Slade and Jenner (1980)	no phase effect
	Jenson (1982)	no phase effect
	Becker et al (1982)	faster in follicular phase compared to menstrual phase
	Ho et al (1986)	no phase effects (accurate responses) faster in ovulatory compared to menstrual phase (overall responses)
	Kluck et al (1992)	no phase effects

1.6.2 Autonomic nervous system (ANS)

Fluctuations in ANS and CNS arousal and activation across the menstrual cycle may vary independently of each other (Asso 1978). Various parameters have been investigated in the assessment of ANS arousal, a summary of studies is shown in table 1.4.

Increases in self-reported autonomic reactivity have been recorded in the premenstrual phase (e.g. Moos et al 1969; Asso 1986; Ussher and Wilding 1991). Some studies of physiological changes have echoed this, with increases in electrodermal activity (EDA) (Asso and Brier 1982; Asso 1986) and heart rate (HR) (Little and Zahn 1974) found in the premenstrual phase. Others have found no significant phase effects in EDA (e.g. Kopell et al 1969; Zimmerman and Parlee 1973; Strauss et al 1983) and HR (Doty et al 1981; Ussher and Wilding 1991) or increases in EDA in the follicular or ovulatory phases (Little and Zahn 1974; Gómez-Amor et al 1990a,b). Gómez-Amor and co-workers (1990a) have suggested that these contradictory results may be due in part to methodological differences in the studies, and they addressed particularly the question of the use of within- or between-subjects designs. They found no menstrual cycle phase effects on EDA when using a within-subjects design, but identified an increase in EDA in the ovulatory phase in a between-subjects study design. However, Asso and Braier (1982) also used a between-subjects study design, but found an increase in EDA in the premenstrual phase. The advantages and disadvantages of these designs are discussed in more detail in section 4.3.

Fluctuations in ANS arousal across the menstrual cycle may be influenced by levels of stress. Induced stress has been found to increase adrenocortical reactivity in women in the premenstrual phase (Marinari et al 1976). Collins et al (1985) also found psychoneuroendocrine stress responses, as estimated by urinary excretion of adrenaline and noradrenaline, to be significantly higher in the luteal phase compared with mid-cycle and follicular values, suggesting that women's responsivity to stress is mediated by their menstrual cycle. More recently Weidner and Helmig (1990) measured cardiovascular reactivity to a stressful mental arithmetic task and found no significant differences between follicular and luteal phases.

It is apparent that there is a considerable lack of agreement in this area, with some studies suggesting heightened arousal in the ANS premenstrually, but others failing to support this. The relationship between ANS and CNS activation, and behaviour across the menstrual cycle remains unclear.

Table 1.4 Arousal and activation in the ANS across the menstrual cycle

Task	Author(s)	Results
Autonomic balance ($\overline{A}$)	Wineman (1971)	lowest in luteal phase
Electrodermal activity (skin conductance levels)	Kopell et al (1969)	no phase effect
	Zimmerman and Parlee (1973)	no phase effect
	Little and Zahn (1974)	increased in ovulatory phase
	Slade and Jenner (1979)	no phase effect
	Asso and Braier (1982)	increased premenstrually
	Strauss et al (1983)	no phase effect
	Asso (1986)	increased premenstrually
	Gómez-Amor et al (1990a)	no phase effect (within subjects design) increased in ovulatory phase (between subjects design)
	Gómez-Amor et al (1990b)	increased in ovulatory phase
Heart rate	Phillips (1967)	no phase effect
	Little and Zahn (1974)	increased in luteal phase
	Doty et al (1981)	no significant phase effect
	Becker et al (1982)	increased around ovulation and in early luteal phase
	Collins et al (1985)	no significant phase effect
	Ussher and Wilding (1991)	no significant phase effect
Cardiovascular reactivity to stress	Weidner and Helmig (1990)	no phase effect
Adrenocortical activity to stress	Marinari et al (1976)	increased premenstrually
Susceptibility to acquirement of conditioned galvanic skin response	Asso and Beech (1975)	enhanced susceptibility premenstrually
Urinary excretion of epinephrine and norepinephrine under stress	Collins et al (1985)	increased premenstrually
Pupil diameter	Barris et al (1980)	no change across ovulatory phase

1.7 Premenstrual Syndrome

Frank (1931) was the first to coin the term 'premenstrual tension' to describe the main features of a condition occurring 7-10 days prior to menstruation, characterised by severe tension, weight gain, headaches, and oedema. Premenstrual changes have predominantly been described in both research literature and the media as an increase in unfavourable swings of mood, and negative changes in behaviour, occurring prior to menstruation (Sutherland and Stewart 1965; Clare 1977; Blank et al 1980; Reid and Yen 1981). More recent studies have challenged this negative view, having also identified positive premenstrual changes (Parlee 1980; Logue and Moos 1988; Stewart 1989).

1.7.1 Definition and diagnostic criteria

Premenstrual syndrome (PMS) has been defined as the presence of symptoms occurring regularly at the same phase of each menstrual cycle, followed by a symptom-free phase (Dalton 1982). The symptoms experienced may be emotional, behavioural and/or somatic. At least 150 symptoms associated with the menstrual cycle have been documented in the literature (Moos 1969; Rubinow and Roy-Byrne 1984), complicating attempts at diagnosis. Other authors have suggested different definitions when attempting to diagnose PMS (Rubinow and Roy-Byrne 1984; Halbreich and Endicott 1985; Hsia and Long 1990; Ekholm et al 1992). A diagnostic definition of PMS, renamed Late Luteal Phase Dysphoric Disorder (LLPD) was included in the appendix of the revised third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) (American Psychiatric Association 1987), and now has full diagnostic status in DSM-IV as Premenstrual Phase Dysphoric Disorder (PPDD) (American Psychiatric Association 1994). However, the name LLPD (Halbreich et al 1993; Severino 1993), the diagnosis itself, and its inclusion in the DSM, have received some criticism, with the belief that diagnosing a premenstrual phase dysphoric disorder is problematic in itself and there are risks of both under- and over-diagnosis (Hamilton and Gallant 1990). Furthermore, in his recent review of the published literature on PMS, Bancroft (1993) suggested that for 'both research and clinical purposes no attempt should be made to define a condition called 'premenstrual syndrome'. Instead we should identify cycle-related patterns of *specific symptoms* (his italics) or changes (e.g. depression or food craving), with no preconceptions about their precise temporal relationship to menstruation or the ovarian cycle' (p. 7).

In much of the research to date, the distinction between physical and emotional changes has been poorly drawn. Although changes in physical symptoms, e.g. pain, associated with menstrual cycle phase are reasonably well documented (McFarland et al 1989; Beck

et al 1990), there is greater controversy about the presence of emotional change (Slade 1981, 1984).

The reported prevalence of PMS varies considerably according to the type of symptom measured and the severity criteria used. Stewart (1989) found that 95% of women report at least one symptom of negative change premenstrually, while Logue and Moos (1986) suggest that premenstrual changes fall on a continuum of severity where 'at least 40% of women experience mild to moderate perimenstrual symptoms and 2-10% experience severe symptoms' (p. 396). Despite the prevailing belief, both in the scientific literature and the media, of the existence of PMS, with increases in negative affect premenstrually, many studies have failed to produce any evidence of mood fluctuations across the menstrual cycle (e.g. Sommer 1973; Zimmerman and Parlee 1973; Little and Zahn 1974; Wilcoxon et al 1976; Swandby 1981; McFarlane et al 1988).

For most women negative affects appear to be randomly distributed across the cycle (Slade 1984), and more often related to stressful life events than to menstrual cycle phase (Wilcoxon et al 1976; Strauss and Appelt 1983). A generally stressful daily life has also been found to influence perimenstrual symptoms (Woods et al 1985). Other work has demonstrated greater mood fluctuations over day of the week than over the menstrual cycle (Englander-Golden et al 1986; McFarlane et al 1988; Mansfield et al 1989), although physical symptoms and food cravings have a significantly larger cycle phase effect than that of day of the week (Gallant et al 1991). Various methodological problems influence the results of studies of mood changes across the menstrual cycle (for review see Parlee 1973,1974; McFarlane et al 1988).

1.7.2 Aetiology and treatment of PMS

There have been many theories, both biological and psychological, as to the aetiology of PMS (for review see Reid and Yen 1981; Bancroft and Bäckström 1985; Halbreich et al 1988; McFarlane and Williams 1990; Bancroft 1993). The most popular biomedical theory has been that of progesterone deficiency (Dalton 1982). Suggested treatments for PMS are also numerous (for review see Robinson and Garfinkel 1990; Bancroft 1993), the most widely publicised of which is the administration of progesterone. However, when careful methodologies are used, no treatment has been found to be more effective than a placebo (McFarlane and Williams 1990; Tucker and Whalen 1991), suggesting a psychological aspect to PMS (Bernsted et al 1984). In fact, as Severino (1993) points out, in the 62 years since Frank (1931) coined the phrase Premenstrual Tension 'no-one has discovered either the cause or the single most effective treatment for the condition' (p. 229).

1.7.3 The effect of Oral Contraceptives on PMS

There is some evidence to suggest that women who take OCs experience less menstrual cycle mood fluctuation than normally cycling women (Paige 1971; Rossi and Rossi 1977; Boyle and Grant 1992). However, other researchers have found little or no difference between the two groups (Baisden and Gibson 1975; Sampson and Jenner 1977; Rogers and Harding 1981; Swandby 1981; Hallman 1986; Walker and Bancroft 1990; Yuk et al 1991). The general conclusion from well designed, double-blind, placebo controlled studies, is that OCs in use today are unlikely to have any significant effect on paramenstrual symptomatology (Richardson 1991a).

1.8 Cognition and the menstrual cycle

The general belief amongst both men and women is that women typically experience an impairment in their ability to function intellectually during the paramenstruum (Parlee 1974; Golub 1981). Prospective (McCance et al 1937) and retrospective (Moos 1968; Richardson 1989) self-report measures of symptomatology have reported a decrease in intellectual performance premenstrually. However, as Richardson (1989) points out, subjective reports are inadequate as evidence of impaired performance. Dalton (1960b, 1968) reported a decline in school performance associated with the premenstrual and menstrual phases of the cycle, but this work has been criticised due to methodological flaws and inadequate statistical evaluation (Sommer 1982). The weight of the present literature fails to show any significant impairment of cognitive performance in the paramenstruum (for review see Sommer 1982, 1991).

1.8.1 Performance and symptomatology

Changes in performance across the menstrual cycle may be related to fluctuations in self-reported mood and physical symptoms. Self-report measures have identified the concurrent reporting of 'psychological' (e.g. concentration, negative effect) and 'physical' (e.g. pain, water retention) symptoms (Moos and Leiderman 1978). The authors suggest that there may be a causal relationship such that 'it is the menstrual pain which results in behaviour changes...' (p. 35). However, these are subjective reports, and there is less evidence to show that objective performance fluctuates in conjunction with reported changes in symptomatology.

Although women may complain of poorer cognitive ability premenstrually (e.g. Moos 1968; Richardson 1989), this is repeatedly not borne out by their performance on various tasks (e.g. Sommer 1991). Other authors have also found little evidence to directly link

symptom change and performance (Altenhaus 1978; Slade and Jenner 1980; Jenson 1982; Hartley et al 1987; Richardson 1988).

There has been little attempt to correlate fluctuations in sensory performance and symptomatology. Ward and co-workers (1978) identified both a decrease in visual detection and an increase in symptoms of water retention premenstrually, but no change in mood across the cycle. The authors suggest that corneal oedema caused by increased water retention may have led to the decrease in visual performance. DeMarchi and Tong (1972) found that the measured increase in TFFT (i.e. decrease in sensitivity) premenstrually was due to criterion changes and suggested that supposed changes in mood associated with the menstrual cycle influence performance. More recently Dye (1989) has failed to find any significant correlation between fluctuations in CFFT and measures of symptomatology across the menstrual cycle.

Of additional interest in this area is the work of Rodin (1976) who has provided evidence to suggest that an individuals' perceived impairment of cognitive function premenstrually, and the ability to attribute this to her menstrual cycle phase, may encourage compensatory action and increase frustration tolerance, and hence improve actual performance.

Although menstrual cycle symptomatology may play a small role in reducing performance (Slade and Jenner 1980), it is impossible to infer a direct causal link between mood changes and performance. However, there is some evidence to suggest that physical symptoms may influence sensory fluctuations across the menstrual cycle.

1.9 Summary

Changes in visual performance across the menstrual cycle may derive from one of two sources; changes in ocular parameters or the effect of hormonal changes on the central nervous system (CNS). From the studies to date it has been difficult to show a direct relationship with any ocular change. The effect of individual hormones on the CNS has yet to be fully understood, and from merely the identification of the existence of a temporal relationship between visual performance change and hormonal fluctuations, it is impossible to assume a direct causal link.

Much of the work reviewed here can be criticised in methodology in some way and comparisons between studies are complicated by different study designs. Many studies have used very small subject groups, often with no control groups. Data collection is often limited to particular phases or days of the cycle, and in the large majority of studies

only one cycle of data has been collected and presented (table 1.2). However, some tentative conclusions may be drawn.

In the studies into ocular changes across the menstrual cycle, there is reasonable evidence to show that the cornea, and possibly the conjunctiva, are oestrogen sensitive tissues. The weight of evidence also indicates that IOP decreases in response to oestrogen and progesterone, however, the results are variable and as a consequence female hormones have not found a place as a standard glaucoma therapy.

Visual sensitivity may increase around ovulation and decrease premenstrually, but there are notable exceptions to this (Scher et al 1985; Dye 1989, 1991). Changes in visual performance across the menstrual cycle appear to be task specific and further work with sound methodologies is required before firm conclusions can be drawn.

CHAPTER 2

Rationale for the research

2.1 Introduction

Accident rates have been found to vary with menstrual cycle phase, most predominantly reported to increase in the paramenstruum (Whitehead 1934; Balsam 1954, cited Liskey 1972; Dalton 1960a; Liskey 1972). It has been suggested that changes in visual performance, particularly in the visual field, may contribute to this increase (Lanfair and Smith 1974).

Visual performance has been reported to fluctuate with menstrual cycle phase, most frequently decreasing in the premenstrual phase (Kopell et al 1969; De Marchi and Tong 1972; Braier and Asso 1980; Asso and Braier 1982; Lanfair and Smith 1974; Ward 1978) and increasing around ovulation (Diamond et al 1972; Wong and Tong 1974; Friedman and Meares 1978; Barris et al 1980; Scher et al 1981; Becker et al 1982; Asso 1986). Most of these studies have used laboratory based psychophysical tests that may not relate to the clinical situation. Visual field assessment using manual kinetic perimetry has identified constriction of the peripheral field in the premenstrual phase (Finkelstein 1887; Lorenzetti 1926 (cited Lanfair and Smith 1974); Lanfair and Smith 1974), although as yet modern methods of perimetric assessment have not been utilised to confirm these findings. With the advent of automated perimetry, in which numerical values of threshold are stored on computer discs, more accurate, reproducible data can now be obtained and statistically analysed.

Serial visual field examinations are carried out in the monitoring of ocular pathology e.g. glaucoma. Interpretation is confounded by the variability inherent in the measurement of contrast threshold at a location (section 3.3). The menstrual cycle may provide an additional source of variability which may need to be accounted for in the assessment of visual field data.

The assessment of cyclical fluctuations in menstrual-related symptomatology provides additional information about the menstrual cycle experiences of a subject population. Changes in visual performance across the menstrual cycle may be related to fluctuations in self-reported mood and physical symptoms. In the few studies that have attempted to correlate sensory performance and symptomatology (DeMarchi and Tong 1972; Ward et al 1978; Dye 1989) the results are contradictory (section 1.8.1). Again, the emphasis in

this work has been on laboratory based psychophysical tests, with little clinical application.

2.2 Aims and plan for experimental work

The aims of this thesis are to examine fluctuations in visual function, particularly in automated static threshold perimetry, and changes in self-report symptomatology across the normal female menstrual cycle. Of particular importance is the clinical significance of any fluctuation in visual performance found, in terms of both the possibility of contributing to accidents, and the potential of the menstrual cycle to be a confounding factor in visual field assessment. The presence of a relationship between visual performance measures and symptomatology across the menstrual cycle is of additional interest.

For the preliminary study on the effects of the menstrual cycle on automated perimetry, the full field to 60^{o} will be assessed. Subjects naive to automated perimetry are expected to need training sessions to eliminate the potential influence of learning on the data. Although the effects of learning on the central field have been well documented (section 3.2.7), there is little published data on learning in the peripheral field, and none relating to the Humphrey Field Analyser (the visual field instrument available for this research). An investigation must therefore be undertaken to determine the extent of perimetric learning in the peripheral field. Of particular importance is the number of sessions that are required before learning can be assumed to be complete (Chapter 5).

A pilot study will then be carried out to investigate the effects of the menstrual cycle on automated perimetry over the full field, and to assess menstrual cycle symptomatology in a subject group of young women with normal menstrual cycles (Chapter 6). The vast majority of previous work has reported data from one cycle alone, and none has reported data from two full cycles (table 1.2). This study will collect data over at least two menstrual cycles in each subject in order to assess the repeatability of any changes in automated perimetry found across the menstrual cycle.

This preliminary study will lead onto the main study investigating the effect of the menstrual cycle on visual performance (Chapter 7). Larger subject numbers will be used and two control groups, consisting of women taking oral contraceptives and men, will be included. Data will again be collected over at least two menstrual cycles. Additional measures of visual performance will also be incorporated, with a protocol design which takes into account the conclusions drawn from the pilot study.

CHAPTER 3

Automated Perimetry

3.1 Introduction and development

The visual field has been defined as 'that portion of space in which objects are simultaneously visible to the steadily fixating eye' (Harrington 1976 p.1). Measurement of the visual field, otherwise known as perimetry, is an established clinical and research tool used to aid the detection and localisation of lesions in the visual pathway, and to evaluate the progression of visual field defects associated with these lesions.

Computer-assisted perimetry has been defined as a form of visual field examination in which part or all of the examination is controlled by a microcomputer or microprocessor instead of by a human examiner (Greve 1982). Automated perimetry is the term used when the decision-making process of the examination strategy is exclusively controlled by the computer. Automated perimetry was developed to overcome some of the disadvantages of manual perimetry and in an attempt to improve the accuracy of detection, and subsequent follow-up of the progression of field defects in pathological conditions such as glaucoma.

Automated perimetry offers several advantages over manual perimetry:

1. The examination is controlled by the instrument, reducing the subjective element of operator influence,
2. The program used is defined and reproducible,
3. A clinician or skilled perimetrist is necessary only for interpretation purposes,
4. Programs can be customised for individual requirements,
5. Data storage, retrieval and analysis is possible with the relevant software,
6. Depending on the instrumentation used, it allows the assessment of patients' performance through the calculation of the time taken for the test, the number of stimulus presentations, and various error checks, or reliability parameters, incorporated into the test regime.

Over the past ten years automated static perimetry has become an accepted standard method, particularly within hospital practice and in research. It is now widely accepted that computerised static perimetry is more sensitive than kinetic perimetry in evaluating the visual fields of glaucoma patients (Koerner et al 1977; Weber and Dobek 1986; Katz et al 1995).

The full history of the development of automated perimetry is beyond the scope of this thesis and interested readers are referred to alternative works (Wild 1988; Fankhauser 1985).

3.2 Extraneous factors affecting the measurement of the visual field

3.2.1 Age

As age increases there is a gradual reduction in the eye's sensitivity. This loss is predominantly due to neural losses affecting the sensitivity of the retina and visual pathway (Johnson et al 1989) caused by nerve fibre layer dropout (Balaszi et al 1984; Sommer et al 1984), although other factors such as changes in pupil size and media transparency may play a contributory role.

Age-related decline in perimetric sensitivity has been demonstrated by Drance et al (1967) who identified a linear decrease in isopter area with age. The age-related sensitivity loss in automated perimetry is manifested as a linear reduction in threshold sensitivity (Heijl et al 1987d; Haas et al 1986; Jaffe et al 1986; Iwase et al 1988; Zulauf 1994) and has been found to be between 0.6 and 0.9dB/decade (Brenton and Phelps 1986; Haas et al 1986; Collin et al 1988; Johnson et al 1989; Flanagan et al 1993a; Zulauf 1994; Zulauf et al 1994).

Several authors have found an increase in the age-related sensitivity loss with increasing eccentricity (Haas et al 1986; Jaffe et al 1986; Katz and Sommer 1986; Heijl et al 1987a,d; Collin et al 1988; Johnson et al 1989) suggesting not only a depression, but also a steepening of the hill of vision with age. Brenton and Phelps (1986) failed to find evidence for this steepening across the central field, suggesting that the conflicting results may be due to the thresholding strategy used by other workers, where the peripheral points of the central 30^{o} tend to be the last points tested and may therefore be influenced by fatigue effects.

Several studies have shown the age-related sensitivity decline to accelerate beyond a certain age. Iwase and co-workers (1988) found mean sensitivity to be constant until the age of 30 to 45 years, while in older individuals mean sensitivity declined linearly at a rate of 1.2dB per decade. In a re-analysis of previous data (Jaffe et al 1986; Haas et al 1986), Johnson and Choy (1987) identified an increase in the rate of deterioration of threshold sensitivity in subjects over 50 years of age. In support of this, Vivell and co-workers (1993) found an increase in the rate of loss of mean sensitivity over 55 years of age, and Johnson and co-workers (1989) also identified an accelerated visual field

sensitivity loss in normal individuals over 50 years of age after performing a moving averages smoothing of their data. However, they also found an increase in individual variability in this older age group (see section 3.3.1(i)), and suggested that the importance of this apparent accelerated loss of sensitivity in the over 50 age group with regard to the assessment of early pathological change required further investigation.

The degree of age-related sensitivity loss is also dependent on test point location and is more pronounced in the superior region of the field (Haas et al 1986; Katz and Sommer 1986). Matsumoto and co-workers (1991) found the decrease in visual sensitivity due to ageing was more pronounced with smaller stimuli within the central 10^{o} of the field, the rate of deterioration being 0.56 and 1.00dB/decade for stimulus sizes V and I respectively.

3.2.2 Pupil size

A decrease in pupil size will both reduce the amount of retinal illumination and increase diffraction effects. The detection of a stimulus at photopic levels depends largely upon Weber's law, where the ratio between the stimulus luminance, ΔL, and the background luminance, L, is a constant (Fankhauser 1979). A decrease in retinal illumination will dim both the background and the stimulus illumination, thereby retaining the contrast of the stimulus, and thus in photopic conditions, where Weber's law applies, alterations in pupil size should not affect stimulus visibility. Automated perimeters operate at relatively low background illumination levels, and it has been suggested that at these levels Weber's law may break down with small pupil sizes (Klewin and Radius 1986; Heuer et al 1989). However, these studies have been criticised for their lack of adequate control of pupil size (Herse 1992), and Wood et al (1988a) found that the influence of change in pupil size on perimetric sensitivity is similar at background luminances of 10 and 45 asb, suggesting that Weber's law remains constant over this range of adaptation levels. The conflicting evidence is such that it is difficult to conclude whether Weber's law does break down with small pupils. However, other factors such as increase in diffraction effects may reduce the sensitivity with pupillary diameters below 2.4mm (McCluskey et al 1986).

Normal variations in pupil size are not thought to be sufficient to influence perimetric sensitivity (Bedwell and Davies 1977; Brenton and Phelps 1986). This result is supported by Herse (1992) who found no significant differences in foveal sensitivities or slopes of retinal profiles between 3mm and 8mm diameter pupils, and Greve (1973) who found that a change in pupil diameter from 6mm to 2mm in a 20-year old normal subject had no noticeable influence on the level of the sensitivity curve.

Many glaucoma patients may be using therapeutic miotics for the control of IOP. Pharmacologically induced miosis has been found to depress the sensitivity of the central field, as assessed with automated perimetry, by 0.2 log units (Fankhauser 1979). Mikelberg et al (1987) found a reduction in absolute pupil size due to thymoxamine 0.5% to be strongly positively correlated with proportionate change in mean sensitivity, although no significant changes in the visual field indices (described later) were found. Lindenmuth et al (1989) found an average decrease of 0.67dB in the visual field index mean defect (MD), in normal subjects after the instillation of pilocarpine 2%. However, the authors question the clinical significance of such a small change in normal subjects.

Increased retinal illumination occurs as the pupil diameter increases, and under mesopic conditions threshold sensitivity would be expected to improve (Lindenmuth et al 1990). In support of this theory, an increase in the retinal sensitivity has been found with increasing pupil diameter using 10% phenylephrine for mydriasis and 0.5% thymoxamine for miosis (Wood et al 1988a). This effect was more pronounced peripherally, i.e. a flattening of the sensitivity profile, such that the sensitivity of the more peripheral locations is increased with respect to that obtained with the smaller pupil size. The authors suggest that this may be due to an increase in intra-ocular light scatter with the larger pupil diameter, where the greater capacity for spatial summation peripherally allows this scattered light to be preferentially utilised, thus facilitating the increased peripheral sensitivity. Wood and co-workers (1988a) also noted an overall increase in variability of threshold measures with miosis. Rebolleda et al (1992) also found an average improvement in mean defect (MD) of 3.14dB in glaucoma patients being treated with miotics, after the installation of 10% phenylephrine to dilate the pupil. Conversely, a decline in MD of 0.83dB has been found after instillation of 1% tropicamide causing an increase from baseline in pupillary diameter of 1-3mm in normal subjects (Lindenmuth et al 1990). The authors suggest that chromatic and spherical aberrations may account for this decline in threshold sensitivities.

3.2.3 Refractive error and defocus

The major effect of defocus is to increase the size and decrease the luminance of a target image on the retina. The effect of these changes on the perimetric thresholds depends on the size and location of the stimulus. Smaller stimuli are more sensitive to defocus than large ones (Sloan 1961; Atchison 1987; Mutlukan 1994). The presence of blur has been shown to decrease the retinal sensitivity over the central 30^{o} in manual perimetry using stimulus size I (Fankhauser and Enoch 1962) and sizes I and II (Sloan 1961). However, with the larger stimulus sizes III, IV and V, a +3.00D blur failed to influence the perimetric threshold, even at the fovea (Sloan 1961). Benedetto and Cyrlin (1985) reported little change in sensitivity, as measured by Octopus automated perimetry

(Goldmann stimulus size III), either in the central 12^{o} or 30^{o} with spherical refractive blur of up to ±2.00D. A greater decrease in sensitivity was found, more pronounced in the central 12^{o}, when the blur was larger than 3.00D. Decreases in retinal sensitivity in the central field of 1.2-1.4dB for +1.00D and 1.4-2.9dB for +2.00D have also been identified (Weinreb and Perlman 1986; Goldstick and Weinreb 1987; Heuer et al 1987). Collin et al (1993) used hydrogel contact lenses to simulate refractive errors of up to 10.00DS of both myopia and hypermetropia. A decline in sensitivity of 1.27dB and 1.01dB per dioptre of myopic and hyperopic defocus respectively was found over the 60^{o} visual field using the Humphrey Field Analyser (HFA).

The effect of blur in the peripheral field is minimal (Sloan 1961; Aulhorn and Harms 1972; Atchison 1987). The retinal image of a test stimulus in the periphery is distorted and blurred due to the oblique path of light, thus a displacement of the image in front of or behind the retina, due to uncorrected refractive error, is not as important in the peripheral field as in the central or paracentral regions (Aulhorn and Harms 1972). Additionally the greater facility for summation in the peripheral field may reduce the effect of blur on the threshold. A more recent study however, did find significantly reduced sensitivity of the temporal peripheral field when refractive blur of greater than -4.00D and +6.00D was simulated with contact lenses (Collin et al 1993).

The correction of a refractive error with a supplementary lens may lead to field defects due to the rim of the lens. The resulting defect usually occurs at the edge of the central $25\text{-}30^{o}$ field (Henson 1993), and most commonly presents as a combination of absolute and relative defects involving the temporal quadrant alone, or in combination with another quadrant (Zalta 1989). Lens rim artefacts are more common in the elderly, in patients with high hyperopic corrections (Zalta 1989), and in automated, as opposed to manual perimetry (Henson 1993). In a retrospective study on the HFA, Zalta (1989) found the incidence of these artefacts to be 10.4%, with an improvement in this figure to 6.2% in a prospective study where efforts were made to minimise the occurrence.

Refractive scotomas may be caused by areas of localised myopia, as in posterior staphyloma, or hypermetropia, as in macular elevation (Harrington 1976 p. 103). These visual field defects are decreased with the appropriate increase in prescription (Odland 1967).

Wood et al (1988b) reported that transient blurring of perimetric stimuli due to accommodative microfluctuations play a minor role in determining the magnitude of sensitivity within the central 5^{o} and are also a minor component of intra-test variability.

3.2.4 Ocular media opacities

Media opacities have two potential effects on the retinal sensitivity, they act as a filter thereby reducing the amount of light reaching the retina, and they scatter the incoming light. If Weber's law is applicable, the contrast of the stimulus will remain constant due to the filtering action alone. It is therefore the scattering properties of the opacities which will cause the major effects on perimetric threshold measurement.

The presence of cataract leads to a diffuse loss in threshold sensitivity, the effect being greater in the central field (Greve 1973; Guthauser et al 1987). The type of cataract and the stimulus configuration influences the effect on the perimetric profile, with nuclear cataracts depressing perimetric sensitivity at the fovea to a greater extent than in more peripheral regions, whilst the reverse is found for non-nuclear cataracts when measured with large projected stimuli (Wood et al 1989). Attenuation of the perimetric sensitivity has also been identified in normal eyes with induced intra-ocular light scatter (Urner-Bloch 1987; Wood et al 1987b,c; Dengler-Harles et al 1990) and with a reduction in the level of retinal illumination using neutral density filters (Klewin and Radius 1986; Heuer et al 1989).

Corneal and vitreous opacities may also cause intra-ocular light scatter. Faschinger (1987) reported a uniform loss in perimetric thresholds of between 5 and 12dB in lattice corneal dystrophy.

3.2.5 Accuracy of fixation

Eye movements, specifically the loss of accurate fixation, in a visual field examination limit the accuracy of the results. The Heijl-Krakau (Heijl and Krakau 1975b) technique has been introduced and checks fixation periodically by presenting a suprathreshold stimulus in the region of the patient's blind spot. Fixation targets need to be of high contrast to ensure accurate accommodative responses in those subjects who are able to accommodate, as a loss in accommodation may produce similar effects to those of defocus (Henson 1993).

3.2.6 Eccentricity

It is well documented that retinal sensitivity declines with increasing eccentricity in both manual (Sloan 1961; Aulhorn and Harms 1972; Johnson et al 1978) and automated perimetry (Wild et al 1986, 1987; Wood et al 1986, 1988a; Goldstick and Weinreb 1987; Heuer et al 1989; Flanagan et al 1991; Zulauf 1994). The slope is not linear, with an initial steep slope from fixation to around 5^{o}, becoming flatter from 5^{o} to 30^{o} (Hoskins

and Migliazzo 1985). The rate of decline over the central 5^{o}-6^{o} of the field has been reported to be in the range of -0.38dB/degree to -0.86dB/degree (Weinreb and Perlman 1986; Heuer et al 1989; Herse 1992). Over the central 30^{o} the rate of decline is generally reported as flatter with a range of -0.22dB to -0.44dB per degree (Brenton and Argus 1987; Heuer et al 1989; Zulauf 1994).

The perimetric profile becomes flatter, i.e. the differential between central and peripheral locations decreases, with larger stimulus sizes (Sloan 1961; Wood et al 1986; Flanagan et al 1991) and with lower background luminances (Barnes et al 1985; Flanagan et al 1991). Steepening of the profile occurs with increasing age (e.g. Jaffe et al 1986), with increasing intra-ocular light scatter (e.g. Wood et al 1987b) and under the influence of alcohol (Wild et al 1990).

3.2.7 Patient experience

The results of psychophysical testing of various sorts are affected by learning. The phenomena of both fatigue and learning have been observed in the continuous recording of a visual differential threshold (Haider and Dixon 1961). It has been recognised that learning takes place in manual perimetric measurement (Aulhorn and Harms 1972), and automated perimetry is certainly not exempt from these effects. It is essential to be aware of any learning effects as they may influence, and mislead the interpretation of, perimetric results. An increase in mean sensitivity (MS) and a decrease in variability of the results from consecutive visual field examinations may both be indicative of a learning effect.

The presence of a learning effect in normal subjects, naive to automated perimetry, is well established (Heijl and Krakau 1975a; Rabineau et al 1985; Wood et al 1987a; Heijl et al 1989a; Autzen and Work 1990). However, Kosoko and co-workers (1986) found little difference in the time taken to complete both a full threshold and a suprathreshold screening test in normal controls, glaucoma patients and ocular hypertensives. They concluded from this that there was no evidence of either learning or fatigue effects. However, they only compared tests between right and left eyes, and they did not compare mean sensitivity between tests. It is also possible that the fatigue and learning effects 'cancel' each other out. This counterbalancing effect between learning and fatigue has also been suggested elsewhere (Katz and Sommer 1986; Brenton et al 1986). Baum and Schwartz (1992) also failed to find a learning effect on mean sensitivity for normals over the first four central fields with the Octopus.

Increasing age may influence the degree of learning that takes place in naive subjects. Heijl et al (1989a) found no relationship between age and the extent of the learning

process as assessed by an increase in MS. In contrast to this, Autzen and Work (1990) found a MS increase due to learning to be significantly positively correlated with age in the inferior field. The superior field showed no such relationship, and the authors suggest that the increased variability in this region of the field may account for this.

The magnitude of the learning effect is dependent on test point location, being greater with increasing eccentricity (Wood et al 1987a; Adelson et al 1988; Heijl et al 1989a; Wild et al 1989b) and in the superior region of the field in both normal subjects (Wood et al 1987a) and in glaucoma patients (Wild et al 1989b). This increase in learning effect demonstrated in the superior field may be due to the subject consciously learning to raise their upper lid.

More recently Rudnicka and co-workers (1993) investigated learning in normals in the central 30^{o} field with the HFA over six sessions. Conventional analysis with MD and MS failed to identify any significant learning effect. Alternative pointwise analysis with the calculation of a learning proportion index identified a significant learning effect between sessions one and two, with the majority of learning found in the peripheral points of the central field, particularly in the superior field. After the subsequent application of a spatial filter to remove possible outliers and enhance or smooth the data the learning effect appeared more randomly distributed across the field. The authors suggest that the apparent increase in learning effect in the peripheral and superior fields is partly a function of extreme values (outliers) which tend to occur in these regions of the field.

Learning effects have also been identified in stable glaucoma patients (Gloor et al 1981; Niles and Trope 1988) and in glaucoma suspects (Werner et al 1990; Adelson et al 1988). However, other workers have failed to find evidence of a learning effect on mean sensitivity in stable glaucoma patients (Werner et al 1988b; Gramer et al 1986). Marra and Flammer (1991) found a larger learning effect between eyes in patients with higher refractive errors, particularly myopes.

There is some evidence to suggest that subjects naive to automated perimetry, but experienced in manual perimetry, undergo little or no learning. Werner and co-workers (1988b) found a reduction in the variability, but no improvement in MS in the first four consecutive automated field plots in 20 stable glaucoma patients, all of whom had previously undergone at least one manual visual field examination. This is in agreement with previous work on patients with prior manual perimetric experience (Katz and Sommer 1987). Werner and co-workers (1988b) suggest that a single 'baseline' examination is adequate in the majority of patients with prior manual perimetric experience.

The transfer of learning between eyes tested at the same session (Wild et al 1989b; Searle et al 1991a,b) has been demonstrated, with the second eye showing less pronounced improvement over time than the first. Of interest in the long-term follow-up of the visual field, is that the learning effect appears to be retained over periods of up to nine months (Searle et al 1991a; Wild et al 1991a).

From a clinical and research viewpoint the number of tests that should be performed before learning is considered to be complete is important. In using automated perimetry in research, some authors have assumed a learning effect, and allowed for it by discarding data from the first (Flammer et al 1984a) or first two (Wilensky and Joondeph 1984) fields. Overall there appears to be much inter-individual variation in the depth and extent of learning that takes place in subjects undergoing serial automated visual field examinations. In some subjects the majority of learning takes place within the first examination (Gloor et al 1981; Wood et al 1987a; Adelson et al 1988; Heijl et al 1989a; Rudnicka et al 1993) while others continue to learn beyond this (Wood et al 1987a; Heijl et al 1989a). This retention of the ability to learn is more apparent in subjects with an initially low sensitivity (Heijl et al 1989a; Wild et al 1989b) or in learning associated with the peripheral field (Wood et al 1987a).

3.2.8 Fatigue

As a psychophysical test continues, the attentiveness and concentration of the subject may diminish. Fatigue in perimetric assessment may manifest as an apparent decrease in sensitivity, an increase in variability and in the number of false responses made with increasing examination time.

Fatigue effects have been demonstrated in continuous perimetric testing over 20 minutes (Langerhorst et al 1987; Johnson et al 1988), 30 minutes (Heijl 1977a; Holmin and Krakau 1979; Heijl and Drance 1983a,b) and 60 minutes (Mills et al 1987; Heijl 1977a). Rabineau et al 1985 tested normal subjects for up to 3 hours continuously and concluded that during a period of one hour neither fluctuation nor threshold determination are influenced by fatigue. However, half of the eight subjects were trained psychophysical observers and this may have influenced the results.

Much of the interest in fatigue effects in automated perimetry has been in their potential use as a diagnostic tool in the identification of early glaucomatous defects. Patients suffering from glaucoma, and those with suspected glaucoma, demonstrate a greater fatigue effect than normal subjects (Langerhorst et al 1987; Johnson et al 1988), particularly in, and adjacent to, affected areas of the field (Heijl 1977a; Holmin and Krakau 1979; Heijl and Drance 1983a,b). This effect is independent of background

luminance (Heijl and Drance 1983a,b) but is increased slightly with increasing age (Langerhorst et al 1987). The increase in fatigue effects in pathological fields may help to explain the exaggeration of visual field defects in automated as compared with manual perimetry (Heijl 1977a; Koerner et al 1977).

Testing times of between eight and ten minutes have been suggested as optimum to reduce the effects of fatigue on the results of automated perimetry (Johnson et al 1988). In support of this, Marra and Flammer (1991) found no change in MS for the repeated testing of three locations over a time period of five to eight minutes in normals and glaucoma patients.

During most visual field examinations both eyes are tested with a short break between each test. Jaffe et al (1986) noted a greater degree of variability in the second eye tested at the same session, and suggested that this was caused by fatigue. A recent study has demonstrated fatigue effects in normal subjects both within one eye, and transferable to the second eye tested at the same visit (Searle et al 1991a,b), with an enhanced effect found in the superior field of the second eye. Coman et al (1994) also demonstrated transferable fatigue effects between eyes, and found that various strategies applied in an attempt to minimise these effects were unsuccessful.

Recent work (Hudson et al 1993) has further described the locus and magnitude of fatigue effects, with a progressive loss in sensitivity comprising a general sinking of, and an asymmetrical steepening of, the hill of vision. Generalised loss over time was found to be more pronounced in both the inferior hemifield and beyond 17^{o} eccentricity, while localised loss was greater in both the superior and nasal regions and beyond 17^{o} eccentricity.

Fatigue effects in static perimetry have also been noted in various diseases of the optic nerve, including optic neuritis or papillitis (Enoch et al 1970; Wildberger and Robert 1988).

3.2.9 Other factors

Other factors reported to influence the results of perimetric assessment include anatomical features, such as prominent eyelashes or droopy eyelids (Brenton et al 1986), alcohol consumption (Zulauf et al 1986; Wild et al 1989c, 1990) and general health (Langerhorst et al 1989). The use of either antihistamines (Wild et al 1990) or short-term treatment with diazepam (Haas and Flammer 1985) was found to have little influence on the results of automated perimetry. Smith and Baker (1987) assessed 15 patients with known functional visual field loss (hysterical or malingering) using

automated perimetry. Although visual field abnormalities were found, these were indistinguishable from defects caused by organic loss. Reliability parameters also failed to characterise functional loss and the authors conclude that manual perimetry remains the procedure of choice in these patients.

3.3 Variability in visual field measurement

The concept of a threshold in psychophysical testing has been described as 'a definite quantity to be disentangled from the 'errors' inevitably introduced in the process of determining it' (Oldfield 1955). In all quantitative tests, especially psychophysical tests, the outcome tends to fluctuate (Flammer 1985). Fluctuations that take place in the determination of a visual differential threshold are due to various measurement errors that must be taken into consideration when assessing the results of an automated visual field examination.

In the measurement of the visual field by manual perimetry, any unexpected result is usually rechecked by the examiner. The temptation in this situation is to accept the 'most likely' result, often discarding the atypical one. With the advent of automated techniques, these atypical results can no longer be ignored. Instead of trying to avoid scatter in the measurement of the visual field, fluctuation can now be quantified and used to give additional information about the examination and results (Flammer et al 1984 a,c).

3.3.1 Within subject

The first and basic description of the concept of fluctuation in automated perimetry was provided by Bebie and co-workers (1976). They described both short-term fluctuation (SF) and long-term fluctuation (LF), the latter being made up of correlated and uncorrelated components, now known as the heterogenous and homogenous components of LF (Flammer et al 1983, Flammer 1985).

The total variance (σ^2) is made up of the components of SF (σ_S^2) and LF (σ_L^2):

$$\sigma^2 = (\sigma_S^2) + (\sigma_L^2) \qquad \text{(Flammer 1985)}$$

3.3.1 (i) Intra-test variability

Thresholds measured at the same location more than once within one examination will show some degree of variance or intra-test variability. This is known as short-term

fluctuation and is principally due to the psychophysical measurement of the threshold itself, and to the tendency of the retinal sensitivity to fluctuate over hours and days (Flammer et al 1984a). SF is calculated as the root mean square of repeated thresholds at a number of points.

$$SF = \sqrt{\frac{1}{m}\sum_{i=1}^{m}\frac{\sum_{r=1}^{R}\{x_{ir} - x_i\}^2}{R-1}}$$

where

m = number of locations with double determinations

r = particular repetition of a threshold

R = total number of threshold repetitions at a given location

x_{ir} = measured threshold at location i and repetition r

x_i = mean of R thresholds at location i

Average values found for SF in normal subjects with the HFA range between 1.3dB and 1.86dB (e.g. Brenton and Phelps 1986; Brenton and Argus 1987; Heijl et al 1987d; Iwase et al 1989; Crosswell et al 1991). The frequency distribution of SF at normal locations is very close to normal, and is symmetrical (Flammer and Zulauf 1985). SF may also be influenced by subject reliability (see section 5.6). Bebie et al (1976) found normal values for SF ranging between 1dB for stable observers and 4dB for unstable observers.

It has been suggested that an increase in SF occurs with increasing age in both the central (Katz and Sommer 1987; Autzen and Work 1990) and peripheral field (Katz and Sommer 1987). However, the majority of studies to date have consistently shown no such increase in both normal and glaucomatous subjects (Heijl 1977b; Werner et al 1982; Flammer et al 1984b; Brenton and Phelps 1986; Nelson-Quigg et al 1989) in the central 30^{o} of the field.

Intra-test variability is dependent upon test point location, increasing with increasing eccentricity within the central 30^{o} (Heijl 1977b; Parrish et al 1984; Wilensky and Joondeph 1984; Katz and Sommer 1986; Lewis et al 1986; Heijl et al 1987d, 1989b; Nelson-Quigg et al 1989; Zulauf 1994), to an eccentricity of 60^{o} (Brenton and Phelps 1986) and in the superior field (Katz and Sommer 1986; Jaffe et al 1986). However, in contradiction to this, SF has been found to be independent of eccentricity within the central 15^{o} (Werner et al 1982; Flammer and Zulauf 1985) and 27^{o} (Flammer et al 1984b) of the field.

Increases in variability in static perimetry have been suggested to be early indicators of visual field damage (Werner and Drance 1977; Gloor et al 1984; Heijl 1989). SF has been shown to be greater in abnormal fields, particularly in disturbed areas (Flammer et al 1984a,b; Werner and Drance 1977; Stürmer et al 1985; Langerhorst et al 1985; Gramer et al 1986; Piltz et al 1986; Werner et al 1987; Heijl et al 1987c). Flammer et al (1984a) suggested that in glaucoma patients this may be due in part to a generalised reduction in sensitivity in chronic open-angle glaucoma. It was also noted that areas of the field in patients with no apparent field defects also showed increased fluctuation, as did fields of glaucoma suspects. The increase in variability in automated perimetry found in glaucoma patients may be the result of disturbed homeostasis, loss of nerve fibres, increased fatigue effects and poor fixation (Flammer et al 1984a; Henson and Bryson 1990). In support of the relationship between variability and abnormal fields, an association between increasing variability with decreasing threshold sensitivity has been reported (Holmin and Krakau 1979; Flammer et al 1984a,b; Stürmer et al 1985; Starita et al 1987; Weber and Rau 1992).

Variability of SF has been shown to increase with the number of locations used for its determination (Casson et al 1990). It was also shown that using a larger number of determinations and smaller number of locations gives a greater consistency in SF. More recently Flanagan and co-workers (1993b) compared SF as calculated by the standard 10 double determined locations and that calculated from all available double determined locations. They found that SF increased with an increase in the number of double determinations of threshold and concluded that SF would better reflect intra-test variability if all available double determinations of threshold were used to calculate the index. Chauhan et al (1991) found that increasing the number of determinations at each location does not effect global SF, however, local SF (the threshold variability at a discrete visual field location) initially increased as the number of determinations increased, followed by a stabilisation after five determinations. This suggests that programs using double determinations may underestimate local SF.

An alternative method for calculating SF using surface trend analysis (Schulzer et al 1990; Mills et al 1991) has been proposed, removing the necessity for double determinations. A polynomial surface is fitted to a grid of single determinations to give an estimate of a second determination for each location. The residual deviations between the measured threshold and the fitted surface value are used to calculate an estimate of SF. Higher order polynomials were required for abnormal fields, and fitting became more difficult in fields with severe loss.

SF has also been reported to increase with an increase in fixation target luminance (Safran et al 1992), decreasing background luminance (Crosswell et al 1991; Langerhorst

et al 1991), and after the use of an non-centrally acting antihistamine preparation (Wild et al 1989c). A trend towards increasing SF has also been reported with an increase in blood alcohol level (Zulauf et al 1986). Increasing stimulus size (Wall et al 1993; Zulauf and Caprioli 1993) and a decrease in the number of locations used (Casson et al 1990; Fujimoto and Adachi-Usami 1992a,b) decreases SF. A change in stimulus duration from 0.065 to 0.5 seconds (Pennebaker et al 1992) or short-term treatment with diazepam (Haas and Flammer 1985) did not significantly influence SF. Short-term fluctuation may also be influenced by the degree of learning and fatigue (see sections 3.2.7 and 3.2.8).

3.3.1 (ii) Inter-test variability

Long-term fluctuation, or inter-test variability, is the variance in threshold measurements over more than one examination, and has been defined as 'the statistical variance of repeated measurements of the differential light sensitivity at each test location' (Zulauf et al 1991a, p.184). Uniform change in threshold over all test locations is referred to as the homogenous component of the LF, whilst the heterogenous component of LF is statistically independent for all locations in the visual field (Bebie et al 1976; Flammer et al 1983). LF has been found to be significantly positively correlated with SF (Flammer et al 1984c; Boeglin et al 1992), however, this is not a strong relationship and LF cannot be accurately predicted by SF (Flammer et al 1984c).

Higher levels of LF are found with increasing eccentricity in both normal subjects (Heijl 1977b; Heijl et al 1987a,d, 1989b; Parrish et al 1984; Lewis et al 1986; Wall et al 1993) and in glaucoma patients (Heijl 1987; Magee et al 1987). The superior field has also been found to be more affected by inter-test variability in normal subjects (Katz and Sommer 1987; Boeglin et al 1992). Boeglin et al (1992) and Werner et al (1991) however, corrected for the differences in sensitivity in different parts of the field and found LF to be no longer dependent on test point location in glaucoma patients. Rutishauser et al (1989) also failed to find a correlation between LF and eccentricity. Werner et al (1991) suggests that the apparent increase in fluctuation with increasing eccentricity is due to the changes in sensitivity rather than test point location. In support of this LF has been found to increase with decreasing sensitivity (Werner et al 1987; Zulauf et al 1991a; House et al 1993), and with progressive compared with stable visual field loss (Boeglin et al 1992). Zulauf and co-workers (1991a) reported significant correlations between LF and both eccentricity and sensitivity, with inter-test variance increasing towards the periphery of the central 30^{o} field by an average of $0.1dB^2$ per degree and increasing by $0.5dB^2$ for each dB decrease in sensitivity.

Heijl (1985a) identified larger inter-test variability in areas of the field which subsequently developed defects. Although Katz and Sommer (1987) found an increase

in LF with increasing age, this has not been reproduced in a more recent study (Boeglin et al 1992). LF is unaffected by a change in the stimulus duration from 0.065-0.5 seconds (Pennebaker et al 1992), but dependent upon stimulus size (Wall et al 1993) with a reduction in LF with larger stimulus size, particularly in areas of lower sensitivity. A long-term fluctuation in threshold sensitivity of greater than 4dB may occur at a single location in a normal field (Wilensky and Joondeph 1984; Lewis et al 1986) and 7-15% of locations may differ by 6dB or more (Keltner et al 1985). These normal long-term fluctuations are sufficiently large to be potentially mistaken for true defects, and thus warrant careful clinical consideration. Indeed, Werner et al (1987) have suggested that a location has to change by 5-7dB in order to be detected by automated perimetry 95% of the time. In support of this finding, Hoskins et al (1988) indicate that a change in mean sensitivity of between 4dB and 7dB, depending on the region analysed, is required to have 95% confidence that the negative trend will be continued in the subsequent field.

3.3.1 (iii) Between eyes

Intra-individual comparisons in the visual field between eyes may aid in the assessment of abnormal fields in unilateral disease. This method assumes that one eye has a normal visual field, and that the fields of each eye in a normal individual are symmetrical.

In addressing this latter assumption, Brenton and co-workers (1986) investigated the degree of symmetry of the central 30^{o} field with the HFA between fellow eyes of normal subjects. Inter-ocular differences in single locations ranged between 0-9dB, with larger differences occurring in the superior field. It was calculated that an asymmetry in overall mean sensitivity exceeding 1.4dB should occur in fewer than 1% of normal subjects. Complicating factors in this study are the presence of transferable fatigue and learning effects from the first to the second eye tested at the same session. In a study addressing this issue, Searle et al (1991c) found the sensitivity of the second eye tested at the same session to be significantly lower for all subjects and thus question the validity of utilising asymmetry as a diagnostic criterion. Zulauf et al (1991b) have suggested that an inter-ocular asymmetry in MS of greater than 2dB is suspicious of early disease.

3.3.2 Between subjects

Variability in threshold sensitivity also exists between subjects. Inter-subject variability is dependent on test point location, increasing with increasing eccentricity (Brenton and Phelps 1986; Wild et al 1986; Heijl 1987; Heijl et al 1987a,d; Rutishauser et al 1989; Gundersen 1993; Zulauf 1994) and in the superior field (Brenton and Phelps 1986; Crosswell et al 1991). Brenton and Phelps (1986) found a more marked inter-subject

variation for subjects over 60 years of age in the peripheral 30-60° field, but no such age-related change in variability in the central 30° field.

Pathological fields have a greater degree of inter-subject variability (Flammer et al 1984a; Heijl et al 1987c). Werner et al (1982) also found increases in variability between subjects with ocular hypertension in the absence of any field defect, and those with normal IOPs in the central 5° field. A reduction in background luminance from photopic to mesopic levels increases the inter-individual variability (Crosswell et al 1991).

Reductions in inter-subject variability occur with increased experience in automated perimetry (Heijl et al 1989a) and with larger test stimuli (Gundersen et al 1993). Changing the stimulus presentation time from 0.065s to 0.5s has little effect on inter-individual variation (Pennebaker et al 1992). Wild et al (1986) suggested that inter-individual variation may be due to differences in peripheral refraction, pupil size, intra-ocular light scatter or variations in the experience of, or ability to perform perimetric tasks. In support of the latter, Heijl et al (1987c) suggests that a large proportion of the between subject variability, particularly in normal subjects, can be explained by differences in perimetric reliability.

Sex differences in the left and right hemifields of normal subjects with automated static perimetry have been reported recently (Cohn et al 1994). Thirty-nine normal volunteers (23 women and 16 men) with right hand, eye and foot dominance underwent right and left visual field examination with the HFA, program 24-2. Female subjects were found to have a significant decrease in sensitivity in the left hemifield, equivalent to a difference of 0.34dB per tested point. This was not found in male subjects, when all subjects were combined, or in a comparison between eyes in either sex. The authors suggest that these sex differences across the vertical meridian are likely to be physiological in the absence of supporting neurological signs or symptoms, and may be due to real differences in retinocortical perception or to asymmetry of the gross anatomy of the cortex between the sexes. Gynaecological status and menstrual cycle phase at testing of female subjects was not reported, and all subjects were naive to automated perimetry (see section 3.2.7), and these factors may have influenced the results.

3.4 Optimal configuration of test locations

Fankhauser and Bebie (1979) suggested that a grid of stimulus locations with a resolution of 6° is superior to a similar number of locations positioned along the 180° and 90° meridians with a resolution of 1.5° in the detection of small circular scotomas. The authors also note that for very small scotomas with radii of less than 1° the

detection probability is extremely low and independent of grid choice. It has been suggested (Weber 1987; Heijl 1989) that the standard grid resolution of 6^{o} is sufficient for detection purposes. However, King et al (1986) found that a 6^{o} grid resolution failed to identify the physiological blind spot in one eye of up to 22% of 100 glaucoma suspects, suggesting that the standard 6^{o} grid may not be adequate in the detection of scotomas the size and depth of the blind spot. Weber and Dobek (1986) also presented a case where the 6^{o} grid resolution of the 30-1 program of the HFA failed to identify the blind spot. They suggested different stimulus location separation depending on eccentricity, with resolutions of 3^{o} within the central 10^{o}, 4.2^{o} between 10^{o} and 20^{o} and 6^{o} between 20^{o} and 30^{o} from fixation, for optimal detection of glaucomatous defects. Spatially adaptive programs, where higher resolution is automatically applied in defective areas, are another alternative (Häberlin et al 1980; Funkhauser et al 1988a,b).

3.5 Humphrey Field Analyser

The instrument available for this research is the Allergan Humphrey Field Analyser 630 and all further technical detail refers to this instrument alone.

3.5.1 Technical information

Following the development of an automated perimetric instrument in the 1970s (Heijl and Krakau 1975a,b; Heijl 1977a,b; Krakau 1978) the Allergan Humphrey Field Analyser has become a standard instrument in automated perimetric assessment. The HFA is a single-unit instrument consisting of a stimulus generation system, a computer, a cathode ray tube unit, a printer and a double floppy disc drive system (Heijl 1985b). Static, random stimuli are generated through a projection system using an incandescent lamp as a light source, and projected onto a hemisphere of 33cm radius. The background bowl luminance is fixed at the Goldmann standard of 31.5asb. Stimulus size may be varied with a range of 0.25-64mm^2 (corresponding to Goldmann sizes I-V) with a default of the standard Goldmann size III (4mm^2). Stimulus luminance can be varied over a 5.1 log unit range (0.08-10,000asb), with the response of the visual system being represented in terms of sensitivity as decibels (dB), where 0dB represents the maximum stimulus luminance and is equivalent to Goldmann V4e stimulus or 10,000 asb. Duration of the stimulus is 0.2 seconds.

Suprathreshold screening and full threshold programs are available, together with the facility for custom designed programs. All programs used in this thesis employ the full threshold strategy and further information refers to this strategy alone.

3.5.2 Thresholding strategy

The differential light threshold can be defined as the value at which the probability for a stimulus to be detected is 50% (Flammer et al 1984a). The HFA employs a repetitive staircase technique with diminishing step size (0.4, 0.2 log unit) and double crossing of the threshold to determine the threshold[1]. An initial stimulus is presented at an intensity the patient is expected to see (estimated from the threshold values of neighbouring points), stimulus intensity is then reduced (or increased if the stimulus is not seen) in 4dB steps until the threshold is crossed, then increased (or reduced) in steps of 2dB until it is seen, with the last seen value recorded as the threshold at that location. The full threshold strategy of the HFA begins by twice thresholding four 'primary' locations, one in each of the four quadrants. The average threshold for locations is computed. If the actual threshold is more than 4dB away from the expected value, that location is thresholded again. These four primary locations are used to determine starting values to threshold neighbouring locations. The process continues until each location in the field test has been thresholded. If any location differs from that expected by more than 4dB, based on the threshold of its neighbouring points, the threshold is found again.

3.6 Subject reliability

The interpretation of automated perimetric results must include an assessment of the reliability or co-operation of the subject undergoing the test. Results from an unreliable subject should be treated with caution before any conclusions about the pathological state of the field are drawn.

In modern automated perimeters, several 'catch trials' are performed throughout the test, and these, together with other basic properties of the test, help the interpreter to judge unreliable tests and to take this into consideration in the analysis of the field plot. Basic properties of the test that give additional information as to the subject's reliability include the total number of times a light threshold was presented throughout the test, or the number of questions asked, and the time taken to complete the test. There are three types of 'catch trial' regularly used in automated perimetry, false positives (FP), false negatives (FN) and fixation losses (FL).

The HFA uses a projection system to present the stimuli onto the background bowl of the perimeter. The movement of the projection system between each stimulus

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[1]Humphrey Field Analyser Operator's Manual (1986), Allergan Humphrey, San Leandro, California, section 8.

presentation is audible to the subject. A FP trial is when the projection system moves as if to present a new stimulus, but none is shown. If a subject responds to this noise by indicating that a stimulus was seen it is noted as a false positive error by the instrument. FP errors are an indication that the subject's comprehension of the test is at fault.

From time to time as the test proceeds, the HFA program presents stimuli of the brightest intensity available at locations at which measurable differential thresholds have already been determined. If a subject fails to respond to this it is recorded as a FN error, and is an indication of the attentiveness of the subject throughout the test. FN errors may also be a reflection of intra-test variability.

In order to check that fixation is constant throughout the test, the Heijl-Krakau method (Heijl and Krakau 1975a,b) is employed, where suprathreshold stimuli are presented in the predetermined blind spot. If recorded as seen by the subject these are an indication that fixation has been lost, or that a FP error has been made. The HFA 630 also employs a telescope system to allow direct assessment of fixation by the perimetrist.

The HFA contains recommendations of the percentage of errors made in these catch trials that designate a particular field test results unreliable. Field tests with one or more error scores of >33% for FP or FN, and >20% for FL are flagged as unreliable[2].

Recent work has shown that many normal subjects, glaucoma suspects and patients with glaucoma demonstrate a FL rate above the HFA designated 20% reliability limit (Katz and Sommer 1988; Nelson-Quigg et al 1989; Bickler-Bluth et al 1989; Katz et al 1991; Sanabria et al 1991). This may be due to an incorrectly plotted blind spot at the start of the test (Sanabria et al 1991), a false positive error where the subject is responding to the motor noises (Katz and Sommer 1988,1990), or to scattered light from the bright stimulus presented at each trial (Nelson-Quigg et al 1989), rather than true fixation losses. It is not clear why the manufacturers set the 20% limit, and increasing the limit to 33% in line with that of FP and FN, to reduce the number of fields flagged as 'unreliable', has been suggested (Katz and Sommer 1988; Nelson-Quigg et al 1989; Bickler-Bluth et al 1989). Sanabria and co-workers (1991) found a decrease in the rate of fields flagged as unreliable due to FL from 26% to 14% when perimetrists were instructed to interrupt tests to replot the blind spot if two FL were made.

While there are large inter-individual variations in reliability (Nelson-Quigg et al 1989), there appears to be no relationship between low reliability and advancing age (Heijl et al

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[2]Statpac Users Guide (1987), Allergan Humphrey, San Leandro, California, pp11.

1987c; Jenni and Flammer 1987; Katz and Sommer 1988; Nelson-Quigg et al 1989; Bickler-Bluth et al 1989).

The extent of damage to the visual field may influence the results of reliability testing. The rate of FN errors (Heijl et al 1987c; Jenni and Flammer 1987; Starita et al 1987; Katz and Sommer 1988; Katz et al 1991; Johnson et al 1988), FP errors (Johnson et al 1988) and an increase in FL with increasing test time (Heijl 1977a) have been reported to be greater in glaucoma patients than in normal subjects. It has been suggested that this increase in errors may be due to increased visual fatigue and/or variability in the pathological fields (Werner et al 1982; Flammer et al 1984a,b; Katz and Sommer 1988), or, with FN errors, due to the correlation found between these errors and mean sensitivity (Jenni and Flammer 1987). Contrary to these studies no difference in the rates of FP (Flammer et al 1984a; Heijl et al 1987c; Katz and Sommer 1988) or FN errors (Flammer et al 1984a) have been found between normals, glaucoma suspects and glaucoma patients.

Cascairo and co-workers (1991) investigated the effect of intentionally increasing the number of FP, FN errors and FL on the normal visual field using the HFA. They found significant differences in the global indices and probability maps when the prevalence of FN errors was >20% and FP errors and FL was >33%, and concluded that, although the numbers of missed catch trials are often recorded incorrectly by the instrument, together with mean defect and the number of questions asked, they do help to identify unreliable fields.

A patient's reliability must be taken into consideration when comparing consecutive fields for the identification of field loss. This has been highlighted by McMillan and co-workers (1992) who found a significant increase in the variation in mean defect in patients with two consecutive unreliable fields compared with reliable patients. Changes in mean defect should therefore be viewed with greater suspicion in patients with unreliable fields.

Subject reliability has also been shown to be affected by alcohol, with an increase in the number of stimulus presentations, FP and FN errors, and SF (Zulauf et al 1986; Wild et al 1990).

3.7 Data analysis

With the generation of numerical threshold values stored on floppy disc, the possibility of using mathematical methods to analyse the data is now facilitated.

3.7.1 Presentation

Automated perimetric field tests provide maps of raw threshold values (in dB) for each location thresholded in a particular test (figure 3.1). Although this is the most accurate way of presenting the data, numbers are difficult to interpret (Greve 1982). Also the differential light threshold is known to decrease with increasing age in normal populations (Brenton and Phelps 1986; Heijl et al 1987d), the decline being more pronounced in the mid-periphery than centrally (Heijl et al 1987d), and this adds to difficulties in interpretation of raw values. Age-corrected normal mean threshold values have been established and are stored in the HFA to aid interpretation and analysis of the results. Alternative representations of the results include interpolated grey scales and plots of deviation from estimated normal plots (figure 3.1). These alternative plots are not considered in this thesis and are discussed no further.

3.7.2 Global indices

In order to assist in the interpretation of field plots, summary statistics, or global indices, have been developed (Flammer et al 1985; Flammer 1986). These are mean defect (MD), short-term fluctuation (SF), loss variance (LV) and corrected loss variance (CLV). Heijl and co-workers (1987b) have developed corresponding indices for use with the HFA, weighted to compensate for the difference in variability found at different test locations in the field.

The HFA statistical package (Statpac) calculates four global indices:

Mean deviation (MD)

The MD is the weighted average deviation from the age-corrected normal reference field. It is an estimate of the total field loss (localised and homogenous), or uniform part of the deviation, and is defined as:

$$MD = \left\{ \frac{1}{n} \sum_{i=1}^{n} \frac{(x_i - N_i)}{s_{1i}^2} \right\} \Bigg/ \left\{ \frac{1}{n} \sum_{i=1}^{n} \frac{1}{s_{1i}^2} \right\} \qquad \text{(Heijl et al 1987b)}$$

where x_i is the measured threshold and N_i the normal reference threshold at point i, and s_{1i}^2 the variance of normal field measurements at point i. The number of test points is denoted by n.

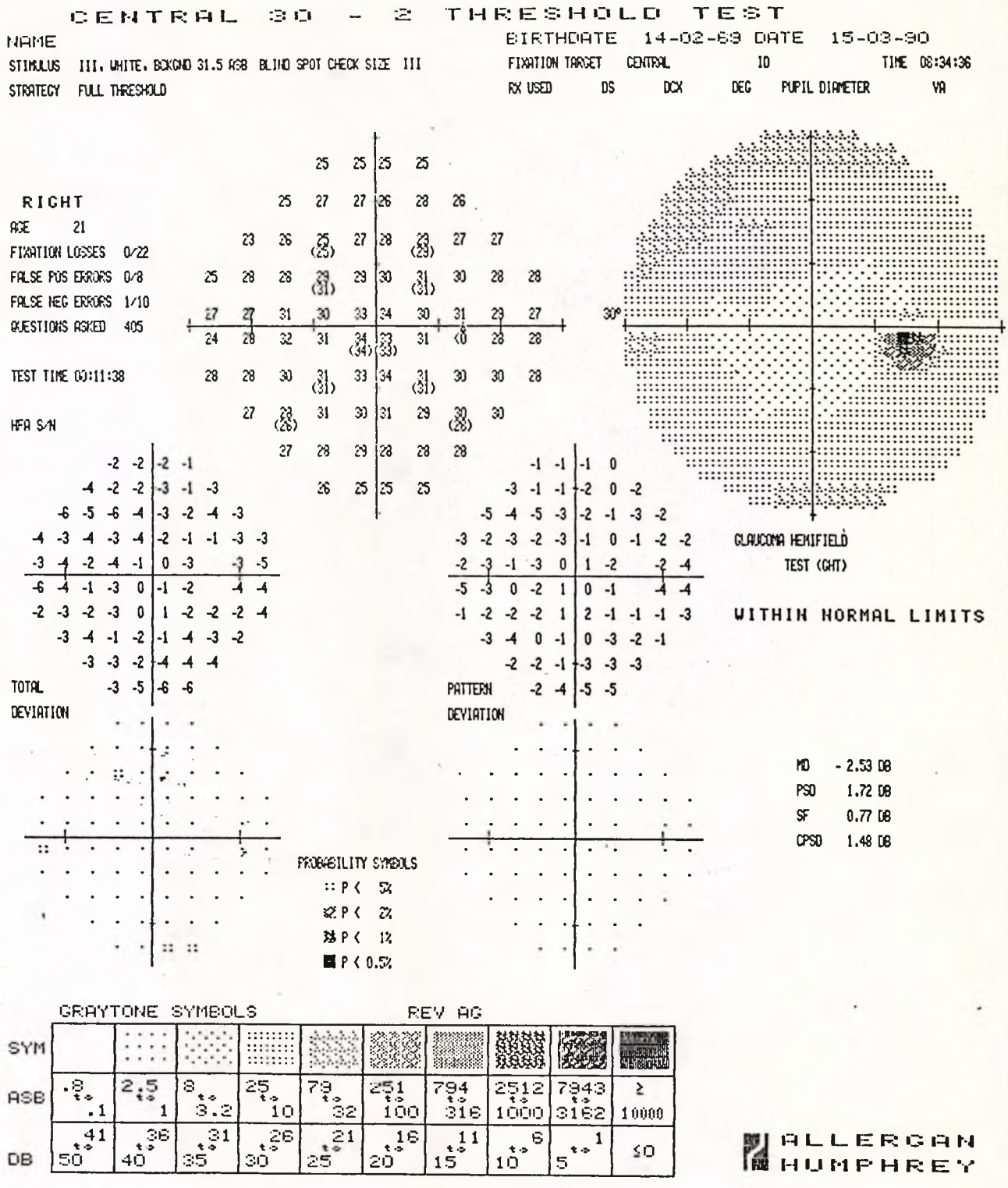


Figure 3.1 Standard printout of central 30-2 program of the HFA

Pattern standard deviation (PSD)

PSD is analogous to LV and is the weighted standard deviation of the point-wise differences between the measured and the normal reference fields. PSD estimates the non-uniform part of the deviation and may be interpreted as the standard deviation of deviation of the threshold pattern (shape of the hill of vision) from normal. PSD identifies early localised field loss. A small value for PSD indicates close agreement in shape between the patient's field and the normal reference field.

$$PSD^2 = \left\{\frac{1}{n}\sum_{i=1}^{n} s_{1i}^2\right\} * \left\{\frac{1}{n-1}\sum_{i=1}^{n}\frac{(x_i - N_i - MD)^2}{s_{1i}^2}\right\} \qquad \text{(Heijl et al 1987b)}$$

Weighting with $1/s_{1i}^2$ minimises PSD^2 in normals.

Short-term fluctuation (SF)

SF is a weighted mean of the standard deviations at ten test points where the threshold is determined twice. SF may be interpreted as an estimate of the measurement error.

$$SF^2 = \left\{\frac{1}{10}\sum_{j=1}^{10} s_{2j}^2\right\} * \left\{\frac{1}{10}\sum_{j=1}^{10}\frac{(x_{j1} - x_{j2})^2}{2 * s_{2j}^2}\right\} \qquad \text{(Heijl et al 1987b)}$$

where x_{j1} is the first and x_{j2} the second threshold value. The normal intra-test variance in point i is denoted by s_{2j}^2. Weighting with $1/s_{2j}^2$ minimises SF^2 in normals.

Corrected pattern standard deviation (CPSD)

CPSD is analogous to CLV and estimates that part of the non-uniform deviation which is not caused by SF. It may be interpreted as the 'true' deviation of the threshold pattern (shape of the hill of vision) from the normal. To adjust for the non-uniform fluctuation pattern we let k be a constant >1 and define

$$CPSD^2 = PSD^2 - k * SF^2 \qquad \text{(Heijl et al 1987b)}$$

The deviations of the measured field from the reference field are divided into a uniform change, estimated by MD and a deviation of shape, estimated by PSD. PSD consists of the true difference in shape, estimated by CPSD, and the measurement error SF. Prediction limits have been calculated for all four indices and if a measured value falls outside of the limits the level of significance is given on the HFA printout along with the values of the indices themselves.

The effect of the weighting factor implemented by Heijl and co-workers (1987a) for the HFA Statpac has been investigated by Flanagan and co-workers (1993). They found that the weighting had little influence on the MD, but caused slight increases in the PSD and CPSD with a slight decrease in SF and concluded that the weighting function had little clinical influence on the visual field indices. Zulauf (1994) found only a small increase in inter-individual variation with eccentricity with the Octopus program G1, and suggested that it was not necessary to weight the global indices for fluctuation.

3.7.3 Statistical analysis

Other data reduction, or summary, statistics have been developed in attempts to aid interpretation of automated perimetric results. Three further indices are available with the Octopus perimeter; the third central moment and skewness or Q statistic (Brechner and Whalen 1984) and the spatial correlation (Bebie 1985). Defect volume, which can be defined as the difference between the normal, or expected, volume of the field and the actual volume (Langerhorst et al 1985; van den Berg et al 1985), representing a three-dimensional measure of the visual field has also been used in analysis (Suzumura et al 1985; Jaffe et al 1986; Wild et al 1987; Wood et al 1987a). In order to utilise the spatial relationship between locations with depressed sensitivity the use of both cluster analysis (Chauhan et al 1989; Åsman 1992; Mandava et al 1993) and cross-meridional comparisons e.g. the Glaucoma Hemifield Test of the HFA Statpac (Heijl et al 1991) have also been proposed.

Of importance in visual field assessment is not only the detection of loss, but also the progression of any loss over time. The HFA Statpac 2 allows the comparison of individual fields with baseline values and provides pointwise change probability maps and linear regression analysis of MD for two or more consecutive fields (Heijl et al 1991). Other authors have also used regression analysis on various data reduction statistics (e.g. Holmin and Krakau 1982; Mikelberg et al 1986; Hoskins et al 1987; Wu et al 1987; Werner et al 1988a; Chauhan et al 1990).

The use of visual field indices may not provide a sufficiently sensitive method for detecting the earliest change in the progression of glaucomatous visual field loss (Chauhan et al 1990). In the Progressor program pointwise linear regression analysis has been combined with graphical representation using colour-coded bars of varying length to represent both the degree of loss and the significance of the progression over time at each threshold location (Poinoosawny et al 1993a; Poinoosawny et al 1993b; Fitzke and McNaught 1994). Pointwise analysis has been used in other studies (e.g. Cyrlin et al 1991; Noureddin et al 1991) and also in conjunction with the modelling of the shape of

the field of vision with a curved surface (Wild et al 1989a, 1991b, and 1993), in the evaluation of the progression in visual field loss.

Image-processing techniques have recently been developed and applied to visual field data to reduce the amount of 'noise' inherent in automated perimetric measurement (Fitzke and Kemp 1989; Rudnicka et al 1993). Sensitivity losses can be enhanced, spatial characteristics of the visual field can be more easily identified, and repeatability between consecutive fields improved (Crabb et al 1994) with the application of image-processing filters.

Artificial neural networks have also been developed to aid in the recognition of visual field loss (e.g. Spenceley et al 1994).

Although many different methods of statistical analysis have been used in the analysis of automated perimetric data, there is continued development of sophisticated statistical approaches providing more reliable data and as yet, no form of analysis has been accepted as a standard.

CHAPTER 4

Methodological Issues in Menstrual Cycle Research

4.1 Introduction

Menstrual cycle research has recently been described as 'a methodological minefield with trip-wires set to ensnare the unwary researcher' (Ussher 1991 p.132). In any review of different menstrual cycle studies, it soon becomes apparent that methodologies differ considerably. This serves to confound attempts to draw conclusions from different studies and may contribute to the mass of conflicting results in this field. Several issues must be considered in the choice of methodology.

4.2 Subject selection

Random population sampling is rarely achieved in human research (Doty and Silverthorne 1975), and that involving the menstrual cycle is no exception. Selection criteria used in menstrual cycle research often limit subjects to those who have severe paramenstrual symptoms or to those with no problems (Sanders et al 1983), and with regular, 'normal' 28 day menstrual cycles. This adds bias to the subject group used, and causes difficulties in extrapolating results to the general population. Subsequent analysis and comparison of different studies becomes a source of confusion when different populations of subjects have been examined.

Many studies have used very narrow samples of the population, often young, nulliparous (women who have had no children) students based at universities, or groups of nurses. A wider age range with different menstrual experiences, and in different occupations would help to reduce this bias.

It has been shown that women who volunteer to take part in research projects are more likely to be in the ovulatory phase than in any other phase of their cycle (Doty and Silverthorne 1975). It can be argued that in a long-term prospective study this is of little relevance as all women are followed through at least one full cycle. However, women who do volunteer to take part in menstrual cycle related research projects may have a different attitude or experience of the menstrual cycle, or may in some way be inherently different from non-volunteers. For example, those women who experience severe paramenstrual symptoms, or those women who menstruate more regularly than the

average (Presser 1974), may be more likely to volunteer to take part in menstrual cycle research than symptom-free women. The symptomatic women taking part may show a behavioural or somatic change, but this finding cannot be extended to women in general as their experiences of the menstrual cycle are so different, and non-symptomatic women may show different patterns of response.

4.3 Study design

Studies comparing performance in different phases of the menstrual cycle have generally used one of two different study designs; between-subjects (comparing groups of women in different menstrual cycle phases) and within-subjects (repeated measures) design. When using between-subjects design (e.g. Dalton 1968; Cormack and Sheldrake 1974; Asso and Braier 1982), particularly with small sample sizes, individual differences may significantly influence the results (Sommer 1983). A within-subjects design allows a woman to act as her own control, and order effects can be controlled by women starting the study at different phases of the cycle (Sommer 1991).

There are several advantages to a longitudinal approach, with repeated measures across one or more cycles, and it has been advocated by a number of authors (e.g. Gannon 1981; Parlee 1983; Rubinow and Roy-Byrne 1984; Strauss and Appelt 1983). The cycle is taken as a whole, and as such, measurements taken in other phases can provide a baseline against which measures in the premenstrual and menstrual phases can be compared. Less emphasis is placed on specific phases of the menstrual cycle, and fluctuations at other phases in the cycle may also be identified e.g. ovulatory phase. If measurements are taken over more than one cycle, repeatability of any fluctuations found can be investigated. Disadvantages of this method lie in both the practicalities of data collection and the subsequent analysis of the results. Logistically it is time-consuming and requires greater subject compliance than one or two measurements. The analysis of longitudinal measurements is complicated by the serial dependency inherent in the data.

Whilst acknowledging the drawbacks, a within-subjects longitudinal study design appears to be most suited to investigations of changes across the menstrual cycle and as such is used throughout this thesis.

4.4 Identification of menstrual cycle phase

In menstrual cycle research the identification of different phases of the cycle is of importance if any sensory fluctuations found are to be correlated with cycle phase or alterations in hormone levels.

Serial measurements of hormones, basal body temperature and cervical mucorrhoea throughout the menstrual cycle allow the prediction and detection of ovulation (Royston 1991). In about 2% of all cycles in normally menstruating young healthy females, ovulation does not take place (Goldzieher et al 1947; Marshall 1963). These anovulatory cycles need to be identified and excluded from the subsequent analysis as they may confound research data investigating normal ovulatory cycles.

4.4.1 Blood hormone levels

Direct measurement of blood hormone levels will provide absolute values, but are not ideal. There are logistical problems, with difficulties locating facilities for blood letting and analysis, together with high costs involved. Many of the hormonal events occurring throughout the cycle are very short in duration (Udry and Morris 1977), and as such measurements need to be taken regularly. Daily measurements at the same time of day are required, adding difficulties in study design, and adversely affecting subject compliance, volunteering rates and ethical approval.

Even if these problems can be overcome, from a physiological aspect, a single daily measurement of hormone levels in blood plasma may not be representative, due to the pulsatile manner in which the hormones are released (Rojansky et al 1990). The variability in assay methods used is an additional practical problem (Rubinow and Roy-Byrne 1984) when attempting to compare results from different studies. Furthermore, separate menstrual cycles from one individual, and from different women, may show a large degree of diversification and variation in hormonal patterns (Dyrenfurth et al 1974).

Behaviour changes across the menstrual cycle are often assumed to be related to changes in hormone levels in the central nervous system (CNS), yet the hormone concentrations are measured in the blood plasma, and the activities of the substances may differ between the CNS and the periphery (Ruble and Brooks-Gunn 1979). This means that the hormone levels in blood or urine measured using radioimmunoassay techniques may not be used to directly correlate with behavioural changes, and causal relationships cannot be assumed. Urinary hormone levels may provide a somewhat more accessible method of directly monitoring hormone levels (Rojansky et al 1990), although again, concentrations measured in the urine may not reflect those in specific areas of the brain.

4.4.2 Basal body temperature and cervical mucous changes

Basal body temperature (BBT) is the body temperature upon waking. It changes across a normal ovulatory cycle, having a biphasic pattern, with an increase in BBT, due to the hyperthermic properties of progesterone (Marshall 1963), occurring around ovulation and continuing until the beginning of the menstrual flow. This increase is of the order 0.2^0-0.5^0C (Royston 1991), and may take place as a slow or sharp rise. While BBT is not accurate in detecting the precise day of ovulation (Fluhmann 1957), it is a simple and fairly reliable way of assessing retrospectively if a particular cycle was ovulatory. However, it has been suggested that only 25% of all women show a clear-cut midcycle rise in BBT (Oster 1972).

Changes in cervical mucorrhoea across the menstrual cycle can also provide information as to the cycle phase. Around ovulation the mucous becomes thinner in consistency and clear. However, this method is problematic as many women find it difficult to accurately assess changes in their cervical mucorrhoea across the cycle. It is also totally subjective, and as such cannot be relied upon as an accurate method of detecting ovulation under research conditions.

4.4.3 Menstrual diaries

The approximate day of ovulation can be estimated by counting backwards from the onset of the menstrual flow, a convenient marker in the cycle. For individuals or small samples the use of this method as an indicator of the underlying hormonal status is unreliable (Sommer 1991) as the length of the menstrual cycle varies considerably (see section 4.5).

It has been suggested that the length of the postovulatory/luteal phase is fairly constant and independent of total cycle length, lasting 14 ± 6 days (Franz 1988) thus the time of ovulation can be estimated. Counting backwards from menstruation as a method of determining phase of cycle is therefore frequently used in research.

4.5 Menstrual cycle length

The length of a 'normal' human menstrual cycle is considered to be 28 ± 4 days (Franz 1988), with the majority of ovulatory cycles having a length of around 23-36 days (Goldzieher et al 1947; Matsumoto et al 1962). However, there is a wide variation in the length of ovulatory menstrual cycles, and individual cycle lengths vary considerably both

within an individual, and between different women (Arey 1939; Fluhmann 1957; Treloar et al 1967). External factors are also known to influence menstrual cycle length, including psychological stress e.g. anxiety associated with exams or travel (Matsumoto et al 1968), social aspects e.g. menstrual synchrony among women living together (McClintock 1971), metabolic state and physical activity (Harlow and Matanoski 1991).

4.6 Cycle phase designation

There are many ways in which the menstrual cycle has been divided into different phases for data analysis. This can cause problems in the comparison of data and results from different studies. Some authors isolate only the area they are interested in e.g. the premenstrual phase, often taking just two measurements, one in the premenstrual phase by counting back from the expected onset of menstruation, and one postmenstrually (e.g. Altmeus et al 1989) and ignoring the rest of the cycle.

Attempts have been made to standardise phase designation in menstrual cycle research, but no standard has been achieved, with advantages and disadvantages to all designations used due to the individuality of every menstrual cycle.

In an effort to include all major hormonal/physiological events in phases of the cycle, Rossi and Rossi (1977) designed phase groupings that specifically included separate follicular and luteal phases. This method has also been used by other authors (Schilling 1981; McFarlane et al 1988; Gómez-Amor et al 1990a and b). The cycle is divided into the following phases:

menstrual - days 1-4
follicular - days 5-11
ovulatory - days 12-17
luteal - days 18-23
premenstrual - days 24-28

This method of dividing the menstrual cycle depends on 28 day cycles. To facilitate the comparison of data from different women, and that from individual cycles in the same woman, Kendall (1986) suggested a method of adjusting all cycles to a standard 28 days. The actual day of the cycle is multiplied by 28 and then divided by the total number of days in that cycle to give a standardised day. This approach is acceptable for cycles longer than 20-21 days, with those shorter than 20-21 days likely to be anovulatory. Other workers (Dye 1989; Dye and Hindmarsh 1991) have also used this method of cycle standardisation and it is applied in this study.

4.7 Self-reporting of menstrual symptomatology

4.7.1 Retrospective and prospective self-reports

Early work suggests some discrepancy between recalled data and information obtained daily throughout the menstrual cycle (McCance et al 1937; Altmann et al 1941). Retrospective self-reporting of menstrual symptomatology tends to give higher ratings than daily (prospective) reports (Englander-Golden et al 1978, 1986; McFarlane et al 1988; McFarland et al 1989; Ainscough 1990; Boyle and Grant 1992). This is thought to be due to the strong stereotypical beliefs that surround menstruation, with women tending to report changes in mood and behaviour born from their general beliefs about womens' experience of menstruation, rather than those that they are actually experiencing (Parlee 1974). This suggests that prospective reporting is a more accurate way of assessing symptomatology. However, women recording prospectively may still be open to stereotypical beliefs that could influence their recordings, and the possibility that some subjects will record symptoms because they feel they 'ought' to occur can not be avoided (Sampson and Prescott 1981). If they are aware of the current phase of their cycle, and menstrual cycle related studies serve to make this more likely, negative symptoms may be associated with that menstrual cycle phase, and their severity recorded as greater from stereotypical belief.

4.7.2 Study awareness

Self-report biases which may be due to cultural stereotypes are more likely to occur when women are aware that the study is concerned with menstrual-related changes (Ruble et al 1980). This is supported by evidence of an increase in negative symptomatology in the paramenstruum in subjects who are aware of the study focus (Parlee 1974; Englander-Golden et al 1978, 1986; Vila and Beech 1980; AuBuchon and Calhoun 1985). Markum (1976) suggested that whilst subjects who are unaware of the study focus record symptoms more accurately, aware subjects are not necessarily reporting stereotypical changes, but tending to record their own average menstrual cycle experience. More recent work (Gallant et al 1991) has failed to find any significant difference in cyclical variation of physical, behavioural and mood symptoms between aware and unaware women in the premenstrual and menstrual phases. The authors suggest that the difference in their findings compared with that of previous work may be due to their subject group of older, primarily non-students in whom anovulatory cycles were excluded. However, they acknowledge that it is impossible to compare results with previous studies directly due to the differences in study designs, measures of moods and symptoms, and methods of analysis used.

4.7.3 Attribution

It has been suggested that this discrepancy between aware and unaware women in symptom reporting throughout the menstrual cycle may be explained by a tendency for women to attribute negative symptoms occurring premenstrually to the menstrual cycle, while positive symptoms and negative symptoms experienced at other phases in the cycle are attributed to external causes (Ruble and Brooks-Gunn 1979; Bains and Slade 1988). Evidence to support this hypothesis has been provided by Koeske and Koeske (1975) who found that male and female students were more likely to attribute the negative moods of a hypothetical female student to the premenstruum, even when the environment was described as unpleasant. More recent work (Bains and Slade 1988) with an improved methodology also supports this hypothesis, with women attributing negative emotions occurring premenstrually to health factors, while those occurring intermenstrually were attributed to work and personality. This apparent attribution of negative changes to the approach of the menstrual cycle further complicates the interpretation of self-reported symptomatology.

4.8 Data analysis

As the method of cycle phase designation is variable across much of the menstrual cycle research to date, analysing data for each day of the cycle independently is a useful alternative. The menstrual cycle is an ongoing physiological function and fluctuations in hormonal levels between days can be large. By grouping particular days of the cycle into phases, information may be lost and conclusions drawn from phases may be incorrect.

4.9 Summary

There are many methodological problems that need to be addressed in menstrual cycle research, and there is no one standard methodology that is suitable for all menstrual cycle research. The studies in this thesis use a within-subjects design, the focus of the main study being disguised.

CHAPTER 5

The Influence of Learning on the Peripheral Visual Field

5.1 Introduction

The presence of a learning effect on automated perimetry within the central 30^{o} field is well established (see section 3.2.7), and has been found to be greater with increasing eccentricity (Wood et al 1987a; Heijl et al 1989a; Wild et al 1989b). There has been little investigation beyond 30^{o} of the field. It has been suggested that the peripheral field is a relatively unpractised sensory area (Low 1946), and as such might be expected to exhibit a higher degree of learning, maintained over several sessions. Wood et al (1987a) investigated learning effects over eight sessions with the Octopus program 21 which measured threshold sensitivity at 76 points across the full field with a stimulus separation of 15^{o}. Eight of the 10 normal subjects demonstrated some degree of learning, which was greatest at eccentricities of 30-60^{o}, and in the superior field.

5.2 Purpose of the study

The purpose of this study is to establish the optimum protocol for subsequent studies into the effects of the menstrual cycle on the visual field, where serial measurements of the both the central and peripheral visual fields are to be undertaken. It is important for any effects of learning to be accounted for as their presence may confound the interpretation of the data. Published literature on learning in the peripheral field is sparse, and none relates to the Humphrey Field Analyser.

5.3 Materials and methods

5.3.1 Subjects

A group of 12 clinically normal young male subjects of mean age 20.4 years (range 18-23yrs, SD 1.9 years) was selected. Of these, eight were emmetropic and four were low myopes with equivalent spherical error not greater than 3.00DS. All had corrected visual acuities of 6/6 or better. The subjects had no prior experience of automated perimetry and were naive to the purpose of the study.

5.3.2 Method

Full-threshold static perimetry was performed using program 30/60-2 of the HFA 630. This program measures the increment threshold at 68 locations between 30^{o} and 60^{o} eccentricity, with an inter-stimulus separation of 12^{o}. The visual field was investigated at the same time of day for each subject, on five occasions not less than five, and not more than 14 days apart.

5.4 Analysis

5.4.1 Statistical model

The threshold Y_{ijk} at any location in the visual field may be expressed as

$$Y_{ijk} = m_{ijk} + \in_{ijk}$$

where m_{ijk} represents the actual physiological component of threshold, and $\in_{ijk}$ is an error term. The symbol i defines the position of the location in the field, j defines the session and k the number of replications or measurements at a given location during a specific session.

It is assumed that Y_{ijk} has an independent normal distribution with mean given by

$$m_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij}$$

and constant variance σ^2. It also follows that the error term $\in_{ijk}$ has an independent normal distribution with a mean of zero and variance σ^2.

This model has an additive two factor structure involving location and session with an interaction term, and has been used by a number of authors including Hirsch (1985) and Flammer et al (1983).

The validity of such a normal or Gaussian distribution to accurately represent the visual fields has been challenged by Heijl et al (1987d) who found that inter-test point-wise variation did not follow a normal distribution using the 30-2 programme of the HFA. The Gaussian distribution became less valid as the distance from fixation increased. The model used in this study was tested by the standard procedure of an examination of residual plots using the GLIM statistical package. The model was also used to test for interactions between location and session.

5.4.2 Analysis based on mean sensitivity

Values of mean sensitivity (MS), and change in mean sensitivity from session one (MC), were computed for the full field tested, for hemifields, for inner, middle and outer annuli and for quadrants (figure 5.1). Analysis of variance (anova) with was used to compare means.

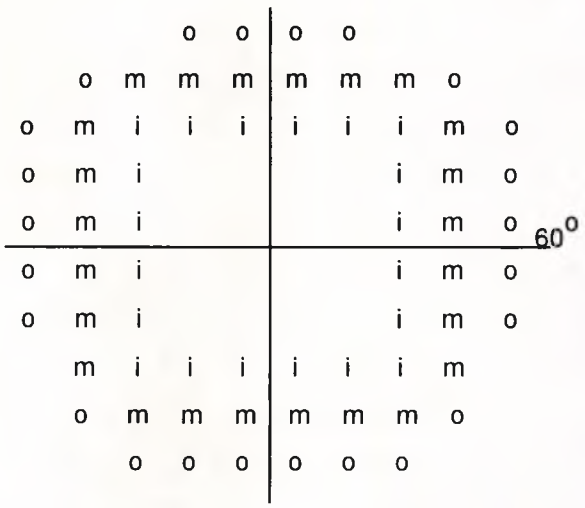


Figure 5.1 Stimulus locations used for annuli, where i, m and o represent locations situated in the inner, middle and outer annuli respectively.

5.5 Results

5.5.1 Statistical model

Residual plots were examined for all subjects. The departures from a classic residual distribution were found to be concentrated in locations at the extremes of the nasal field both superiorly and inferiorly. Excluding those locations missed or seen only at maximum threshold leads to a marked improvement in the residual plots. This supports the view that the Gaussian model tends to break down in the periphery of the field (Heijl et al 1987d). The validity of the model was accepted whilst acknowledging its weaknesses.

The model was used to test each subject for interactions between location and session. Two configurations were tested, with the field divided into either quadrants or three annuli. A significant interaction term could indicate for example, that some sectors of

the field have stable thresholds over five sessions whilst others have thresholds which increase or decrease with session. There was no significant interaction effect for any subject for either configuration ($p>0.05$). Hence learning effects do not appear to be greater in any one region of the field.

5.5.2 Individual variations of mean sensitivity with session

The variations in mean sensitivity from the first session (MC) were calculated and plotted for each subject. It has been assumed that an increase in mean sensitivity is indicative of a learning effect.

5.5.2 (i) Full peripheral field

By inspection subjects were initially divided into those who showed learning effects and those who failed to learn. A further subdivision of the learning group was possible leading to the following classification:

- **Group 1 (figure 5.2a,b)**
  - **Type 1**

    Exhibit a sustained learning effect over at least the first three sessions (four subjects)
  - **Type 2**

    Demonstrate a learning effect delayed until after the second session (two subjects)

- **Group 2 (figure 5.3a,b)** Show no learning effect (six subjects)

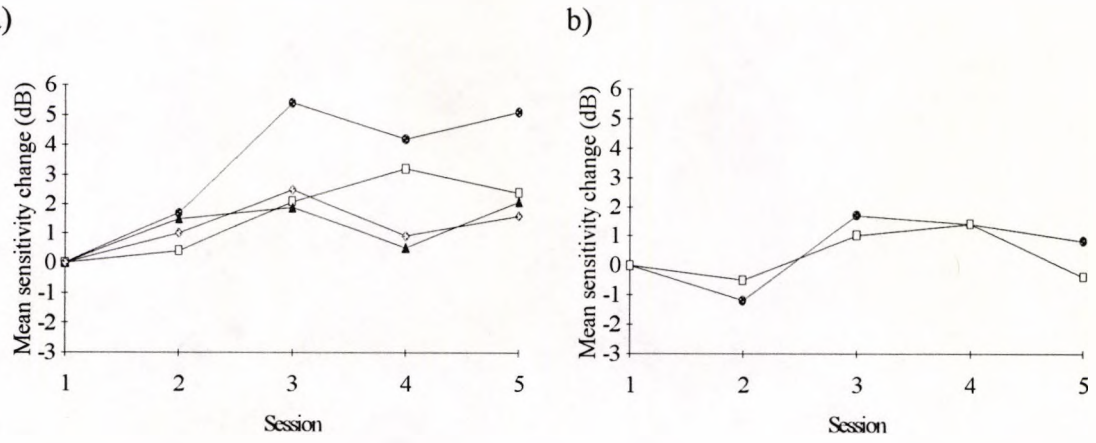


Figure 5.2 Change in mean sensitivity from session one for Group 1 a) Type 1 and b) Type 2 subjects.

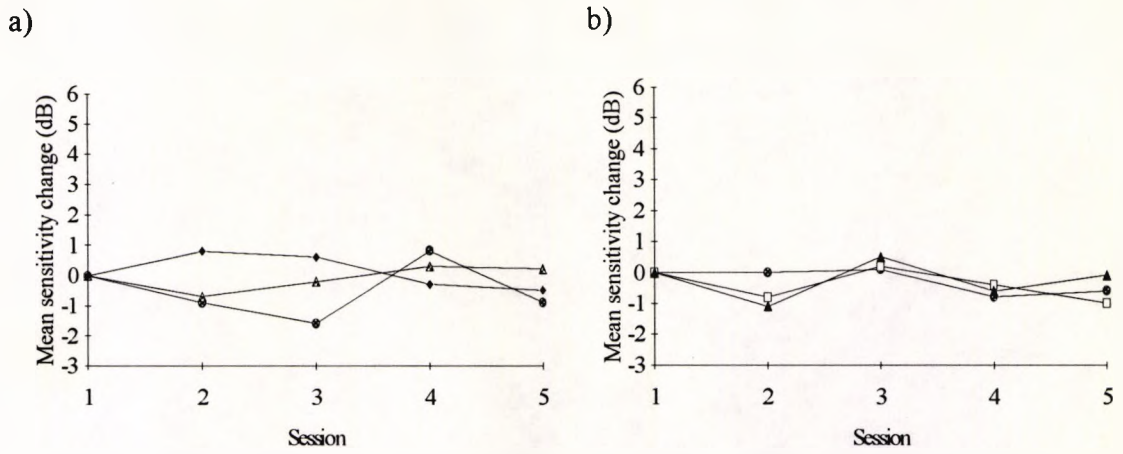


Figure 5.3 a) & b) Change in mean sensitivity from session one for Group 2 subjects.

Means and standard error of the mean for MS for all subjects and for each group were calculated and plotted against session (figure 5.4).

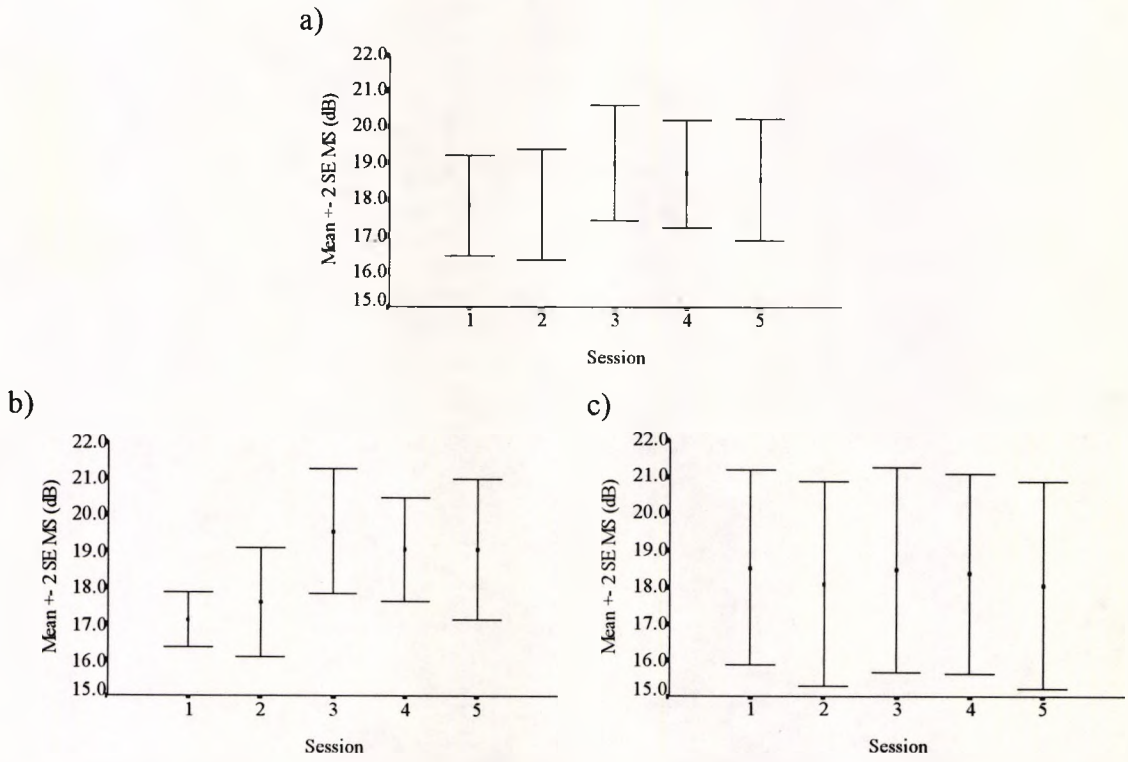


Figure 5.4 Mean sensitivity (±2 standard errors) plotted against session for a) all subjects, b) Group 1 and c) Group 2 subjects.

MS is assumed to be normally distributed around some underlying value for performance of the subject at each session. A simple analysis of variance (anova) approach is therefore appropriate. From the inspection of figure 5.4a) and 5.4b) it appears that learning takes place during the first two sessions and is complete by the third session, such that mean sensitivity is relatively stable over sessions 3, 4 and 5. Of particular interest is whether MS is significantly different in sessions 1 and 2 compared to that in

subsequent sessions. An additive sequence of models was fitted to all subjects' data. Subject effects were invariably fitted first and other effects were then added to the model. The results of the fitting were examined using standard anova techniques. The sequence of models was as follows:

- Mean sensitivity and variation between subjects
- Mean sensitivity and variation between subjects and between first, second and subsequent sessions taken together (3+4+5)
- Mean sensitivity and variation between subjects and between each session

In addition the same sequence was used but with the addition of a factor indicating whether the subject showed signs of learning.

Significant differences in MS were found both between subjects ($F(11,48)=28.76$, $p<0.001$) and between sessions 1, 2 and subsequent sessions taken together ($F(2,46)=6.90$, $p<0.002$). In both cases (with or without division into learners and non-learners) variation in MS between sessions 3, 4 and 5 was not significant ($p>0.4$).

5.5.2 (ii) Hemifields

Percentage change in sensitivity from sessions one to five for hemifields was calculated (table 5.1) and plotted for each subject group (figure 5.5).

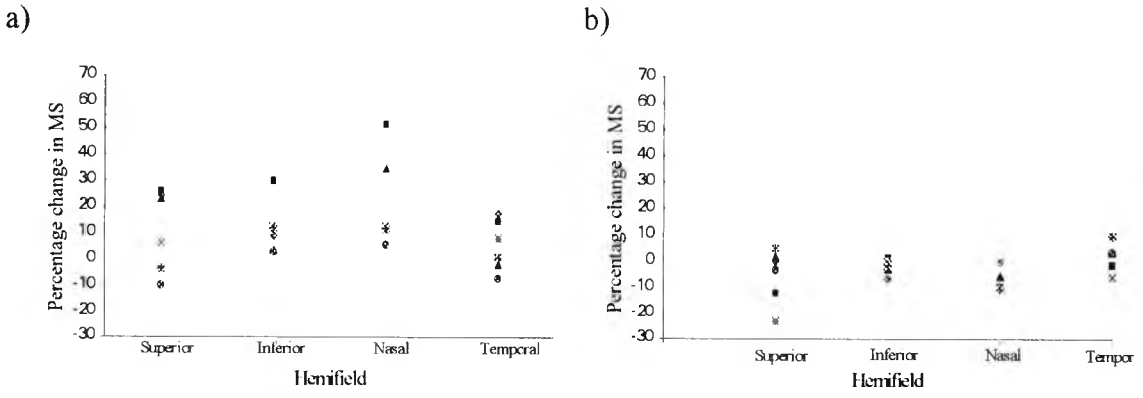


Figure 5.5 Percentage change in mean sensitivity between sessions one and five for hemifields in a) Group 1 and b) Group 2, where each subject is represented by a different symbol.

Group 1 showed greater learning in the nasal than in the temporal hemifield, but no obvious differences between superior and inferior hemifield. Group 2 subjects showed

little difference between either the inferior and superior, or nasal and temporal hemifields. In both subject groups the inter-subject variability is greater in the superior compared with the inferior hemifield.

5.5.2 (iii) Annuli

Percentage change in mean sensitivity from sessions one to five with eccentricity was calculated (table 5.1) and plotted for both subject groups (figure 5.6).

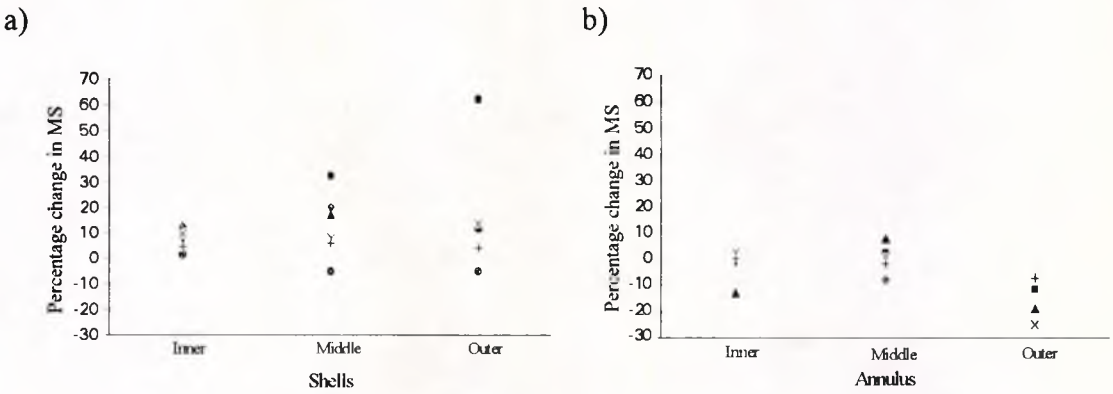


Figure 5.6 Percentage change in mean sensitivity between sessions one and five with eccentricity in a) Group 1 and b) Group 2 subjects, where each subject is represented by a different symbol.

In the inner annulus all group one subjects showed either a small learning effect or remained effectively unchanged. Results are considerably less stable in the middle and outer annuli. There is little evidence to suggest increased learning with increasing eccentricity, despite the spectacular performance of subject 1. Amongst group two subjects there was a consistent decrease in mean sensitivity in the outer annulus between the first and last session.

Table 5.1 Percentage change in mean sensitivity for all configurations between sessions 1 and 5.

		Change in mean sensitivity (%)										
		Hemifield				*Annuli*			*Quadrant*			
Subject		Superior	Inferior	Nasal	Temporal	Inner	Middle	Outer	Lower temporal	Lower nasal	Upper temporal	Upper nasal
Group 1												
	Type 1											
	1	26	29.8	51.3	14.5	9.1	32.4	62	13.3	55.9	15.5	44.9
	2	24.2	8.9	11.8	17.4	12.2	20	11.4	9.5	8.3	29.9	15.2
	3	23	3.7	34.6	-1.8	6.1	16.9	12.2	-7.7	21.3	6	59
	4	6.4	12.2	12.5	7.9	9.5	7.8	13.5	5.8	26.9	10.6	0
	Type 2											
	5	-9.9	2.9	5.4	-7.2	1.4	-5.3	-5.3	0.8	6.1	-18.9	4.2
	6	-3.7	11.9	11.6	0.8	4.3	6.1	4.1	6.1	21.2	-5.9	0
Group 2												
	7	-12	1.3	-9.6	-1.5	-0.9	-7.9	-6.3	1.6	1.2	-4.8	-22.1
	8	-0.2	-6.7	0	-5.7	2.8	1	-25	-6.8	-7	-4.2	7.1
	9	1.8	-2.7	-5.5	3.6	1.1	2.7	-11.6	2.6	-9.7	5	-1
	10	-23.2	-0.3	-9.5	-6	-12.8	8.1	-18.9	4.6	-9.1	-24.5	-12.5
	11	-3.4	-1.3	-10	3.3	0.2	-1.8	-7.2	3.3	-7.1	3.5	-14.6
	12	4.8	-1.5	-10.5	9.5	4	-0.2	-1.3	6.6	-12.8	13.6	-8.2

5.5.2 (iv) Quadrants

Percentage change in mean sensitivity between sessions one and five for quadrants were calculated (table 5.1) and plotted for both subject groups (figure 5.7).

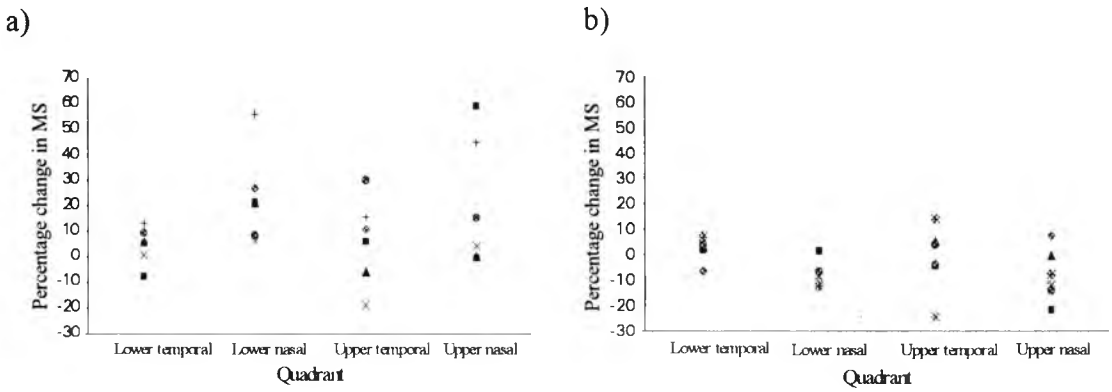


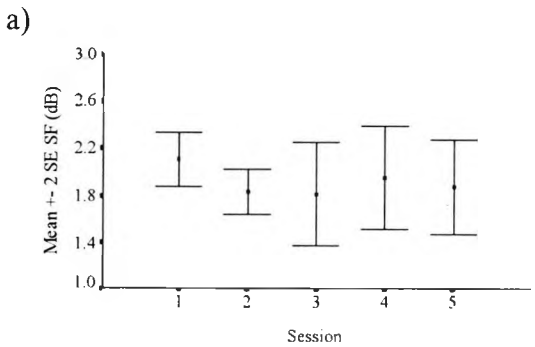
Figure 5.7 Percentage change in mean sensitivity between sessions one and five for quadrants in a) Group 1 and b) Group 2 subjects, where each subject is represented by a different symbol.

There were no obvious differences between either the lower and upper nasal quadrants, or the lower and upper temporal quadrants for either group. The lower temporal quadrant showed the least inter-subject variability.

The learning peak was attained at session three. The above observations apply equally to a comparison between sessions one and three.

5.5.3 Short-term fluctuation

It has been assumed that a reduction in short-term fluctuation (SF) with session is indicative of a learning effect. Mean SF against session for all subjects and for each group were plotted (figure 5.8).



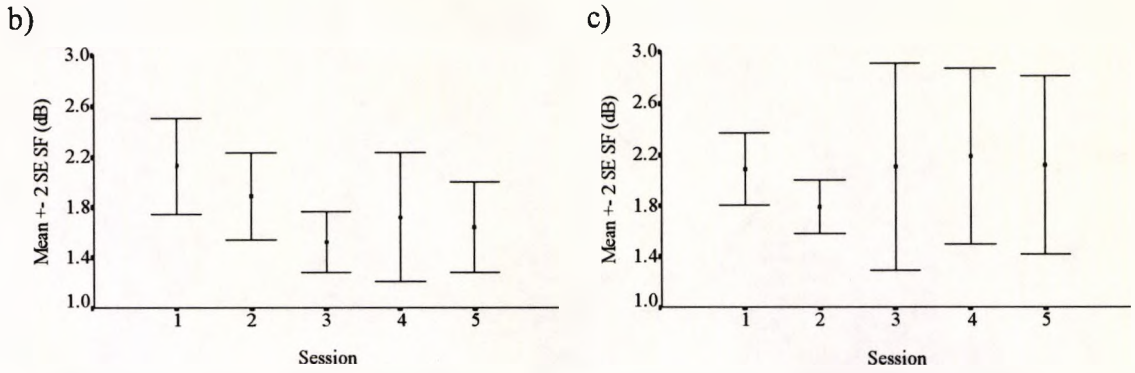


Figure 5.8 Mean short-term fluctuation (±2 standard errors) plotted against session for a) all subjects, b) Group 1 and c) Group 2 subjects.

Anova models as for MS (section 5.5.1) were fitted to all subjects' data. Significant differences were found between subjects ($F(11,48)=2.71$, $p=0.008$). All other comparisons failed to reach significance at the 5% level, for either all subjects, or for the learners alone.

5.5.4 Variability of threshold with location

The coefficient of variation, the standard deviation of mean sensitivity expressed as a percentage of the mean for a particular field region, was calculated for each quadrant and annulus for each subject. Mean values for all subjects are shown in table 5.2.

Table 5.2 Means and SD of coefficient of variation for quadrants and annuli.

	Coefficient of variation						
	LT	LN	UT	UN	Inner	Middle	Outer
Mean	2.8	8.6	8.8	11.4	3.5	6.4	9.1
SD	1.2	4.0	5.3	6.1	1.8	3.9	4.2

The variation of threshold is not a constant across the field, a finding in accord with Heijl et al (1987d). Greater variability occurred in the both the superior compared with the inferior field, with the greatest variability in the upper nasal quadrant and the least in the lower temporal quadrant, and with increasing eccentricity.

5.5 Reliability parameters

Subject reliability may also be affected by experience. False positive errors, false negative errors and fixation losses were plotted against session but no trends emerged for

either group. The number of questions asked, or stimulus presentations for each test, was plotted against session for each group (figure 5.9).

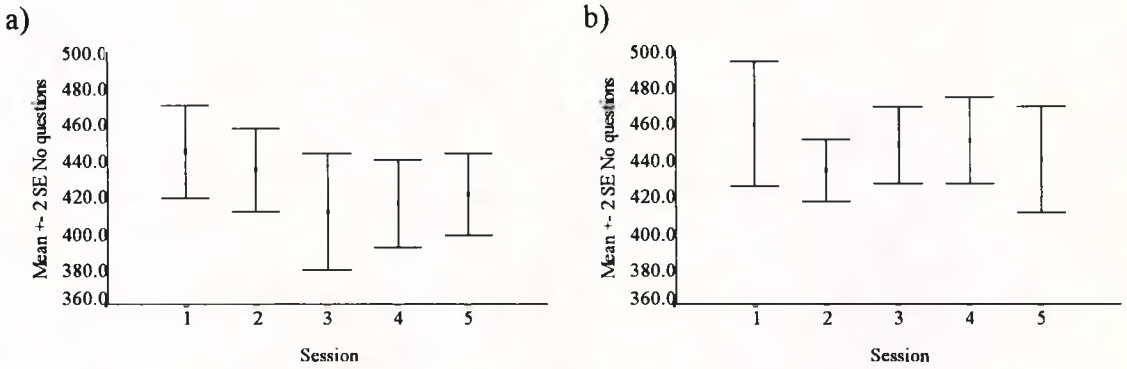


Figure 5.9 Mean number of questions asked against session for a) Group 1 and b) Group 2 subjects.

There was a trend for a decrease in the number of questions over the first two sessions in Group 1 subjects and the first session in Group 2 subjects. However, this trend was not significant, with a two-way anova procedure, with subjects and session as main factors, failing to identify any significant differences between the number of questions asked and session ($p>0.05$).

5.6 Discussion

There is considerable inter-individual variation in perimetric learning in the peripheral field. Half of the subjects showed some degree of learning effect, manifested as an increase in mean sensitivity with session, whilst the remainder revealed no tendency to learn. At session one the average mean sensitivity for Group 1 was 17.12 dB (SD 0.92) whilst for Group 2 it was 18.53 dB (SD 3.27). This supports the possible explanation reported elsewhere (Wood et al 1987a; Heijl et al 1989a) that non-learners are already operating at or close to their peak performance from session one whilst learners reach their peak over time.

Although there was a trend for SF to decrease over the first two sessions in the subjects who demonstrated a learning effect in MS, this was not significant. This fails to support previous evidence of a learning effect on SF (e.g. Wood et al 1987a; Heijl et al 1989a; Autzen and Work 1990).

The relatively large proportion of subjects who did not appear to demonstrate significant learning effects in MS and SF may be due in part to the subject sample used. All subjects were young and may have already had experience in responding to psychophysical

testing, for example in computer games. Also all subjects had undergone at least one manual perimetric examination, and it has been suggested that subjects experienced in manual perimetry may show less learning effects in automated perimetry (Katz and Sommer 1987; Werner et al 1988b).

There were no obvious differences in learning between the superior and inferior hemifield. Nor was there any convincing evidence to suggest increased learning with eccentricity. The interaction term also failed to reach significance for any subject for either quadrants or annuli, supporting the lack of evidence for regional differences in learning.

These findings conflict with those of Wood and co-workers (1987a) who found an increase in learning with increasing eccentricity over the whole field with the Octopus automated perimeter. However, it has been noted that in the HFA the extreme peripheral locations within the central and peripheral field are measured towards the end of the respective examinations (Wild et al 1991a). As such, these locations are likely to be more susceptible to fatigue effects. Indeed, intra-test fatigue effects (Searle et al 1991a,b) increasing with increasing eccentricity (Hudson et al 1993) have been reported. Fatigue effects may be therefore be influencing the data and masking any regional differences in learning effects.

The only finding that may be consistent with previous reports of increasing learning with eccentricity is that amongst Group 1 subjects learning effects were greater in the nasal than in the temporal hemifield. The distribution of stimuli is symmetrical within each quadrant of the HFA 30/60-2 program (figure 5.1). As a result a greater proportion of the locations lie closer to the limits of the nasal field than the temporal. Thus the increased learning in the nasal hemifield may be consistent with the concept of the periphery as an unpractised area (Low 1946). However, there was nothing to suggest a similar phenomenon amongst non-learners, and overall there was little evidence for learning to be affected by test point location.

A reduction in the number of questions asked may reflect an improvement in a subject's appreciation of the differential light threshold, or an increasing confidence in their abilities to judge the threshold. Although there was a trend for the number of questions asked to decrease with session, this was not found to be significant at the 5% level. Thus this study fails to demonstrate any link between learning and the ease with which subjects determined threshold.

Between-subject variability was found to be greater in the superior field in all subjects in accordance with other studies (Brenton and Phelps 1986; Crosswell et al 1991). There

was little evidence of increasing between-subject variability with increasing eccentricity, contrary to other studies (Brenton and Phelps 1986; Wild et al 1986; Heijl 1987; Heijl et al 1987d). However, previous work has examined the central 30^{o} field and variability may stabilise at eccentricities beyond this. In accordance with previous work, within-subject inter-test variability (as shown by the coefficient of variation) was greater in the superior field, particularly in the upper nasal quadrant, (Katz and Sommer 1987; Boeglin et al 1992) and increased with increasing eccentricity (Heijl 1977b; Heijl et al 1987a,d, 1989b; Parrish et al 1984; Lewis et al 1986; Wall et al 1993).

5.7 Conclusions

The presence of a learning effect in the automated perimetric assessment of the peripheral field has been identified in a proportion of normal subjects. This effect is manifested as an increase in mean sensitivity and appears to be independent of field region or eccentricity. Variability both between and within-subjects was greater in the superior field.

For many subjects learning is a major factor in the automated perimetric assessment of the peripheral field and allowance must be made when recording serial fields. Discarding results from the first two sessions appears to be sufficient to eliminate the influence of a learning effect in subsequent tests in most normal individuals. This strategy was adopted for all further studies in this thesis.

CHAPTER 6

The Effect of the Menstrual Cycle on Automated Perimetry: A Pilot Study

6.1 Introduction

Lanfair and Smith (1974) have proposed a link between the increase in the rate of accidents in the premenstrual phase of the menstrual cycle and changes in the visual field across the menstrual cycle. Early work has reported constriction in the peripheral visual field in the premenstrual and menstrual phases using kinetic perimetry (Finkelstein 1887; Lanfair and Smith 1974). With the advent of automated static perimetry, more accurate and reproducible data can now be accessed and analysed. Automated perimetric assessment has become the method of choice in the detection and follow-up of visual fields in many pathological conditions. Any menstrual cycle related fluctuation in the results will influence the data and would need to be taken into consideration in visual field interpretation.

6.2 Aims

This study was undertaken to investigate the effects of the menstrual cycle on the visual field as assessed by automated perimetry. Fluctuations in self-reported symptomatology across the menstrual cycle were also investigated.

6.3 Materials and methods

6.3.1 Instrumentation

Full threshold automated perimetry was carried out using the HFA 630 central 30-2 and peripheral 30/60-2 programs. The central 30-2 program measures contrast threshold at 76 locations in the 30^{o} field with an inter-stimulus separation of 6^{o}, whilst the peripheral 30/60-2 program measures threshold at 68 locations between 30^{o} and 60^{o} eccentricity with an inter-stimulus separation of 12^{o}.

The Menstrual Distress Questionnaire (MDQ), devised by Moos (1968), is the most widely used instrument in the assessment of self-report measures of symptomatology

across the menstrual cycle. There are two versions, a prospective form (T) (appendix A1.1), to record symptoms on a daily basis, and a retrospective form (C) (appendix A1.2), recording experiences from the most recent menstrual cycle. The MDQ consists of 47 symptoms, each of which are rated in severity on a five-point scale. Using factor analysis on data collected from a sample of 839 women, Moos identified eight symptom clusters, or scales, which he labelled Pain, Water Retention, Autonomic Reactions, Negative Affect, Impaired Concentration, Behaviour Change, Arousal and Control (Moos 1968) (table 6.1).

Table 6.1 Menstrual Distress Questionnaire factor scales

Pain
Muscle stiffness
Headache
Cramps
Backache
Fatigue
General aches and pains

Water Retention
Weight gain
Skin blemish/disorder
Painful or tender breasts
Swelling

Autonomic Reactions
Dizziness, faintness
Cold sweats
Nausea, vomiting
Hot flashes

Negative Affect
Loneliness
Anxiety
Mood swings
Crying
Irritability
Tension
Feeling sad or blue
Restlessness

Impaired Concentration
Insomnia
Forgetfulness
Confusion
Poor judgement
Difficulty concentrating
Distractible
Minor accidents
Poor motor co-ordination

Behaviour Change
Poor school or work performance
Take naps, stay in bed
Stay at home
Avoid social activities
Decreased efficiency

Arousal
Affectionate
Orderliness
Excitement
Feelings of well-being
Bursts of energy, activity

Control
Feelings of suffocation
Chest pains
Ringing in the ears
Heart pounding
Numbness, tingling
Blind spots, fuzzy vision

Despite its widespread use, the MDQ has been criticised on several counts. Of the 'normative' sample of 839 'wives of graduates' (Moos 1968), the majority were young,

with a mean age of 25 years (SD 3.9yrs), 420 were taking oral contraceptives, 81 were pregnant and over half had not yet had children (Parlee 1974). Comparisons drawn with Moos' data should thus be viewed cautiously (Hawes and Oei 1992). The inclusion of symptoms which have been found not to vary with the menstrual cycle has been questioned, and some difficulty in the comprehension of some of the symptom descriptions highlighted (Clare 1977; Steiner et al 1980). Hawes and Oei (1992) have questioned the internal consistency of the MDQ items and Richardson (1989) has also suggested that the identification of the symptom clusters by Moos was an 'artefact of imposing an orthogonal rotation upon the extracted factor matrix' (p. 216). In its favour, however, Markum (1976) found Form T to have high internal consistency and test-retest reliability, while Wilcoxon and co-workers (1976) found no instrument deterioration, i.e. systematic increase or decrease in symptoms over time due to loss of interest or effort, using the prospective form T. More recently, Boyle (1992) found the MDQ to have reasonable reliability and validity, and the factor structure appeared reasonably well confirmed.

Whilst acknowledging the drawbacks and criticisms of the MDQ, both forms of the questionnaire are used in this study to assess menstrual cycle symptomatology.

6.3.2 Subjects

Eleven normally menstruating healthy young women, mean age 19.7 years (range 18-22 years), volunteered to take part in a paid study into the effects of the menstrual cycle on the visual field. All were ophthalmologically normal with refractive errors between -4.00DS and +0.50DS, with less than 1.00DC, and corrected acuities of 6/6 or better. Subjects were not taking any medication, and had not taken oral contraceptives for at least six months prior to commencement of the study. All subjects underwent at least two automated central and peripheral visual field examinations prior to the start of the study to overcome learning effects.

6.3.3 Procedure

Subjects attended two to three times weekly for ten weeks. One eye was randomly selected for each subject and all subsequent measurements were made on this eye. At each session full threshold central (30-2) and peripheral fields (30/60-2) were obtained. Appropriate spectacle or contact lens corrections were worn for central field examinations, with either no correction, or contact lenses worn for the peripheral field examination. The central field was always assessed first, followed by the peripheral field after a break of at least 15 minutes. Basal body temperature was taken each morning before rising. Self-report measures of menstrual cycle symptomatology were recorded at

each session using MDQ, form T. At the end of the study the retrospective version of the MDQ, form C, was completed by all subjects.

6.3.4 Analysis

Visual fields

A value of mean sensitivity (MS) for each field was calculated by adding all the threshold values together and dividing by the total number of locations. Two locations situated in the blind spot in the central field were excluded from analysis. Of interest in the analysis is the fluctuation of MS at each session from a baseline value of MS for an individual. A value of mean change (MC) was calculated using equation 1.

$$MC = MS - \overline{MS} \qquad 1$$

where $\overline{MS}$ is the average, or baseline, mean sensitivity across the study period for a subject.

Raw scores do not take into account inter-individual variability. Standardised scores of MC (ZMC), indicating how many standard deviations above or below the mean a value falls, were calculated using equation 2.

$$ZMC = \frac{MC - \overline{MC}}{s} \qquad 2$$

where $\overline{MC}$ is the average mean change over the study period for a subject and s is the standard deviation.

When mean change and standardised scores are computed, the inter-individual variability of the data is considered and a one-way analysis of variance model is appropriate. In the analysis of raw data, two-way analysis of variance with subjects and phase, or day of cycle, as main factors is used.

MDQ

Scores for each of the eight factor scales, Pain, Water Retention, Autonomic Reactions, Negative Affect, Impaired Concentration, Behaviour Change, Arousal and Control, were computed for each questionnaire. The scale score is sum of an individual's scores on the items in that factor scale (table 6.1). The ordinal data set cannot be assumed to have a

normal distribution and thus non-parametric two-way analysis of variance (Friedman test) was used to test for differences in factor scale scores between cycle phases.

6.4 Results

Data was collected over two menstrual cycles for all subjects, giving a total of 22 cycles. Menstrual cycle length varied between 21 and 32 days (mean 26.5 SD3.6) with both inter and intra-subject variations (figure 6.1).

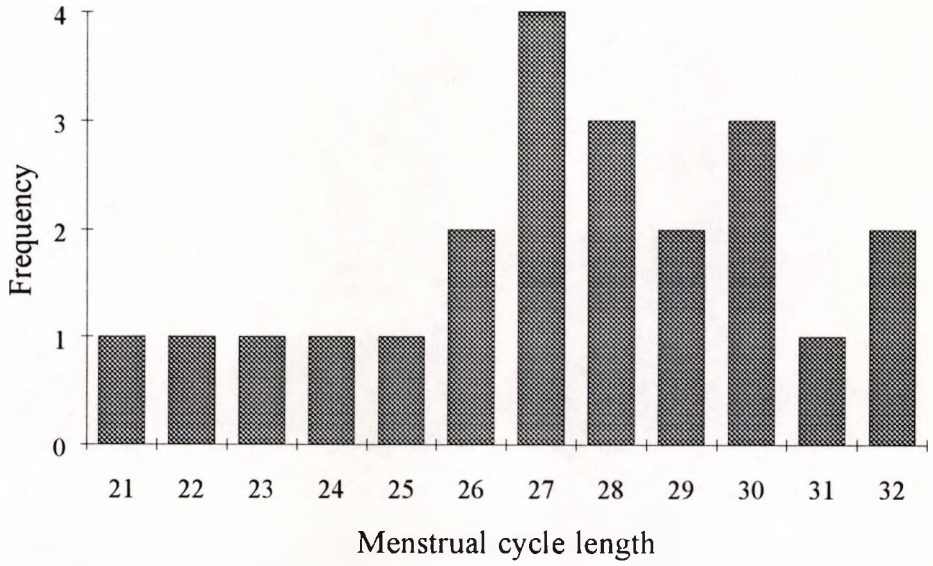


Figure 6.1 Frequency of different menstrual cycle lengths for all subjects.

Analysis of the data is complicated by the differing menstrual cycle lengths. A recognised method of standardising the length of each cycle to 28 days was applied (Kendall 1986; section 4.6). Data was analysed across days of the cycle and also grouped into five menstrual cycle phases: menstrual (days 1-4), follicular (days 5-11), ovulatory (days 12-17), luteal (days 18-23) and premenstrual (days 24-28) (Rossi and Rossi 1977). In graphical presentation of the data the phases are denoted by the numbers 1-5 respectively. Questionnaire data was also divided into the three phases designated by Moos (1985), where the menstrual phase comprises the days of menstrual flow (as self-reported on form T), the premenstrual phase is specified as the four days prior to onset of menstrual flow and the intermenstrual phase comprises the remaining days.

Basal body temperature results were very variable with only 36% (8) of all cycles showing the classic biphasic pattern associated with an ovulatory cycle (see section

4.4.2). Anovulatory cycles are relatively rare, reported to occur in only 2% of all cycles in normally menstruating young healthy females (Goldzieher et al 1947; Marshall 1963). Therefore it is unlikely that all the cycles lacking biphasic patterns in BBT in this study are anovulatory. It has been suggested that only 25% of all women show a clear-cut midcycle rise in BBT (Oster 1972), and that outside of a research unit or hospital, the monitoring of basal temperature by subjects is highly inaccurate with day-to-day variation masking the subtle changes associated with ovulation (Halbreich and Endicott 1985). Moreover, Cargille et al (1969) found mid-cycle peaks in luteinising hormone (i.e. evidence of ovulation) in six young women who were lacking in other indicators of ovulation, including BBT. The authors used this evidence to argue for the inclusion of these subjects in their analysis. The high percentage of BBT charts in this study without a biphasic pattern may indicate that the test is unreliable in this subject sample and thus all cycles were included in subsequent analysis.

6.4.1 Visual fields

6.4.1 (i) Mean sensitivity

Standardised mean change (ZMC) was plotted against day of cycle for the central (figure 6.2) and peripheral (figure 6.3) fields for all subjects. (For individual plots see appendix A2). Different symbols were used for each subject in order to identify individual subject's data. On inspection of the data, some individuals appeared to demonstrate fluctuations in ZMC across the menstrual cycle, although these were often not repeated in both cycles, and many subjects failed to show any obvious change across the cycle. Overall there was much inter-individual variation.

Correlation analysis for individual plots (table 6.2) identified a negative linear trend in the majority of subjects for ZMC across cycle 1 in both the central and peripheral fields. This trend was significant at the 5% level in four subjects for the central field and six subjects for the peripheral field. R^2 values are quite high in a number of these subjects, suggesting a good association between ZMC and day of cycle. However, this negative trend was rarely repeated in cycle 2, with the majority of subjects having a positive linear relationship between ZMC and menstrual cycle day. In general R^2 values are low suggesting that the majority of the variability in ZMC is not explained by a linear relationship between ZMC and day of menstrual cycle for most subjects. One subject (10) had a significant positive trend in cycle 1 in the peripheral field and this may be due to a continued learning effect. On closer inspection of the individuals' plots of ZMC against cycle day, it becomes apparent that ZMC in one subject (7) decreases over the whole study period in both the central and peripheral field. In several other subjects

ZMC decreases over cycle 1, stabilising at that lower level, or increasing slightly in cycle 2 in the central (subjects 5,6,9,10,11) and peripheral (5,6,8,9,11) fields.

Table 6.2 Correlation and linear regression statistics for ZMC against menstrual cycle day for all subjects individually for the central and peripheral fields.

	Central 30-2					
	Cycle 1			*Cycle 2*		
Subject	R^2	*p* value	gradient	R^2	*p* value	gradient
1	0.10	0.44	-0.03	0.61	0.07	-0.08
2	0.02	0.73	-0.02	0.27	0.19	+0.07
3	0.37	0.08	-0.08	0.26	0.13	+0.07
4	0.34	0.06	+0.08	0.12	0.34	-0.04
5	0.80	0.01 ($F_{1,5}$ 19.97)	-0.11	0.18	0.56	-0.02
6	0.11	0.42	-0.03	0.03	0.69	+0.02
7	0.36	0.15	-0.03	0.73	0.004 ($F_{1,7}$ 18.56)	-0.09
8	0.08	0.37	-0.03	0.49	0.01 ($F_{1,10}$ 9.78)	+0.08
9	0.72	0.02 ($F_{1,5}$ 13.09)	-0.12	0.51	0.07	+0.06
10	0.51	0.05 ($F_{1,6}$ 6.17)	-0.08	0.29	0.17	+0.06
11	0.61	0.01 ($F_{1,8}$ 12.4)	-0.08	0.76	0.01 ($F_{1,5}$ 15.62)	+0.11
	Peripheral 30/60-2					
	Cycle 1			*Cycle 2*		
	R^2	*p* value	gradient	R^2	*p* value	gradient
1	0.18	0.30	-0.37	0.42	0.17	+0.21
2	0.55	0.03 ($F_{1,6}$ 7.45)	-0.23	0.11	0.43	+0.22
3	0.39	0.07	-0.03	0.00	0.92	+0.002
4	0.21	0.16	+0.04	0.05	0.54	+0.02
5	0.66	0.03 ($F_{1,5}$ 9.6)	-0.10	0.07	0.66	+0.03
6	0.64	0.02 ($F_{1,6}$ 10.89)	-0.08	0.01	0.78	+0.01
7	0.79	0.007 ($F_{1,5}$ 19.12)	-0.14	0.75	0.002 ($F_{1,7}$ 21.33)	-0.2
8	0.60	0.003 ($F_{1,10}$ 15.22)	-0.12	0.53	0.008 ($F_{1,10}$ 11.11)	+0.06
9	0.08	0.55	-0.23	0.05	0.62	+0.02
10	0.86	0.001	+0.07	0.24	0.22	-0.03
11	0.72	0.002	-0.13	0.01	0.88	+0.003

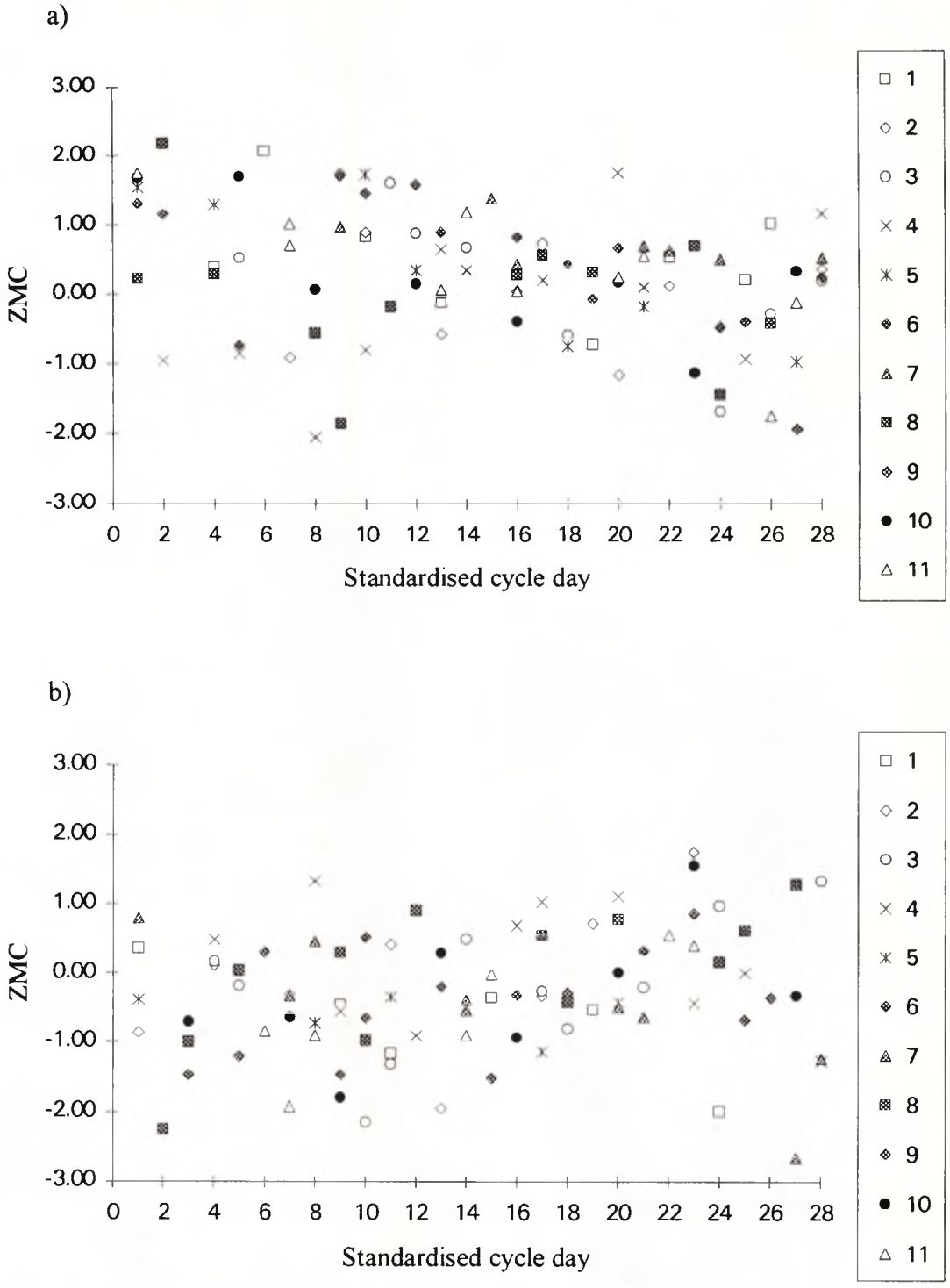


Figure 6.2 ZMC against standardised cycle day for the central field a) cycle 1 and b) cycle 2.

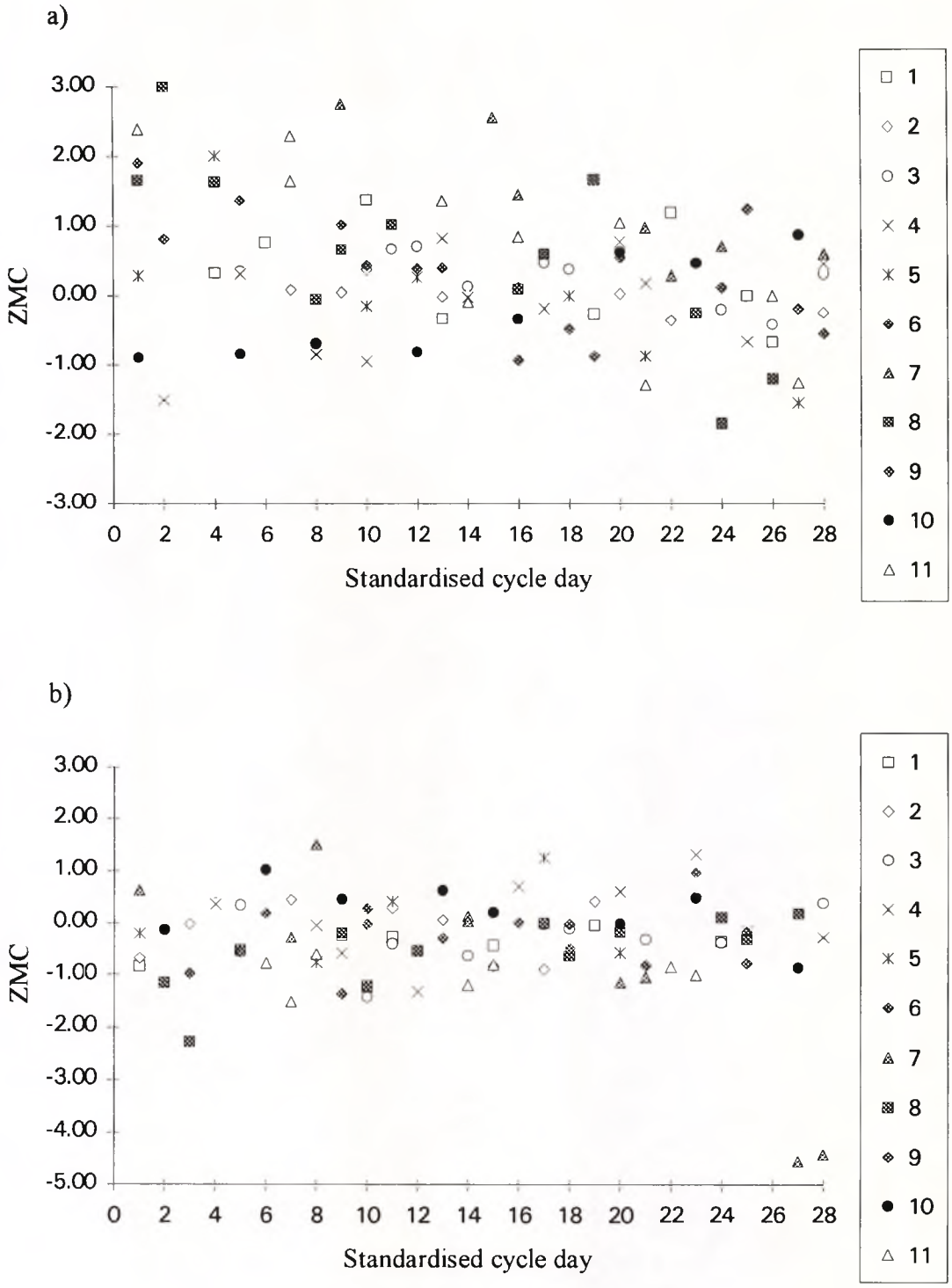


Figure 6.3 ZMC against standardised cycle day for the peripheral field a) cycle 1 and b) cycle 2.

Correlation analysis for the group data (table 6.3) identified a significant negative linear relationship between ZMC and menstrual cycle day for cycle 1 in both the central ($F(1,93)=13.35$, $p=0.0003$) and peripheral ($F(1,93)=14.35$, $p=0.0003$) fields.

Table 6.3 Correlation and linear regression statistics for ZMC against day of cycle for all subjects.

	Central 30-2			Peripheral 30/60-2		
	R^2	*p* value	gradient	R^2	*p* value	gradient
Cycle 1	0.13	0.0003	-0.04	0.13	0.0003	-0.04
Cycle 2	0.04	0.06	+0.02	0.01	0.38	-0.01
	After removal of two outliers			0.01	0.28	+0.01

However the correlation between the variables is poor, with very low R^2 values, again suggesting that the majority of the variability in ZMC is not explained by a linear relationship with menstrual cycle day. The goodness of fit of the linear model is also questionable as residual plots did not show an even distribution. No significant linear relationship was found between ZMC and menstrual cycle day for central or peripheral fields for cycle 2, the trend for the central field being positive, whilst that for the peripheral field remained negative. Again the R^2 values were very low and the residual plots showed an uneven distribution, suggesting both a poor correlation and lack of goodness of fit for a linear model. There are two outliers, or extreme values, in the peripheral field in cycle 2 (figure 6.3b), (days 27 and 28 from subject 7) which may influence the data. These data points were removed and the linear regression analysis repeated (table 6.3). The results show that the previously negative trend has now become positive, highlighting the inter-cycle differences, although this slope is not significant at the 5% level, and the R^2 value is again very low.

Data was grouped together by cycle phase, and ZMC was plotted against menstrual cycle phase for central (figure 6.4) and peripheral (figure 6.5) fields. Where N is the sample size for each phase.

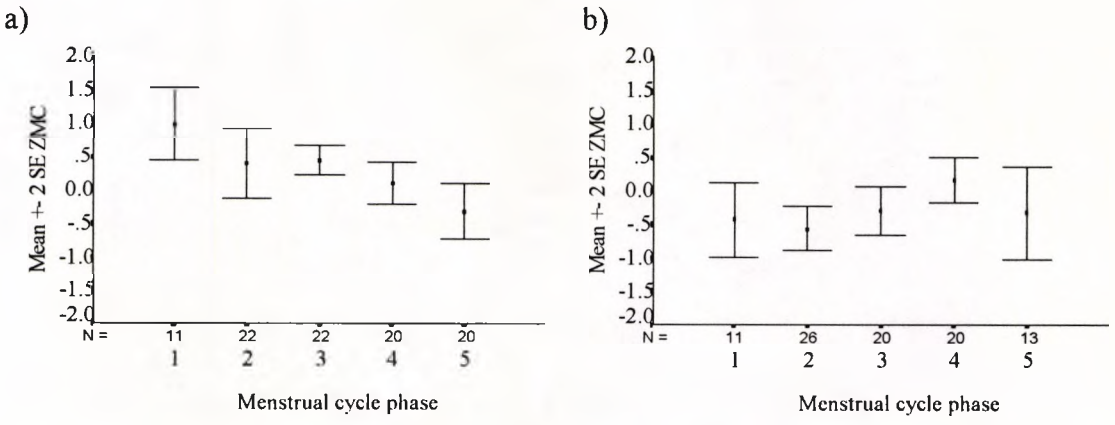


Figure 6.4 Mean ZMC (±2 standard errors) against menstrual cycle phase for a) cycle 1 and b) cycle 2, for the central field.

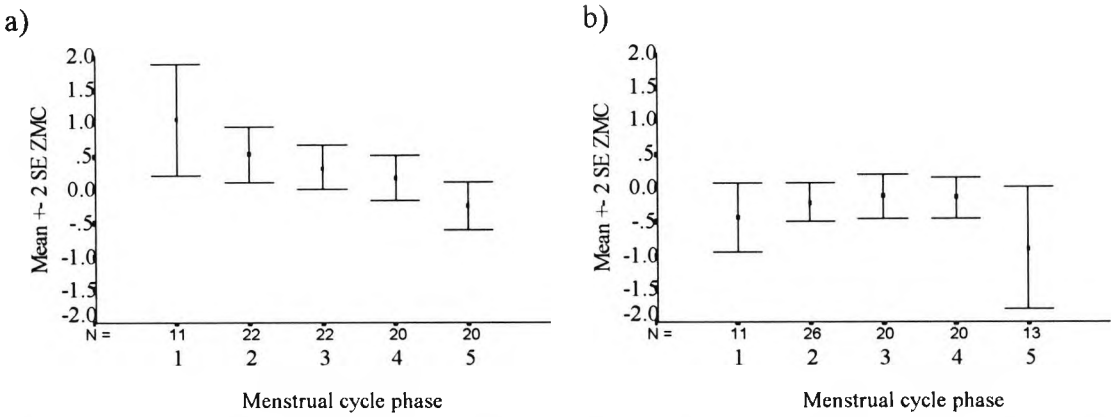


Figure 6.5 Mean ZMC (±2 standard errors) against menstrual cycle phase for a) cycle 1 and b) cycle 2, for the peripheral field.

One-way analysis of variance with Student-Newman-Keuls (SNK) multiple comparison test identified significant differences in ZMC between phases for cycle 1 in the central field ($F(4,90)=4.46$, $p=0.003$). ZMC was significantly lower in the premenstrual compared with the menstrual, follicular and ovulatory phases, and in the luteal compared with the menstrual phase. The results were similar in the peripheral field where ZMC was found to be significantly lower in the premenstrual phase than in the menstrual and follicular phases ($F(4,90)=4.08$, $p=0.004$). No significant differences between phases were found in cycle 2 in either central or peripheral fields ($p>0.05$).

6.3.1 (ii) Global Indices

Mean values of global indices in the central field, and MS and SF in the peripheral field, were calculated for each subject. Sample means of these indices are given in table 6.4.

Table 6.4 Sample mean values (SD) for the global indices for the central and peripheral fields.

	MS (dB) (SD)	MD (dB) (SD)	PSD (dB) (SD)	CPSD (dB) (SD)	SF(dB) (SD)
Central 30-2	28.26 (0.77)	-3.01 (0.70)	2.27 (0.62)	1.56 (0.67)	1.33 (0.24)
Peripheral 30/60-2	16.73 (1.17)	NA	NA	NA	1.86 (0.38)

MD, SF, PSD and CPSD for the central field, and SF for the peripheral field were plotted against menstrual cycle phase for both cycles (figures 6.6 to 6.9).

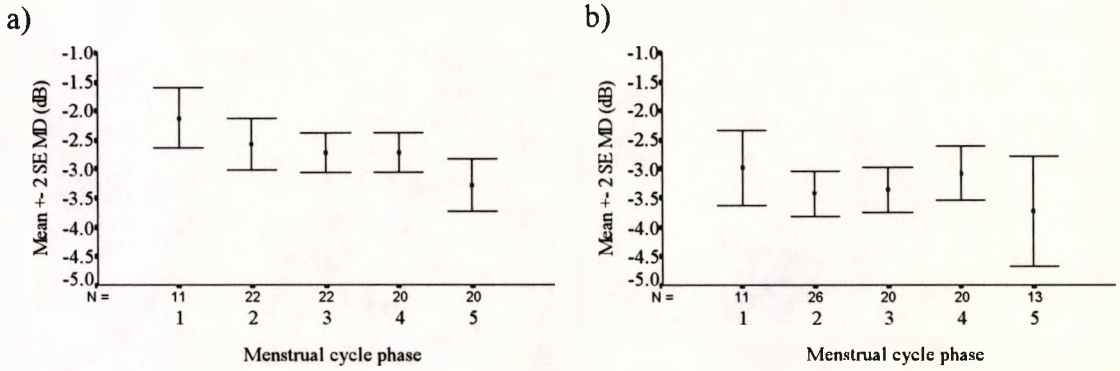


Figure 6.6 Mean MD (±2 standard errors) against cycle phase for the central field for a) cycle 1 and b) cycle 2.

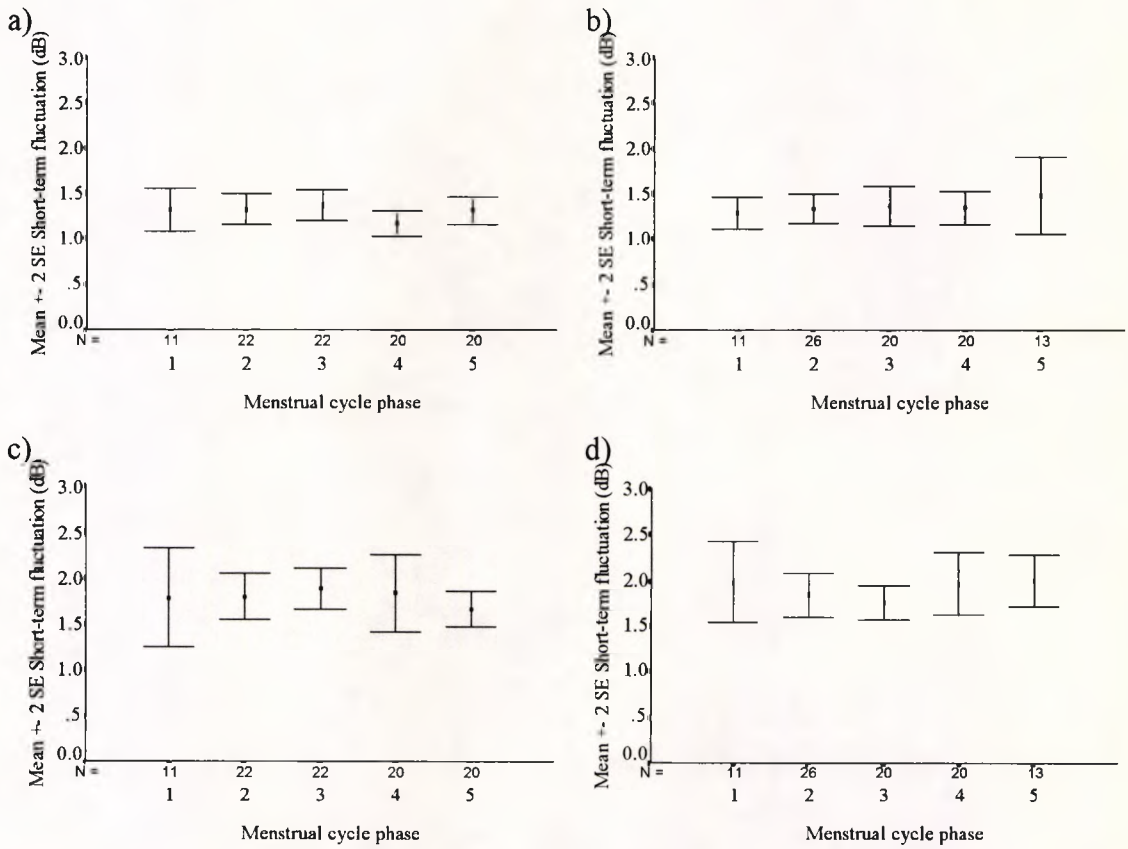


Figure 6.7 Mean SF (±2 standard errors) against cycle phase for the central field for a) cycle 1 and b) cycle 2 and peripheral field c) cycle 1 and d) cycle 2.

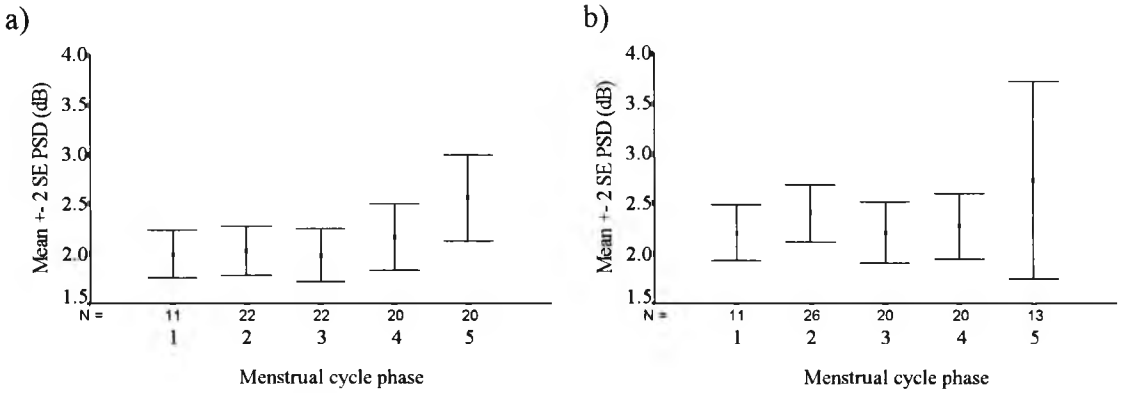


Figure 6.8 Mean PSD (±2 standard errors) against cycle phase for the central field for a) cycle 1 and b) cycle 2.

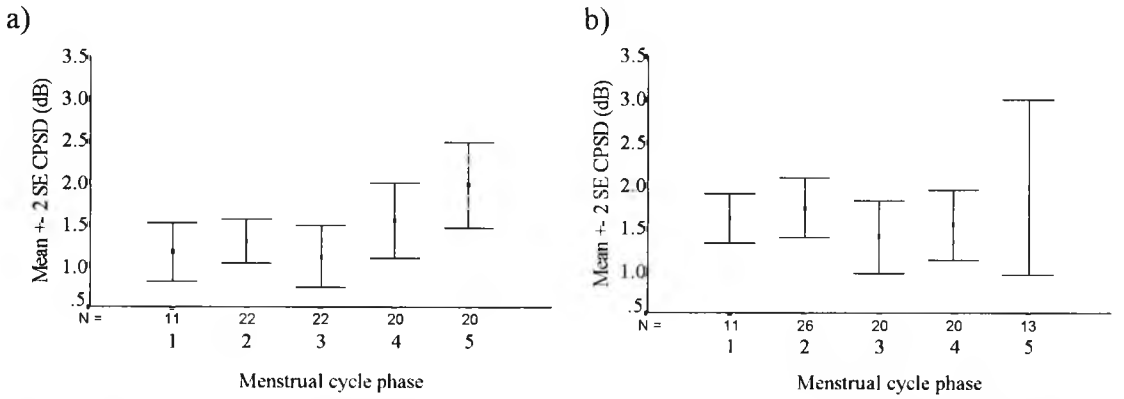


Figure 6.9 Mean CPSD (±2 standard errors) against cycle phase for the central field for a) cycle 1 and b) cycle 2.

Significant differences in MD and CPSD were identified across cycle 1. MD was significantly lower in the premenstrual compared to the menstrual phase ($F(4,90)=3.25$, $p=0.02$), and CPSD was significantly greater in the premenstrual compared to the ovulatory and follicular phases ($F(4,90)=2.96$, $p=0.02$). All other comparisons failed to reach significance at the 5% level.

Mean SF was significantly greater in the peripheral field (1.86dB SD 0.38) than in the central field (1.33dB SD 0.24) using a paired *t*-test on the sample means (t = -4.71 df=10, $p=0.001$).

6.4.1 (iii) Reliability parameters

False positive errors (FP), false negative errors (FN) and fixation losses (FL) recorded by the HFA (see section 3.6) allow an assessment of a subject's reliability throughout each field examination. Reliability may be influenced by menstrual cycle phase.

Percentage scores of all reliability parameters were calculated. There was an overall high level of reliability, with a high proportion of zero values for both FP and FN, with all percentage values for these errors falling within the manufacturers recommended limits (33%) for the central field.

Scatter plots of percentage values for all error scores against the standardised day of the menstrual cycle were plotted for central and peripheral fields for both cycles (figure 6.10 to 6.12). Overlapping or nearly overlapping points are represented by 'sunflowers'. If a cell only contains one point, it is represented by an open circle, with each additional point of the same value being represented by a short line, or 'petal' originating from the circle (Norusis 1993). This representation allows cases with clusters of values to be more easily identified.

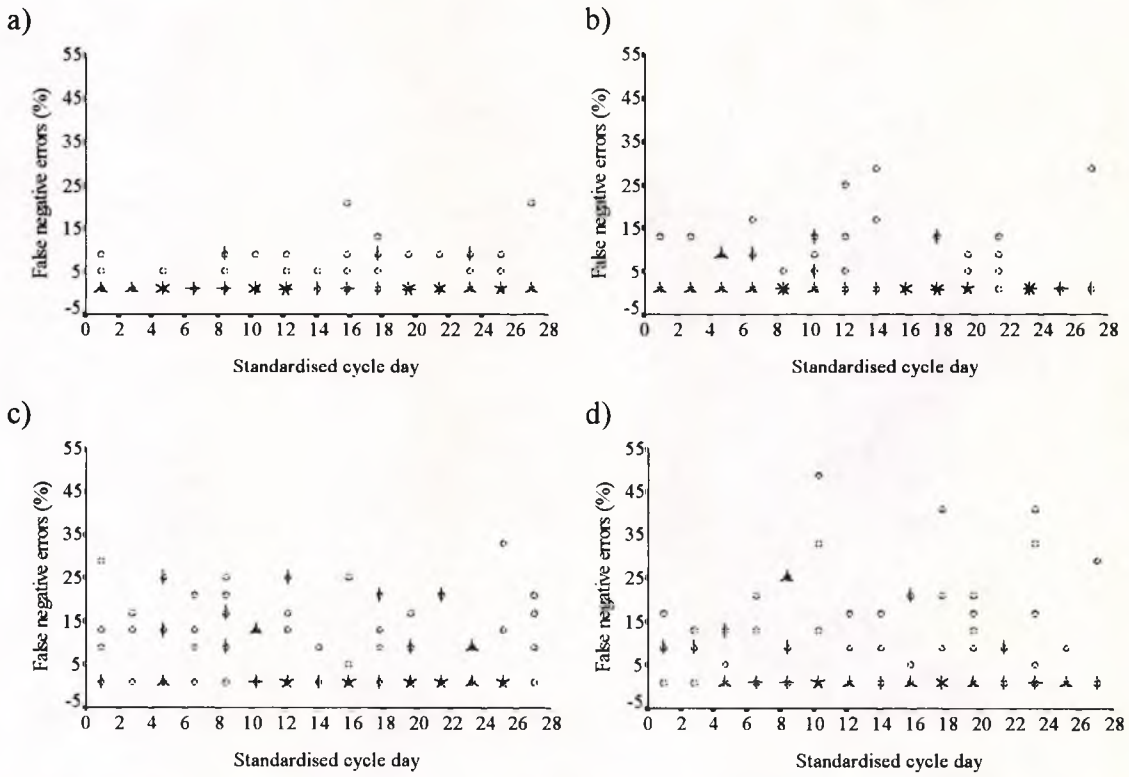


Figure 6.10 Percentage scores of false negative errors against day of cycle for the central field for a) cycle 1 and b) cycle 2 and peripheral field c) cycle 1 and d) cycle 2.

From inspection of figure 6.10 it is difficult to identify any real trends, although there are suggestions of a slight mid-cycle peak, more pronounced in cycle 2. There was a greater percentage of FN in the peripheral field, with three field plots (two from subject 9 and one from subject 6) having greater than 33% FN in cycle 2. As these plots were scattered across the cycle, with no apparent association with cycle phase, they were discarded from further analysis. Two-way analysis of variance with subjects and menstrual cycle phase as main factors identified a significant difference between subjects

for the central field in both cycle 1 (F(10,84)=2.09, p=0.045) and cycle 2 (F(10,79)=3.65, p=0.001) and for the peripheral field in cycle 2 (F(10,70)=2.45, p=0.014) as might be expected, but no significant difference was found between menstrual cycle phases at the 5% level.

Scatter plots of percentage FP against day of cycle were plotted (figure 6.11). Too few FP differed from zero to warrant further investigation.

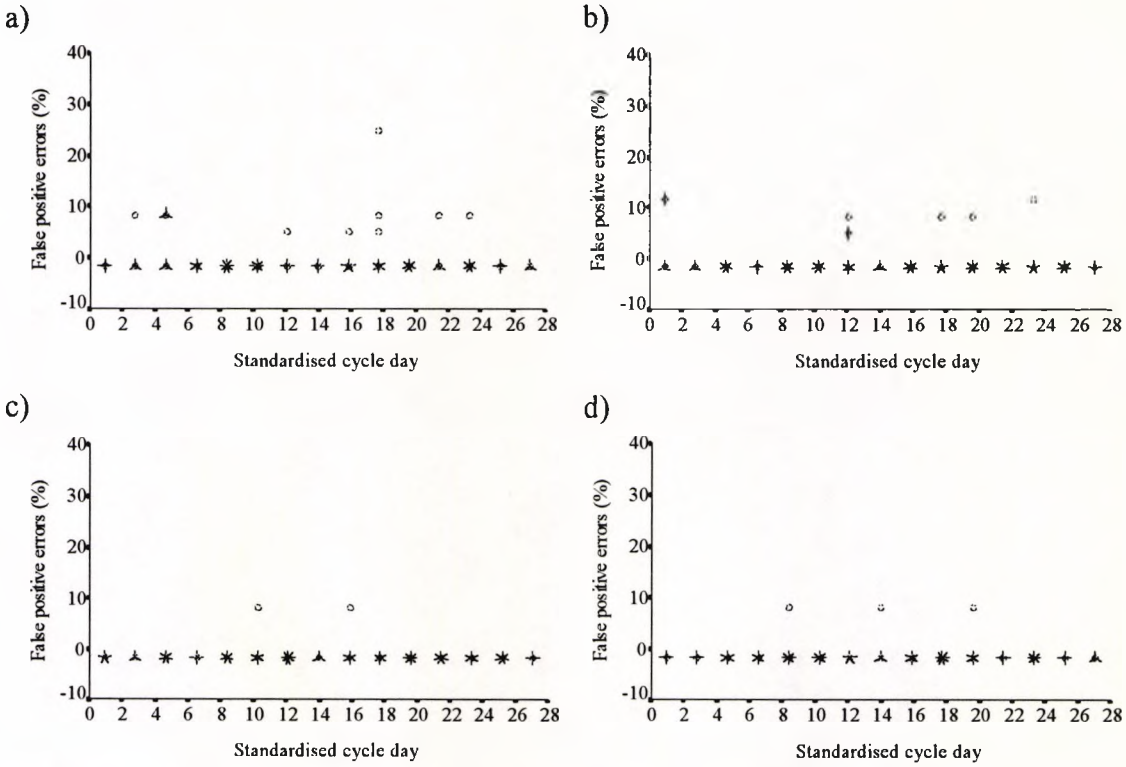


Figure 6.11 Percentage scores of false positive errors against day of cycle for the central field for a) cycle 1 and b) cycle 2 and the peripheral field c) cycle 1 and d) cycle 2.

FL accounted for the few fields that were flagged as unreliable by the HFA, and were more common in cycle 1. Percentages of FL were plotted against cycle day with subject identification numbers used as labels (6.12). It can be seen from these plots that subjects 5 and 7 repeatedly produced 'unreliable' fields due to FL. It has been suggested that subjects with high FL may be responding to stray light from the supra-threshold stimulus presented within the blind spot (Nelson-Quigg et al 1989). Both these subjects reported being aware of this stray light, and responding to it. If the manufacturers limits for FL were increased to 33%, in line with that of FP and FN (Bickler-Bluth et al 1989), all FL would fall within this limit. Efforts were made to minimise FL, with subject encouragement and replotting of the blind spot if necessary. Examiner observation via the telescopic image of the subject's eye indicated no FL losses, thus these plots were included in the analysis.

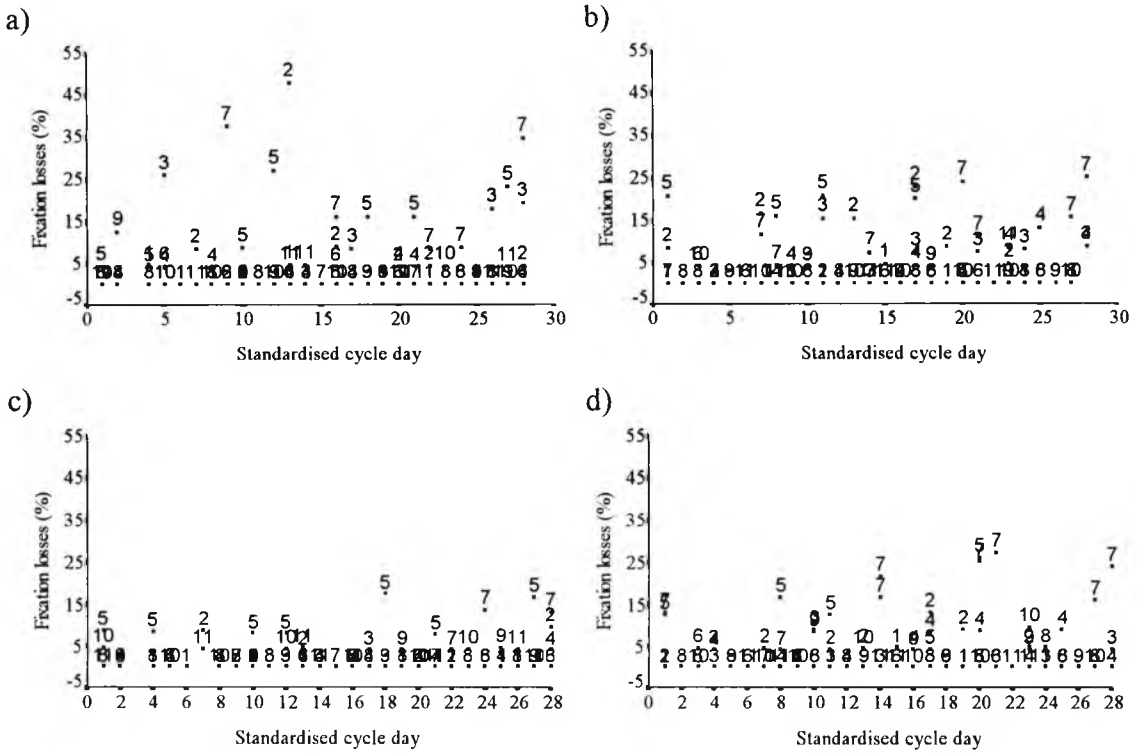


Figure 6.12 Percentage scores of fixation losses against day of cycle for the central field for a) cycle 1 and b) cycle 2 and the peripheral field for c) cycle 1 and d) cycle 2.

Two-way analysis of variance with subjects and menstrual cycle phase as main factors identified a significant difference between subjects for both cycle 1 ($F(10,84)=4.49$, $p<0.0001$) and cycle 2 ($F(10,79)=7.39$, $p<0.0001$) for the central field, and for both cycle 1 ($F(10,84)=10.1$, $p<0.0001$) and cycle 2 ($F(10,79)=13.22$, $p<0.0001$) for the peripheral fields. No significant differences were found across menstrual cycle phase at the 5% level.

6.4.1 (iv) Time taken and number of stimulus presentations

The time taken to complete the field test, and the number of stimulus presentations made, or questions asked, are also available from the HFA and may be influenced by menstrual cycle phase. Standardised scores of the difference from a subject's baseline value of the time taken (ZT) and the number of stimulus presentations (ZQ) were calculated and plotted against cycle phase (figures 6.13 and 6.14).

One-way analysis of variance identified a significant difference between phases for ZT in the central field for cycle 1 ($F(4,90)=3.23$, $p=0.016$), with the field test taking longer in the premenstrual phase compared with the ovulatory, follicular and luteal phases. This trend was not reproduced cycle 2 or in either cycle of the peripheral field, and all other comparisons failed to reach significance at the 5% level.

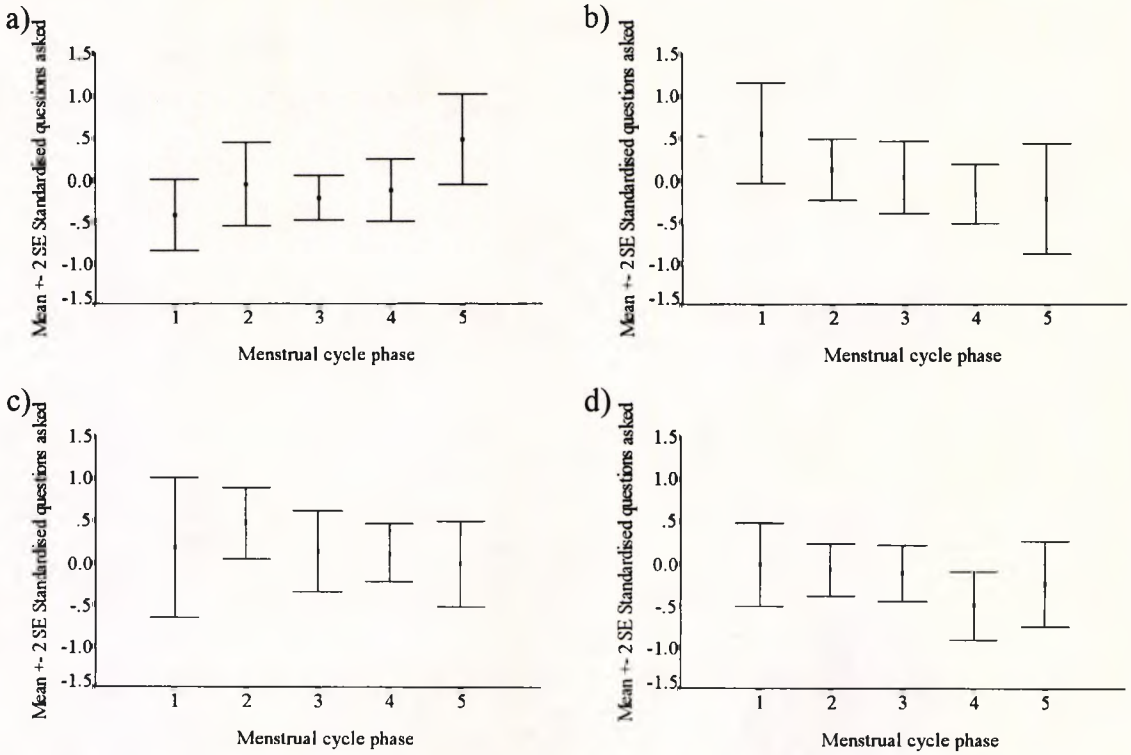


Figure 6.13 Standardised scores of questions asked (±2 standard errors) against cycle phase for the central field for a) cycle 1 and b) cycle 2 and peripheral field c) cycle 1 and d) cycle 2.

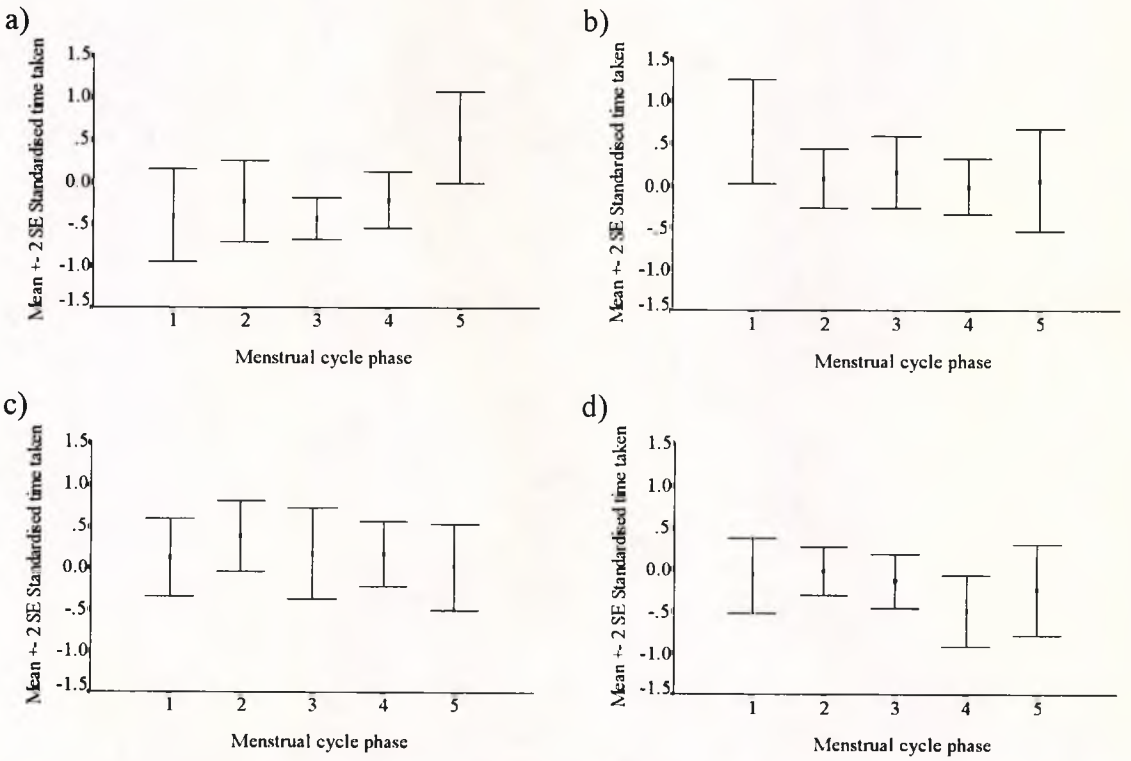


Figure 6.14 Standardised scores of time taken (±2 standard errors) against cycle phase for the central field for a) cycle 1 and b) cycle 2 and peripheral field c) cycle 1 and d) cycle 2.

Mean time taken for the field examination was significantly greater for the peripheral field (862s SE 16s) than for the central field (808s SE 25s) using a paired sample *t*-test on the sample means (t=2.70, df=10, p=0.02).

6.4.2 Menstrual Distress Questionnaire

6.4.2 (i) Form T

Mean values for factor scale scores were calculated for each menstrual cycle phase in both cycles (table 6.5). Friedman two-way analysis of variance failed to identify any significant differences between menstrual cycle phases in any of the eight factor scales for either cycle. Paired sample *t*-tests, for subjects with data for both cycles (as compared with table 6.5 where mean values are for all subjects), failed to identify any significant differences in scores between phases in cycle 1 and cycle 2, suggesting good instrument stability over time.

These results are very different to those of Moos (1985) who reported significant differences across three menstrual cycle phases in all factor scales except Arousal and Control. Thus, scores were also computed for the original three phases used by Moos (1985), where the menstrual phase (phase 1) comprises the days of menstrual flow (as self-reported on form T), the premenstrual phase (phase 3) is specified as the four days prior to onset of menstrual flow and the intermenstrual phase (phase 2) comprises the remaining days, to allow a direct comparison (table 6.6). Of note are the consistently lower standard errors in the intermenstrual phase. This is likely to be due to the larger sample size in this phase, as in the 3 phase designation the intermenstrual phase includes many more days than either of the other two phases. Standard errors are also generally smaller in Moos' data due to the larger subject group (n=399).

Table 6.5 Mean MDQ factor scale scores (SE) for the five phase designation for C1 (cycle 1) and C2 (cycle 2) for all subjects.

		Menstrual cycle phase				
MDQ factor scale		Menstrual	Follicular	Ovulatory	Luteal	Premenstrual
Pain	C1	4.38 (0.92)	2.44 (0.39)	3.42 (0.67)	2.56 (0.67)	3.13 (0.57)
	C2	5.61 (0.85)	2.61 (0.62)	3.41 (0.87)	2.20 (0.55)	3.20 (0.95)
Water	C1	2.77 (0.88)	1.09 (0.23)	1.00 (0.22)	1.23 (0.28)	2.07 (0.50)
Retention	C2	2.72 (0.65)	1.27 (0.29)	1.21 (0.31)	1.30 (0.51)	1.83 (0.68)
Autonomic	C1	0.92 (0.47)	0.09 (0.06)	0.89 (0.62)	0.41 (0.27)	0.38 (0.21)
Reaction	C2	0.28 (0.15)	0.67 (0.31)	0.62 (0.35)	0.30 (0.11)	0.48 (0.26)
Negative	C1	4.25 (0.96)	5.03 (1.49)	5.94 (1.90)	5.47 (1.28)	5.92 (1.85)
Affect	C2	5.78 (1.71)	5.33 (1.51)	5.06 (1.29)	3.65 (0.89)	4.85 (1.62)
Impaired	C1	3.40 (0.96)	2.59 (0.80)	3.30 (0.76)	3.71 (0.89)	3.73 (0.92)
Concentration	C2	4.44 (0.91)	3.42 (0.86)	3.62 (1.27)	2.30 (0.68)	2.70 (1.12)
Behaviour	C1	2.60 (0.79)	2.59 (0.53)	3.36 (0.60)	3.05 (0.59)	3.48 (0.87)
Change	C2	4.83 (0.80)	3.71 (0.88)	2.74 (0.92)	2.65 (0.80)	3.87 (0.90)
Arousal	C1	5.90 (1.45)	6.35 (0.52)	5.53 (0.85)	5.00 (0.66)	5.25 (0.96)
	C2	4.00 (1.11)	6.08 (0.54)	5.85 (0.88)	5.90 (0.80)	7.17 (1.47)
Control	C1	0.79 (0.26)	0.56 (0.17)	1.38 (0.71)	0.85 (0.25)	1.40 (0.50)
	C2	0.67 (0.29)	1.03 (0.32)	0.73 (0.30)	0.40 (0.30)	0.41 (0.16)

Table 6.6 Mean MDQ factor scale scores (SE) for three phase designation for C1 (cycle 1), C2 (cycle 2) and for Moos' (1985) normative data in italics (n=399). Where *p<0.05 significant difference between C2 and Moos (1985) data (*t*-test). Further statistical details (*t* values and df) are included in appendix A2.3.

		Menstrual cycle phase		
MDQ factor scale		Menstrual	Intermenstrual	Premenstrual
Pain	C1	4.50 (0.84)	2.64 (0.41)	3.41 (0.78)
	C2	*5.15 (0.93)	2.95 (0.63)	2.63 (0.97)
	Moos (1985)	*3.83 (0.12)*	*2.71 (0.10)*	*3.41 (0.12)*
Water Retention	C1	2.46 (0.81)	1.21 (0.22)	2.09 (0.47)
	C2	2.35 (0.61)	1.19 (0.28)	2.56 (0.76)
	Moos (1985)	*2.30 (0.07)*	*1.34 (0.05)*	*2.21 (0.08)*
Autonomic Reaction	C1	0.81 (0.43)	0.47 (0.28)	0.36 (0.20)
	C2	0.53 (0.26)	0.62 (0.24)	0.19 (0.19)
	Moos (1985)	*0.88 (0.06)*	*0.53 (0.05)*	*0.69 (0.05)*
Negative Affect	C1	5.22 (1.24)	5.20 (1.31)	6.23 (1.75)
	C2	*7.82 (2.24)	4.57 (1.01)	3.94 (1.43)
	Moos (1985)	*4.73 (0.16)*	*4.41 (0.16)*	*5.21 (0.18)*
Impaired Concentration	C1	3.24 (0.83)	3.11 (0.77)	3.95 (0.90)
	C2	*5.62 (1.41)	2.91 (0.63)	2.13 (0.90)
	Moos (1985)	*3.12 (0.11)*	*2.58 (0.11)*	*3.05 (0.12)*
Behaviour Change	C1	2.31 (0.64)	3.05 (0.54)	3.59 (0.78)
	C2	*5.28 (1.04)	*2.97 (0.68)	*3.75 (0.86)
	Moos (1985)	*2.22 (0.09)*	*1.86 (0.08)*	*2.12 (0.08)*
Arousal	C1	6.24 (1.35)	5.57 (0.54)	5.86 (0.97)
	C2	4.62 (1.01)	*5.98 (0.65)	*7.44 (1.62)
	Moos (1985)	*4.24 (0.10)*	*4.30 (0.11)*	*4.33 (0.10)*
Control	C1	0.87 (0.27)	0.82 (0.24)	1.45 (0.48)
	C2	1.27 (0.68)	0.62 (0.19)	0.44 (0.18)
	Moos (1985)	*1.01 (0.07)*	*0.73 (0.06)*	*0.95 (0.06)*

Friedman's two-way analysis of variance failed to identify any significant differences between phases in any factor scale in cycle 1 at the 5% level. Significant differences in symptom scores between phases were found in the Pain (χ^2=6.5, df=2, p=0.04), Impaired Concentration (χ^2=7.36, df=2, p=0.025) and Arousal (χ^2=10.70, df=2, p=0.005) factor scales in cycle 2. Pain and Impaired Concentration are increased in the menstrual phase, while Arousal scores increase across the cycle (figure 6.15).

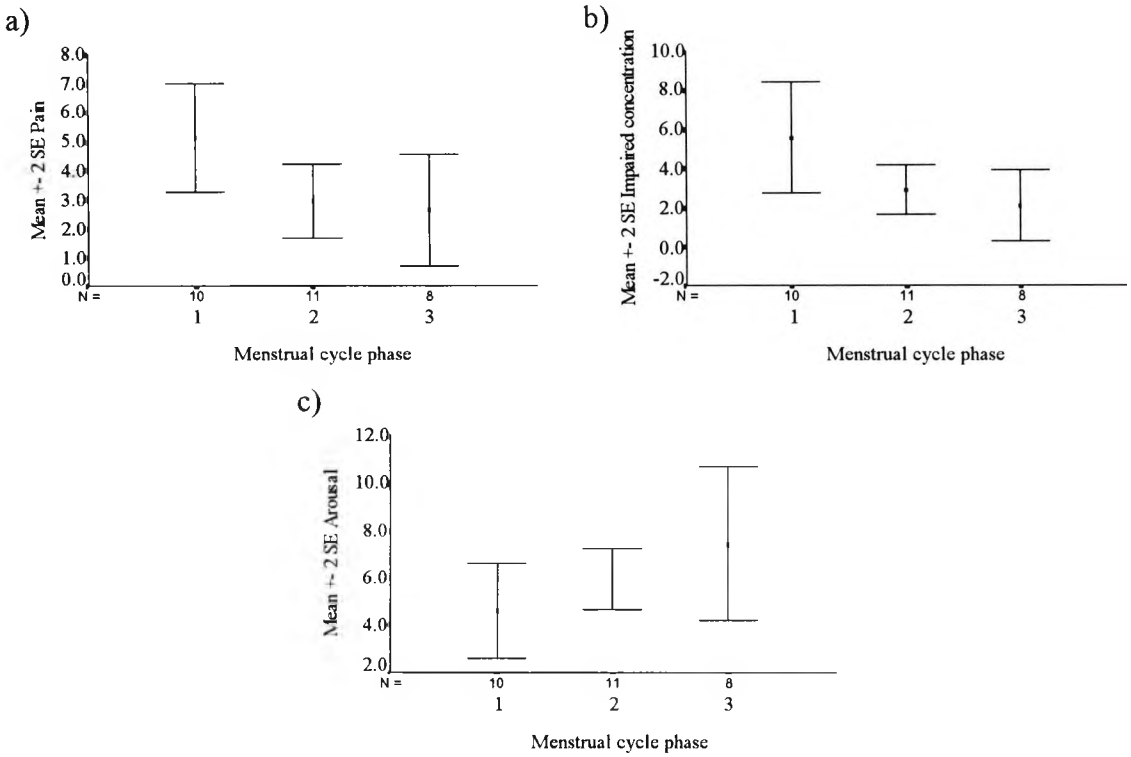


Figure 6.15 Mean (±2 standard errors) MDQ factor scale score for a) Pain, b) Impaired Concentration and c) Arousal across menstrual cycle phase for cycle 2. Where N = the sample size for each phase.

Again, stability of symptom reporting over the two cycles was good, with no significant differences at the 5% level between cycle 1 and 2 for any factor scale in any phase with paired sample *t*-tests. A comparison with the normative data of Moos (1985) with two sample *t*-tests suggested some differences in overall reporting levels between the present study sample and that of Moos (1985). Significant differences ($p<0.05$) in the levels of scoring were found across all phases in the Behaviour Change factor scale, in the menstrual phase in Pain, Negative Affect and Impaired Concentration and in the intermenstrual and premenstrual phases of the Arousal factor.

6.4.2 (ii) Form C

Scores for each of the eight factor scales, Pain, Water Retention, Autonomic Reaction, Negative Affect, Impaired Concentration, Behaviour Change, Arousal and Control, were computed for each questionnaire (table 6.7). For comparison with prospective data of form T, cycle 2 data was used as form C was completed at the end of the study and assessed symptoms over the same cycle.

Table 6.7 Mean MDQ form C factor scale scores (SE), for normative data (Moos 1985) in italics, n=2381 and for form T, cycle 2 (TC2).
Where *p<0.05 significant difference between form C and form T, cycle 2 data, and †p<0.05, significant difference between form C and normative data (*t*-test). Further statistical details (*t* values and df) are included in appendix A2.3.

		Menstrual cycle phase		
MDQ factor scale		Menstrual	Intermenstrual	Premenstrual
Pain	C	11.82(1.58)	3.18 (1.35)	6.18 (1.75)
	Moos (1985)	*5.22 (0.06)*†	*1.80 (0.04)*†	*4.03 (0.05)*†
	TC2	5.15 (0.93)*	2.95 (0.63)	2.63 (0.97)
Water Retention	C	5.45 (1.10)	1.64 (0.64)	5.73 (0.95)
	Moos (1985)	*3.11 (0.03)*†	*1.02 (0.02)*†	*3.25 (0.04)*†
	TC2	2.35 (0.61)*	1.19 (0.28)	2.56 (0.76)*
Autonomic Reaction	C	2.91 (1.11)	0.91 (0.55)	1.82 (0.82)
	Moos (1985)	*1.08 (0.03)*†	*0.35 (0.80)*†	*0.78 (0.02)*†
	TC2	0.53 (0.26)	0.62 (0.24)	0.19 (0.19)
Negative Affect	C	13.00 (2.99)	8.18 (2.68)	14.55 (2.45)
	Moos (1985)	*6.17 (0.08)*†	*2.99 (0.05)*†	*6.40 (0.08)*†
	TC2	7.82 (2.24)	4.57 (1.01)	3.94 (1.43)*
Impaired Concentration	C	9.91 (2.54)	5.09 (1.90)	7.55 (2.25)
	Moos (1985)	*2.57 (0.05)*†	*1.46 (0.04)*†	*2.33 (0.05)*†
	TC2	5.62 (1.41)	2.91 (0.63)	2.13 (0.90)*
Behaviour Change	C	6.36 (1.94)	3.09 (1.68)	6.09 (1.63)
	Moos (1985)	*2.49 (0.04)*†	*0.93 (0.02)*†	*1.81 (0.04)*†
	TC2	5.28 (1.04)	2.97 (0.68)	3.75 (0.86)
Arousal	C	4.64 (1.04)	7.45 (0.90)	6.18 (1.31)
	Moos (1985)	*3.42 (0.04)*	*3.77 (0.05)*†	*3.39 (0.05)*†
	TC2	4.62 (1.01)	5.98 (0.65)	7.44 (1.62)
Control	C	2.55 (1.11)	1.27 (1.08)	2.55 (1.22)
	Moos (1985)	*0.94 (0.03)*†	*0.52 (0.02)*†	*0.74 (0.02)*†
	TC2	1.27 (0.68)*	0.62 (0.19)	0.44 (0.18)

Friedman's two-way analysis of variance identified significant differences between menstrual cycle phases in the factor scales Pain (χ^2=16.55, df=2, p=0.0003), Water Retention (χ^2=12.18, df=2, p=0.002), Negative Affect (χ^2=10.77, df=2, p=0.005), Impaired Concentration (χ^2=12.68, df=2, p=0.002), Behaviour Change (χ^2=8.73, df=2, p=0.01) and Arousal (χ^2=6.05, df=2, p=0.05) (figure 6.16). Scores were greater in the menstrual and premenstrual phases compared with the intermenstrual phase in all these

factor scales except Arousal, where the intermenstrual score was greater than in the other two phases.

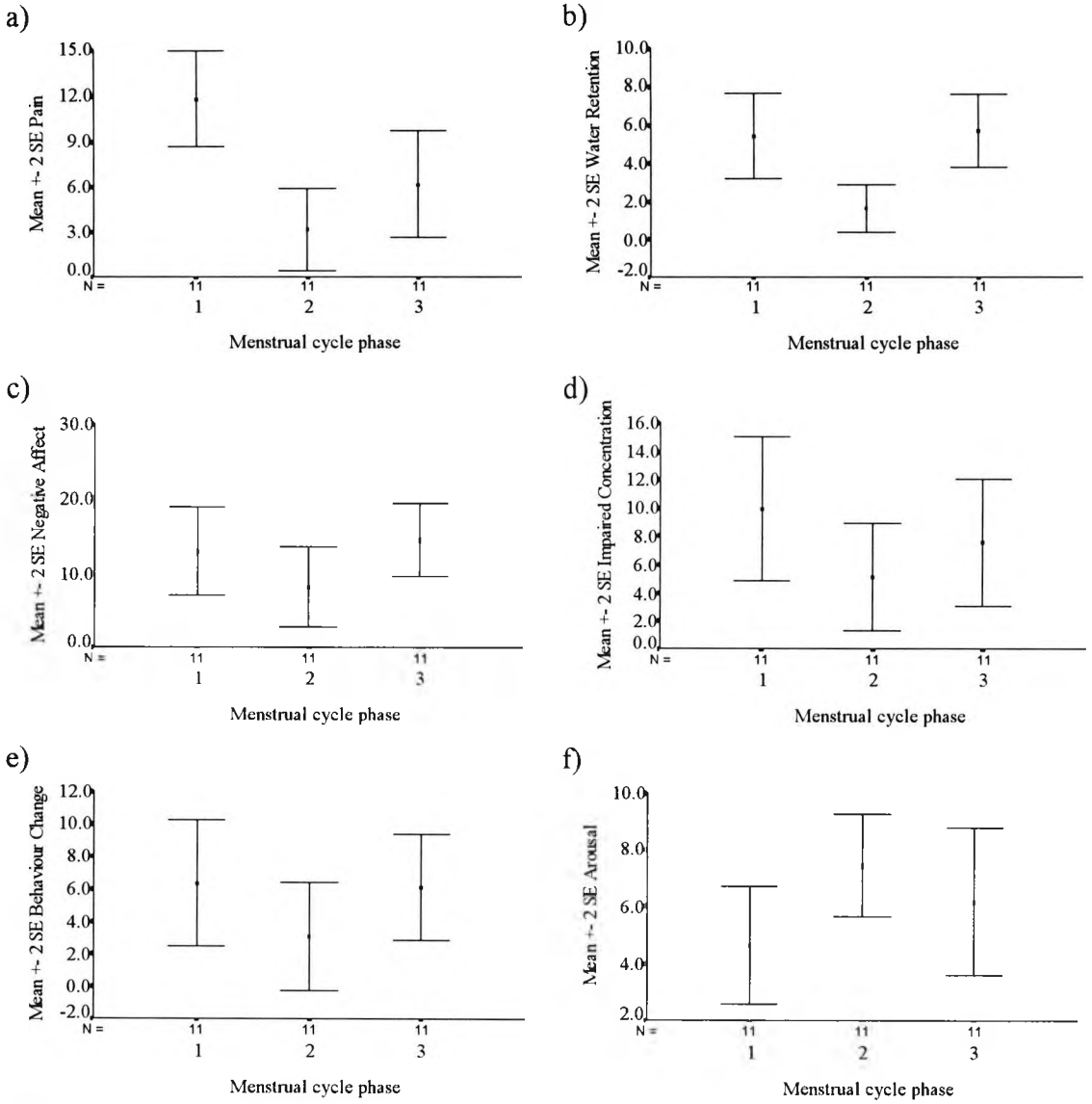


Figure 6.16 Mean (±2 standard errors) MDQ factor scale score for a) Pain, b) Water Retention, c) Negative Affect, d) Impaired Concentration, e) Behaviour Change and f) Arousal across menstrual cycle phase. Where N=sample size for each phase.

To assess the differences in this subject group between retrospective and prospective reporting, paired *t*-tests were carried out between form C data and form T, cycle 2 data. Significant differences were identified in the factor scales Water Retention, Pain and Control in the menstrual phase and in Negative Affect, Impaired Concentration and Water Retention in the premenstrual phase. Scores on form C were generally higher than those in form T. In a comparison with the normative data for the retrospective questionnaire quoted by Moos (1985) using two sample *t*-tests all scores for all phases in every factor scale were significantly higher ($p<0.05$) in the present study, with the exception of Arousal in the menstrual phase.

6.5 Discussion

6.5.1 Visual fields

There was considerable inter- and intra-individual variation in automated perimetric results across the menstrual cycle. Some subjects appear to demonstrate fluctuations in ZMC across the menstrual cycle, whilst others show no change.

The results of the grouped data for cycle 1 indicated a significant decrease in performance across the menstrual cycle with a loss of sensitivity over the whole field, an increase in CPSD, and in the time taken to complete the central field plot, in the premenstrual phase compared with the first half of the cycle. Taken alone, the results of the first cycle would suggest a premenstrual decrease in visual sensitivity.

Other studies using different measures of visual performance have identified similar changes with decreases in threshold sensitivity in the premenstrual phase for TFFT (Kopell et al 1969; Demarchi and Tong 1972; Braier and Asso 1980; Asso and Braier 1982) and dark-adapted visual detection (Ward et al 1978). It also appears to support in part the results of previous studies on kinetic perimetry (Finkelstein 1887; Lanfair and Smith 1974) where constriction of fields was found paramenstrually. However, it is difficult to compare studies using different measures of visual performance with different methodologies and analyses. All but one of the above studies collected data over only one menstrual cycle. Kopell and co-workers (1969) collected data for five days in two cycles, but then combined the data into one cycle, a step which is not strictly appropriate (Dye 1991), as successive cycles may have been influenced differently by extraneous variables. In the present study data was collected over two cycles for all subjects and each cycle was analysed separately to assess the repeatability of any fluctuations in visual performance. The results found in the second cycle were very different from those in the first. No significant difference in ZMC at the 5% level was found across the menstrual cycle in either the central or peripheral field, with the overall trend across the cycle being in the opposite direction to that in cycle 1. There were also no differences found in the time taken to complete the tests and in the number of stimulus presentations required. Other studies have also found little or no change in TFFT (Clare 1976) and in a visual detection task (Scher et al 1981) across the menstrual cycle. The same caveats apply when making comparisons with these studies.

Overall subject performance was good, with subject reliability and intra-test variability, SF, remaining stable across menstrual cycle phase in both cycles. The differences in the results between the two cycles highlights the necessity of collecting data over at least

two cycles and assessing repeatability in any changes found before any conclusions can be drawn.

The menstrual cycle is an ongoing physiological cycle. It may be argued that linear regression is not an ideal model to fit menstrual cycle data which may be inherently cyclical in nature. This is borne out by the results of the correlation statistics and residual plots, and curve-fitting or trend analysis may be more appropriate.

Looking beyond the menstrual cycle as a focus, there are some interesting features worth noting. The standardised scores were calculated using the mean of scores over the total number of sessions for each subject, rather than over each cycle independently. This means that trends over the study period as a whole can be observed.

In several subjects ZMC in both the central and peripheral fields tends to decrease over the first half of the study before stabilising or increasing slightly for the remainder of the study. In one subject (7) ZMC decreased across the whole of the study period in both the central and peripheral field. This trend is in the opposite direction to a learning effect and may be due to fatigue or boredom increasing over the study period.

Fatigue effects have been observed between tests taken at the same session (Searle et al 1991a,b), and it is possible that these effects may be carried over from session to session in the frequent serial examinations in this study. The average times taken to complete the central and peripheral field tests were 13.47 minutes (SD 0.42) and 14.37 minutes (SD 0.27) respectively. Optimal testing times of between eight and 10 minutes have been proposed by Johnson et al (1988) in order to reduce the effects of fatigue. The peripheral field was always tested after the central field and might therefore be expected to be more susceptible to any fatigue effects. Intra-test variability (SF) was significantly greater in the peripheral field (1.86dB SD0.38) than in the central field (1.33dB SD0.24) and a fatigue effect may be contributing to this difference. This is in accordance with a previous study by Jaffe and co-workers (1986) who found an increase in variability, attributed to fatigue, in the second eye tested at the same session. These increases in the 'noise' inherent in automated perimetric data may be masking any menstrual cycle fluctuations in sensitivity.

The average mean deviation (MD) for each subject varied between -2.17dB and -4.28dB (mean -3.01dB SD0.70). All subjects therefore have a reduced threshold sensitivity compared to the normative age-matched controls used by the HFA (Heijl et al 1987b). However, subjects were young and healthy, with no history of ocular pathology, and it seems unlikely that they had abnormal visual fields. Table 6.8 gives values for global indices found for normal subjects by other investigators. Negative values for MD in

normal subjects have been reported by other authors (Wild et al 1989c; Rudnicka 1994), and the sample mean for MS (28.26dB SD0.77) in the central field is similar to those previously reported (Collin et al 1988; Rudnicka 1994). Other global indices are also similar, and this adds support to the conclusion that subjects do not have abnormal thresholds as suggested by the MD values, but rather that the age-matched sample population used for the HFA normative values had different threshold sensitivities to those of the present study. Analysis of the HFA global indices using the age-matched normative values in their calculation should thus be interpreted with some caution.

The sample mean for MS in the peripheral field was 16.73dB (SD 1.17 range 15.2-18.6dB). This decrease in sensitivity in the peripheral field compared to the central field is in accordance with well documented evidence of declining retinal sensitivity with increasing eccentricity in both manual (Sloan 1961; Aulhorn and Harms 1972; Johnson et al 1978) and automated perimetry (Wild et al 1986, 1987; Wood et al 1986, 1988a; Goldstick and Weinreb 1987; Heuer et al 1989; Flanagan et al 1991; Zulauf 1994). MS in the peripheral field is reduced in comparison with other studies (Brenton and Phelps 1986; Collin et al 1988), and this may be due to the fatigue and boredom effects noted above. The increase in inter-subject variability in the peripheral field, with a standard deviation of the mean of 0.77 in the central field increasing to 1.17 in the peripheral field is in agreement with previous reports of increasing between-subject variability with increasing eccentricity (Brenton and Phelps 1986; Wild et al 1986; Heijl 1987; Heijl et al 1987a,d; Rutishauser et al 1989; Gundersen 1993; Zulauf 1994).

Overall the vast majority of MS scores were within ±2.00dB of the baseline values for subjects. This is within normal limits for variability (e.g. Wilensky and Joondeph 1984; Lewis et al 1986), but may be masking subtle menstrual cycle related changes in the threshold sensitivity. Variability increases with fatigue (Jaffe et al 1986) and with eccentricity both within a test (Brenton and Phelps 1986; Wall et al 1993) and between tests (Heijl 1977b; Heijl et al 1987a,d, 1989b; Parrish et al 1984; Lewis et al 1986). By employing a shorter test time and smaller test field some of the 'noise' inherent in the data can be reduced, and fluctuations associated with the menstrual cycle may be highlighted.

Table 6.8 Mean values for global indices for HFA central 30-2 fields for normal subjects

Authors	Number of subjects	Age range (mean ±SD)	MS (dB) (±SD)	MD (dB) (±SD)	SF (dB) (±SD)	PSD (dB) (±SD)	CPSD (dB) (±SD)
Central 30-2							
Brenton & Phelps (1986)	17	20-29	30.4 ±1.5				
Heijl et al (1987c)	84	not stated		-0.05 ±1.73	1.57 ±0.65	2.42 ±1.13	
Collin et al (1988)	25	22.1±1.6	28.13 ±3.88				
Iwase et al (1989)	100	10-60+		-0.36	1.34	1.94	1.11
Lindenmuth et al (1989)	20	24-43 (28.9±4.8)		-0.95	1.40	1.79	0.73
Wild et al (1989c)	8	20.52 ±0.86		-1.87 ±0.43	1.07 ±0.01	2.01 ±0.22	1.52 ±0.27
Flanagan et al (1993a)	98	49.6 ±16.9	27.24 ±2.84		1.36 ±0.52		
Rudnicka (1994)	58	19-35.25 (22.67)	28.72 ±1.26	-2.09 ±1.16	1.26 ±0.27	1.96 ±0.42	1.21 ±0.58
Peripheral 30/60-2							
Brenton & Phelps (1986)			20.5 ±2.7				
Collin et al (1988)			17.85 ±8.58				

6.5.2 Menstrual Distress Questionnaire

Overall there was much inter-subject variability in both prospective and retrospective symptom reporting across the menstrual cycle.

Prospective Form T

Factor scale scores were computed and analysed across both the five phase designation of standardised 28-day cycles and also for three phases (Moos 1985) of unstandardised cycles.

No significant differences in any factor scale score were found over the five phases of the menstrual cycle for either cycle. However, on a re-analysis of the data grouped into the three phases as designated by Moos (1985) significant differences were found across cycle 2. Pain and Impaired Concentration were highest in the menstrual phase, while Arousal increased across the menstrual cycle. No differences in factor scores were found across cycle 1, suggesting inter-cycle differences in patterns of symptom reporting.

The discrepancy between factors showing significant differences across cycle 2 for the three and five phase designations may be due to the methods used to divide the cycle into phases. Moos' original three phase designation is based on unstandardised menstrual cycles, with the menstrual and premenstrual phases comprising actual days of menstrual flow and the four days prior to the onset of menstrual flow respectively. This may be a more accurate way of designating the menstrual and premenstrual phases for an individual than the use of standardised 28 day cycles and the five phase designation. Here, for example, the menstrual phase is fixed as days 1-4 and for some women days of menstrual flow may be greater or less than this. However, there are disadvantages to the three phase designation. It fails to differentiate between follicular, ovulatory and luteal phases, using one 'intermenstrual' phase instead. Also the cycle phases are of greatly differing lengths, with the intermenstrual phase always having many more days than the other two phases, meaning that much more data is included in this phase.

The results are quite different to those of the normative values provided in the MDQ manual (Moos 1985), in which significant differences across the cycle were reported for most factors. These differences may be due to the different subject samples used. Although Moos (1985) states that his 'normative' sample of 399 women was composed 'primarily of young normally cycling women with few perimenstrual symptoms', the actual age range of subjects, and information on other subject characteristics, for example parity and oral contraceptive usage, is not provided. It is therefore difficult to make direct comparisons between the two data sets. The present study group comprised

young, normally cycling, nulliparous women who tend to report few increases in symptomatology in the premenstrual phase (Dalton 1964; Moos 1968).

These results add support to other reports of few or no significant differences in MDQ factor scales, particularly in the psychological symptoms, between menstrual cycle phases in small groups of young women (Baisden and Gibson 1975; Markum 1976; Ward et al 1978; Slade 1981; Lahmeyer et al 1982; Dye and Hindmarsh 1991).

Of interest is the direction of change in the Arousal factor scale in this study, with an increase in positive mood reported across cycle 2. Parlee (1980) has proposed that the existence of positive premenstrual mood states could be a function of satisfactory life circumstances in interaction with a non-specific state of bodily arousal during the premenstrual phase. However, the trend in all the negative factor scales is to be greater in the menstrual and/or premenstrual phases, thus an overall 'premenstrual elation syndrome' as proposed by Parlee (1980) seems unlikely in this subject group. Additionally the Arousal factor is rarely reported as fluctuating significantly across the menstrual cycle (Moos 1985), and considering the lack of significance in other factor scales that have previously consistently shown cycle phase related changes, e.g. Water Retention, this result may be a statistical artefact (e.g. Type I error).

Although the overall level of prospective reporting is generally similar to that of the Moos sample (table 6.6), there were some noteworthy exceptions. Subjects in the present study reported more symptoms of Behaviour Change across the whole of the cycle, together with more Pain, Negative Affect and Impaired Concentration in the menstrual phase, and higher levels of Arousal in the intermenstrual and premenstrual phases. This highlights the inter-sample differences.

Symptom reporting remained stable over the study period (table 6.5) with no significant differences between phase scores in any factor identified between cycle 1 and cycle 2. This is in agreement with other studies (Wilcoxon et al 1976; Lahmeyer et al 1982) reporting little instrument deterioration, i.e. systematic increase or decrease in symptoms over time due to loss of interest or effort, using the prospective form T of the MDQ.

Retrospective Form C

The retrospective MDQ form C was completed by all subjects at the end of the study period. This form asks the subject to report on symptoms experienced during the menstrual, premenstrual and intermenstrual phases of their most recent cycle. Inter-subject variation in symptom reporting was again considerable. Significant phase differences were found in the Pain, Water Retention, Negative Affect, Impaired

Concentration, Behaviour Change and Arousal factor scales. Scores were higher in the menstrual and premenstrual phases compared with the intermenstrual phase in all factors except that of Arousal in which scores were higher in the intermenstrual phase. The physical factor scales of Pain and Water Retention showed the most differentiation between phases, with the highest scores of Pain in the menstrual phase, and increased Water Retention in both menstrual and premenstrual phases. These significant differences between factors are in general agreement with previously reported retrospective studies (e.g. Englander-Golden et al 1978; Moos 1985; Boyle and Grant 1992).

Overall symptom scores were significantly higher than those of the normative data from 2381 women complied by Moos (1985) (table 6.7). On closer inspection of the individual data in the present study it is apparent that one subject in particular scored highly on all factors including the Control scale which is composed of items that are not frequently reported. A high score on this scale reflects a tendency to report varied symptoms, even though they are not associated with the menstrual cycle (Moos 1985). With the small number of subjects in this study, the extreme responses of one subject may bias the results.

The differences between retrospective and prospective symptom reporting over the menstrual cycle are highlighted by the results of a comparison of factor scale scores from forms T and C. Significant differences were identified between questionnaires in the menstrual phase in the factor scales of Water Retention, Pain and Control, and in the premenstrual phase, on factor scales of Impaired concentration, Water Retention and Negative Affect. Factor scores were generally higher with the retrospective form C. The direction of change is in accordance with the stereotypical view of increases in negative moods and a decrease in performance premenstrually with increases in physical symptoms of pain and/or water retention in the menstrual and premenstrual phases. This increase in symptom reporting retrospectively is in agreement with previous work (Englander-Golden et al 1978, 1986; McFarlane et al 1988; McFarland et al 1989; Ainscough 1990; Boyle and Grant 1992).

Overall retrospective reporting yielded both an increase in negative symptom reporting and a greater number of significant differences in factor scores across menstrual cycle phase. In this study subjects were aware that the menstrual cycle was a salient feature and as such it seems likely that individuals are retrospectively reporting either stereotypical beliefs about the menstrual cycle (Parlee 1974; Ruble et al 1980), or their general menstrual cycle experience (Markum 1976), rather than that of their most recent cycle as requested on the MDQ form C.

6.6 Conclusions

Visual fields

There was much inter and intra-variability in automated perimetric results with little evidence for a repeatable linear fluctuation in sensitivity and performance across the menstrual cycle.

Patterns of fluctuation vary considerably between different menstrual cycles, highlighting the importance of collecting data over at least two cycles.

Fluctuations in sensitivity across the menstrual cycle may be masked by the variability inherent in automated perimetric measurement. This variability and noise in the data is greater in the peripheral field. The use of a smaller test field, with fewer locations and thus a shorter test time, would reduce the variability and fatigue effects, such that menstrual cycle fluctuations in threshold sensitivity may be more readily identified.

Menstrual Distress Questionnaire

The sample population of normal, young, nulliparous women report few changes in either physical or psychological symptomatology across the menstrual cycle in prospective self-reports. Retrospective symptom scores are higher overall than those recorded prospectively, suggesting stereotypical menstrual cycle experiences are influencing the data. Prospective collection of data appears to be a more accurate way of assessing menstrual cycle symptomatology.

The MDQ exhibits no sign of instrument deterioration over time and has reasonable test-retest reliability over two menstrual cycles.

Further work

This pilot study highlighted several methodological issues in the investigation into the effects of the menstrual cycle on automated perimetry. The within-subjects longitudinal approach appears to be an appropriate study design for the assessment of menstrual cycle related fluctuations in visual sensitivity, with data collection over at least two menstrual cycles required. Further work is indicated to improve the methodology by the following measures:

- Efforts made to minimise inter- and intra-subject variability in automated perimetry results
- Greater subject numbers
- The use of control groups of subjects
- Masking the true purpose of the study
- Daily reports of symptomatology

The scope of the study could also be extended in the following areas:

- Use of other measures of visual performance
- Inclusion of an objective physiological measure to compare against subjective measures of visual performance.

CHAPTER 7

The Effect of the Menstrual Cycle on Visual Performance

7.1 Introduction

Visual performance has been reported to fluctuate with menstrual cycle phase, most frequently decreasing in the premenstrual phase and increasing around ovulation (section 1.4). Most of these studies have used laboratory based psychophysical tests that may not relate to the clinical situation.

Visual field assessment using manual kinetic perimetry has identified constriction of the peripheral field in the premenstrual phase (Finkelstein 1887; Lorenzetti 1926, cited Lanfair and Smith 1974; Lanfair and Smith 1974). These findings have yet to be confirmed with modern methods of perimetric assessment.

Contrast sensitivity function (CSF) is the threshold contrast needed for the detection of gratings of different spatial frequencies (Abrahamsson et al 1988). The measurement of contrast sensitivity has become recognised as a valuable means of assessing spatial vision, particularly in the detection of subtle visual loss (e.g. Regan 1988; Arden 1978, 1988; Tytla and Buncic 1988). Menstrual cycle related fluctuations in contrast sensitivity have been identified. However, the results of previous studies are inconclusive. Dunn and Ross (1985) reported increases in contrast sensitivity at three spatial frequencies (9, 18 and 26cpd) in the post-ovulatory phase, while Johnson and Petersik (1987) report several peaks in sensitivity across the menstrual cycle, particularly for a spatial frequency of 4cpd, i.e. that closest to the peak of the normal contrast sensitivity function. Differences in the methods of finding threshold lead to difficulties in comparing the results directly. Johnson and Petersik (1987) used a subjective method of adjustment which, although simple and fast, has been reported to be highly criterion dependent with relatively poor repeatability (Woods and Thomson 1993). Dunn and Ross (1985) used a forced choice method which yields more reliable results (e.g. Vaegan and Halliday 1982). Also both studies limited data collection over one cycle, subject numbers were small and subjects were aware of the study focus. Further work in this area is required before any conclusions about fluctuations in CSF across the menstrual cycle can be drawn.

In the only study measuring visual acuity across the cycle, acuity with Landolt rings was found to be improved by 10% in the post-ovulatory phase (Jordan and Jaschinski-Kruza 1986).

Menstrual cycle related symptomatology is reported as greater retrospectively compared to prospectively (Englander-Golden et al 1978, 1986; McFarlane et al 1988; McFarland et al 1989; Ainscough 1990; Boyle and Grant 1992), and in aware subjects compared to those unaware of the menstrual cycle as a salient feature of the study (Parlee 1974; Englander-Golden et al 1978, 1986; Vila and Beech 1980; AuBuchon and Calhoun 1985). Changes in performance across the menstrual cycle may be related to fluctuations in self-reported mood and physical symptoms (section 1.8.1).

Fluctuations in ANS and CNS arousal and activation across the menstrual cycle may vary independently of one another (Asso 1978). Reports of fluctuations in arousal in the ANS across the menstrual cycle are controversial (section 1.6.2), with some evidence suggesting greater ANS arousal premenstrually (Little and Zahn 1974; Asso and Brier 1982; Asso 1986) while others identified little change in various measures of ANS activity across the cycle (Kopell et al 1969; Zimmerman and Parlee 1973; Doty et al 1981; Strauss et al 1983; Ussher and Wilding 1991). It has also been suggested that ANS arousal across the menstrual cycle is mediated by overall levels of stress (Marinari et al 1976; Collins et al 1985).

The accurate measurement of pupil diameter aids in the assessment of normal retinal function, and the integrity of the afferent and efferent pupillary pathways. Fluctuations in ANS activity may be manifested as changes in pupil diameter. In the only study to assess pupil diameter in association with menstrual cycle, Barris and co-workers (1980) reported no significant change in the dark-adapted pupil diameter 'across the menstrual cycle'. However, they only reported measurements over four days around ovulation in one menstrual cycle of three normally menstruating women, and pupil diameter may vary in other phases of the cycle. The measurement of pupil diameter is an objective measure of changes in ANS activity across the menstrual cycle, and this is of interest in this study where visual performance measures are open to subjective bias.

A pilot study failed to identify repeatable changes in automated perimetric results across two consecutive menstrual cycles of 11 normally cycling women (Chapter 6). A large degree of inter- and intra-subject variability was found which may be masking any cycle-related fluctuations. Overall, subjects reported few fluctuations in symptomatology across the menstrual cycle. In the conclusions drawn from the pilot study suggestions were made for improvements in methodology and extensions to the scope of the investigation.

7.2 Aims

The aims of this study were to investigate fluctuations across the normal menstrual cycle in:

- Visual performance as assessed by automated perimetry, contrast sensitivity and visual acuity
- Pupil diameter
- Symptomatology

Control groups comprised women taking oral contraceptives and men. The potential of the menstrual cycle to be a confounding factor in the interpretation of clinical tests is also investigated. Of additional interest is the relationship of symptomatology to visual performance in both women with normal menstrual cycles and in non-cycling individuals.

7.3 Materials and Methods

7.3.1 Instrumentation

Visual Fields

In an attempt to reduce the variability and fatigue effects found in the pilot study, the use of a program with a smaller test field, fewer locations and shorter test time was recommended. Thus the central 24-2 program of the HFA 630 was used to measure the visual field. This program finds contrast threshold at 54 stimulus locations within the central 24° of the field, and is currently used in clinical practice for serial visual field assessment of ocular pathology (e.g. Schulzer et al 1990; Flanagan et al 1993b; Hitchings 1994). The time taken to complete the test is about 10 minutes. Macular threshold was also measured at the beginning of each field test.

Contrast Sensitivity

As a psychophysical test, contrast sensitivity measurements may be affected by learning. However, Kelly and Tomlinson (1987) found no evidence of a learning effect in CSF for six spatial frequencies in 20 normal subjects over five practice sessions with the Nicolet CS-2000 Vision Tester. A staircase method of adjustment was used to find threshold and the authors suggest that other methods for finding threshold may be more susceptible to learning effects. In the present study subjects were given two training sessions to eliminate any potential practice effects.

It has been reported that the use of a forced-choice method of finding threshold yields more reliable results in normal subjects (Vaegan and Halliday 1982; Higgins et al 1984; Woods and Thomson 1993). However, this method is extremely time consuming, taking around an hour for the measurement of five spatial frequencies (Woods and Thomson 1993) and fatigue effects may influence the data with extensive testing. A yes/no random staircase method reduces the time taken to complete the test (about 10 minutes) and is employed in this study. Whilst reducing criterion effects, this method of finding threshold does not eliminate them. However, with the use of a masked study, conscious criterion changes associated with the menstrual cycle will be minimised.

A high resolution CRT display (1280 x 1024 pixels) was used to generate vertical sine wave grating stimuli. The test aperture subtended a visual angle of 5^{o} at a viewing distance of 2m and had a background luminance of $34cd/m^2$. Subjects wore appropriate spectacle corrections and were adapted for at least 3 minutes to the grey background. A random yes/no staircase with variable step size and stimulus presentation time of 500ms was used to obtain contrast threshold at five spatial frequencies (0.75, 1.5, 4, 8, and 14 cpd).

Visual Acuity

Despite the extensive use of the standard Snellen visual acuity charts, both in research and clinical practice, these charts have a number of deficiencies (e.g. Bailey and Lovie 1976; Ferris et al 1982). They have different numbers of letters per line, there is not a regular progression in letter size from the largest to the smallest lines, and the letters used can be of widely varying difficulty. In short the visual task is not the same at each level of visual acuity. Alternative charts have been designed to overcome these problems (Bailey and Lovie 1976; Ferris et al 1982). These charts have five letters on each line, the space between each letter is one letter wide and the space between the lines is equal in height to the letters of the next line. The progression of letter height from line to line is geometric, decreasing by 0.1 log units for each lower line on the chart. An interpolated logMAR (logarithm of the minimum angle of resolution) score can therefore be created by assigning 0.02 logMAR units to each of the five letters on each line, thus potentially allowing fine discrimination between similar levels of visual acuity (Kitchin and Bailey 1981). The test is scored in terms of each letter and this score can be used in statistical analysis. Ten different letters of approximately equal difficulty are used in the charts. A score of 0.0 log units is equivalent to 6/6 Snellen acuity, with negative scores indicating a higher acuity and positive scores a lower acuity.

Visual acuity was measured with Bailey-Lovie logMAR acuity charts of high and low contrasts. Two different versions of each chart were used to minimise any memorising of the letters.

Pupil Diameter

Pupil diameter of the same eye used for visual performance tests was measured with an infrared pupillometer (P_SCAN 100) under mesopic conditions, using a 6/12 Snellen letter as a visual target. Full description of the measurement technique is given by Barbur (in Alexandridis et al 1991).

Daily Questionnaire

A daily questionnaire was devised (appendix A3.2) both to elicit salient information about the menstrual cycles of the women taking part in the study and to create a 'cover' to mask the true purpose of the study. Basal body temperature was recorded in an attempt to identify ovulatory cycles. Details of the amount of sleep, exercise, and nicotine, alcohol and caffeine consumption over the previous 24 hours were recorded. Twenty symptoms were graded on a scale of 0-8, with 0 being total absence and 8 being very strong presence of symptom. Symptoms were modified from those on the MDQ. Of particular interest were those reporting abdominal pain, backache, mood swings, irritability, and positive moods, which have been reported as fluctuating with menstrual cycle phase (e.g. Moos 1985). Other symptoms were included to aid disguising of the study. Subjects were also asked to record any specific illnesses, life events or increases in stress, and women recorded whether or not they were menstruating.

7.3.2 Subjects

All subjects were paid volunteers and were students in the Optometry and Visual Science, Psychology and Clinical Communications departments of the university. A general questionnaire (appendix A3.1) was used to assess individuals' fulfilment of the inclusion criteria.

The subject groups comprised 19 women with normal menstrual cycles (F), eight women taking the oral contraceptive pill (P) (three triphasic, five combined), and four men (M). Time constraints prevented larger control groups. All subjects were healthy, ophthalmologically normal, non-contact lens wearers, with refractive errors of less than ±2.00DS, less than 0.50DC and with Snellen visual acuities of 6/6 or better. Groups were roughly matched for age with means for F of 22.1yrs (range 18-37), for P 22.3yrs (range 18-28) and for M 23.8yrs (range 19-28). All women were nulliparous except one

of the F who had two children. All F reported regular, normal menstrual cycles, and had not taken OCs for at least six months prior to study commencement. Exclusion criteria included the regular current use of prescription and pharmacy medicines, poor general health, diabetes and any history of mental illness.

7.3.3 Procedure

University ethical committee approval was given for the study to be masked as an investigation into the effect of mood and general health on visual performance. The study conformed to a within-subject longitudinal multifactorial design. Subjects attended two to three times each week for six to 10 weeks. Data was collected over one to three menstrual cycles in all women in the study. One eye was chosen randomly for each subject and all subsequent measurements were on this eye alone. The visual performance measures of automated perimetry, logMAR acuity at high and low contrast and contrast sensitivity were completed followed by measurement of pupil diameter. The order of the tests was the same at each session. Daily questionnaires were completed by all subjects and collected every few days in an attempt to prevent subjects identifying their own cyclical trends, as this could introduce a retrospective bias (Sherif 1980).

7.4 Statistical analysis

The purpose of the analysis is to test the null hypothesis that there is no change in visual performance across the menstrual cycle.

Visual Fields

Global indices MD, PSD, CPSD and SF were calculated by the Statpac program of the HFA. An additional global score of mean sensitivity (MS) was calculated for each visual field by finding the mean of all threshold values, except the two values in the blind spot. Values of mean change (MC) in MS from an individual's baseline value were then calculated for all visual fields using the equation

$$MC = MS - \overline{MS}$$

where $\overline{MS}$ is the average, or baseline, mean sensitivity across the study period for a subject.

In the pilot study this MC score was then transformed into a standardised score (section 6.3.4). Although standardising removes individual variability, it may actually mask

menstrual cycle fluctuations. The use of the mean change score allows data from different individuals to be combined and also enables easier interpretation of results, as the original units of measurement (e.g. dB) are retained unlike the standardised score which is unitless.

In addition to the global scores, the visual field was divided into regions to investigate fluctuations in sensitivity across the cycle in different regions of the field. Change in sensitivity from the baseline mean was calculated for the following regions:

- three annuli, inner, middle and outer (figure 7.1)

- superior and inferior, and nasal and temporal hemifields.

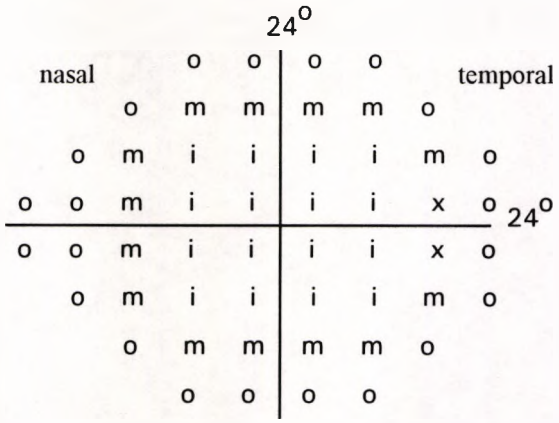


Figure 7.1 Regional map for program 24-2 of the HFA for inner (i), middle (m) and outer (o) annuli. Blind spot locations are represented by x.

Analysis of variance incorporating an additive sequence of models was used to test the hypothesis. The hierarchical model allows the use of raw scores, as variability due to inter-individual differences is taken into consideration.

The menstrual cycle is a physiological time series and thus curve-fitting is an appropriate statistical technique. Sine and cosine curves with a frequency of 28 days, and a model allowing variable phase in these curves, were fitted across both the 84 days encompassing all three menstrual cycles, and across all cycles individually. Attempts were also made to fit higher frequency sine and cosine curves.

Contrast sensitivity, visual acuity and pupil diameter

Repeatability of CSF, logMAR high and low contrast charts and pupil diameter measurements was established using a randomly selected pair of consecutive measurements in the study for each subject. The first two sessions were not used in order to allow for any learning effects.

Similar change from baseline scores were calculated for pupil diameter (PD), contrast sensitivity at all five spatial frequencies and for visual acuity at high (VAHC) and low contrast (VALC). The same hierarchical model as for the visual fields was used to test the null hypothesis.

7.5 Results

Data was excluded from one of the F subjects who failed to provide any data on her menstrual cycle phase and from the third cycle of a P subject who stopped taking OCs half-way through the study period. Menstrual cycle length varied from 20-36 days in the F subject group (mean 27.8 SD 4) with both inter and intra-subject variations (figure 7.2). Data was collected from each subject from between one and three cycles.

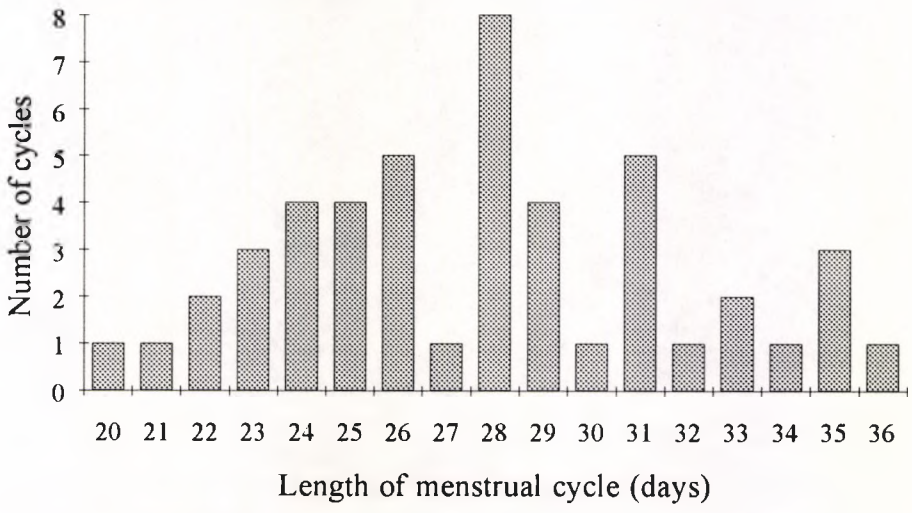


Figure 7.2 Frequency of different menstrual cycle length for female subjects with normal menstrual cycles (F).

From the total number of F cycles from which data was collected (47), complete BBT charts were available for 32 cycles. On inspection of these charts only 16 were found to display a definite biphasic pattern that would be indicative of an ovulatory cycle. This would seem to suggest that 50% of the cycles were anovulatory. As argued in the previous study (section 6.4) BBT would appear to be an unreliable indicator of ovulation

in this study population. The absence of a biphasic pattern was therefore not taken as an indicator of an anovulatory cycle in this study, and all cycles were included in subsequent analysis.

Analysis of the data is complicated by the differing menstrual cycle lengths in the F subjects. Cycles were all standardised to 28 days using the same method as in the pilot study (Kendall 1986). All menstrual cycles in P subjects were 28 days long. Male subjects were randomly allocated 28 day 'menstrual' cycles. Data was analysed across days of the cycle and also grouped into five menstrual cycle phases as before: menstrual (days 1-4), follicular (days 5-11), ovulatory (days 12-17), luteal (days 18-23) and premenstrual (days 24-28) (Rossi and Rossi 1977). In graphical presentation of the data the phases are denoted by the numbers 1-5 respectively.

7.5.1 Repeatability

Automated perimetric assessment of the visual field has become a recognised technique and the variability associated with repeated measurement has been described previously (see section 3.3). Repeatability of pupil diameter, high and low contrast visual acuity and CSF measurements were established using randomly selected consecutive pairs of data from each subject. Mean and difference values were calculated for the pairs of data, together with 95% confidence limits (Bland and Altman 1986) (table 7.1). Plots of the differences between paired values against their mean, together with the 95% confidence limits, are included in appendix 3.3.

Table 7.1 Repeatability results for pupil diameter, visual acuity and contrast sensitivity function comparing two sessions.

Measure	Mean difference	Standard deviation	95% confidence limits
Pupil diameter	-0.05mm	0.51mm	+0.97mm / -1.07mm
High contrast VA	-0.013	0.05	+0.087 / -0.113
Low contrast VA	0.007	0.04	+0.087 / -0.073
CSF 0.75cpd	-4.26	13.8	+23.34 / -31.86
CSF 1.5cpd	2.13	27.26	+56.65 / -52.39
CSF 4cpd	-3.21	18.9	+34.59 / -41.01
CSF 8cpd	4.41	42.7	+89.81 / -80.99
CSF 14cpd	-1.97	25.6	+49.23 / -53.17

7.5.2 Visual performance

7.5.2 (i) Visual field

Mean values for global indices, the time taken and number of questions asked, and the mean sensitivities for field regions for each subject group are given in Table 7.2. No significant differences at the 5% level were found in any score between groups using a one-way anova procedure.

Table 7.2 Mean values (SD) for global indices, time taken and number of questions asked, and mean sensitivities for field regions for all subject groups.

	Subject group		
Global index	F	P	M
MS	29.61 (1.38)	30.64 (1.54)	30.27 (1.36)
MD	-1.87 (1.28)	-0.91 (1.32)	-1.13 (1.37)
SF	1.38 (0.23)	1.22 (0.23)	1.26 (0.15)
PSD	2.23 (0.71)	1.81 (0.69)	2.04 (0.62)
CPSD	1.52 (0.84)	1.11 (0.79)	1.41 (0.69)
Questions asked	339.06 (18.05)	332.73 (21.96)	339.55 (23.72)
Time taken	624.15 (43.10)	586.95 (53.08)	608.98 (52.42)
Field region			
Fovea	37.65 (1.02)	37.53 (0.82)	37.75 (1.02)
Annuli			
Inner	32.14 (1.21)	32.69 (0.84)	32.52 (0.62)
Middle	29.78 (1.36)	30.64 (1.41)	30.31 (1.31)
Outer	27.67 (1.72)	29.15 (2.26)	28.61 (1.92)
Hemifields			
Superior	28.93 (1.45)	30.08 (1.56)	29.27 (1.60)
Inferior	30.30 (1.42)	31.21 (1.55)	31.26 (1.14)
Temporal	29.66 (1.51)	30.71 (1.47)	30.19 (1.33)
Nasal	29.57 (1.32)	30.58 (1.61)	30.34 (1.57)

For the sake of brevity, not all values of the visual field scores investigated are presented, with tables 7.3 to 7.5 including the means of the mean change in MS, macular threshold, sensitivity of the inner annulus and the time taken, and SF. These are arguably the more interesting indices. Plots of mean change in MS, macular threshold, time taken and the number of questions asked, SF, and percentage scores for reliability parameters against standardised cycle day for three cycles for all subject groups are included in appendix 3.4.1.

Table 7.3 Means (SE) for change in visual field indices across menstrual cycle phase for normally menstruating women, where * $p<0.05$ significant difference in scores across cycle phase, where C1 to C3 represent cycles 1 to 3 respectively.

		Menstrual cycle phase				
		Menstrual	Follicular	Ovulatory	Luteal	Premenstrual
Mean sensitivity	C1*	0.01 (0.26)	-0.42 (0.27)	0.22 (0.06)	0.18 (0.11)	0.05 (0.13)
	C2	-0.11 (0.16)	0.14 (0.12)	0.22 (0.16)	-0.14 (0.14)	-0.19 (0.11)
	C3	0.07 (0.13)	-0.08 (0.12)	-0.14 (0.28)	0.01 (0.30)	-0.47 (0.07)
Macular threshold	C1	-0.42 (0.25)	-0.33 (0.16)	-0.73 (0.25)	-0.07 (0.18)	0.02 (0.20)
	C2	0.18 (0.28)	0.32 (0.20)	0.19 (0.17)	0.14 (0.13)	-0.32 (0.22)
	C3	0.27 (0.24)	0.00 (0.18)	-0.07 (0.52)	0.29 (0.34)	-0.62 (0.37)
Inner annulus	C1*	-0.04 (0.31)	-0.44 (0.17)	0.05 (0.11)	0.16 (0.08)	0.01 (0.11)
	C2	-0.03 (0.14)	0.07 (0.10)	0.24 (0.10)	-0.18 (0.13)	-0.03 (0.10)
	C3	0.09 (0.10)	0.02 (0.12)	0.00 (0.22)	-0.12 (0.36)	-0.48 (0.11)
Time taken	C1	-18.68 (6.26)	-6.48 (12.48)	32.57 (13.57)	13.84 (10.84)	7.49 (9.15)
	C2	1.83 (10.79)	-3.83 (6.98)	-10.00 (9.70)	-0.16 (7.32)	-14.19 (7.72)
	C3	1.14 (8.14)	-6.50 (6.96)	4.01 (21.02)	-9.60 (22.26)	-15.41 (10.16)
SF	C1	1.42 (0.06)	1.37 (0.13)	1.26 (0.09)	1.28 (0.09)	1.36 (0.09)
	C2	1.46 (0.13)	1.30 (0.06)	1.41 (0.09)	1.33 (0.07)	1.43 (0.09)
	C3	1.25 (0.10)	1.50 (0.10)	0.96 (0.04)	1.44 (0.13)	1.57 (0.59)

Table 7.4 Means (SE) for change in visual field indices across menstrual cycle phase for women taking oral contraceptives, where C1 to C3 represent cycles 1 to 3 respectively.

		Menstrual cycle phase				
		Menstrual	Follicular	Ovulatory	Luteal	Premenstrual
Mean sensitivity	C1	-0.64 (0.55)	-0.26 (0.33)	-0.35 (0.22)	-0.02 (0.20)	0.37 (0.22)
	C2	-0.22 (0.20)	0.04 (0.14)	0.30 (0.26)	0.25 (0.21)	0.29 (0.18)
	C3	0.31 (0.25)	0.15 (0.21)	0.44 (NA)	0.32 (NA)	NA
Macular threshold	C1	-0.95 (0.22)	0.04 (0.31)	-0.57 (0.45)	0.11 (0.24)	-0.70 (0.71)
	C2	-0.54 (0.30)	0.05 (0.36)	-0.16 (0.64)	0.46 (0.31)	0.49 (0.24)
	C3	1.00 (0.77)	0.22 (0.74)	1.29 (NA)	-0.71 (NA)	NA
Inner annulus	C1	-0.41 (0.26)	-0.30 (0.18)	-0.55 (0.32)	-0.06 (0.15)	-0.30 (0.16)
	C2	-0.07 (0.18)	-0.01 (0.29)	0.19 (0.19)	0.36 (0.13)	0.30 (0.12)
	C3	0.28 (0.23)	0.08 (0.18)	0.42 (NA)	0.67 (NA)	NA
Time taken	C1	-1.80 (20.94)	-5.96 (7.93)	-8.70 (27.05)	1.24 (7.01)	-11.82 (12.85)
	C2	7.78 (11.82)	3.86 (10.18)	-10.46 (13.46)	1.81 (11.72)	8.70 (9.07)
	C3	10.11 (16.62)	-20.16 (9.66)	-8.06 (NA)	37.94 (NA)	NA
SF	C1	1.05 (0.14)	1.54 (0.24)	1.12 (0.14)	1.23 (0.07)	1.29 (0.08)
	C2	1.24 (0.15)	1.06 (0.08)	1.20 (0.18)	1.13 (0.08)	1.33 (0.13)
	C3	0.91 (0.14)	1.00 (0.07)	1.16 (NA)	0.98 (NA)	NA

Table 7.5 Means (SE) for change in visual field indices across 'menstrual cycle' phase for men, where * $p<0.05$ significant difference in scores across 'cycle' phase, where C1 to C3 represent 'cycles' 1 to 3 respectively.

		Menstrual cycle phase				
		Menstrual	Follicular	Ovulatory	Luteal	Premenstrual
Mean sensitivity	C1	0.30 (0.22)	0.16 (0.24)	-0.20 (0.22)	-0.60 (0.34)	-0.59 (0.24)
	C2*	-0.94 (0.38)	-0.07 (0.11)	0.32 (0.05)	0.08 (0.18)	-0.24 (0.26)
	C3	0.93 (0.41)	-0.69 (0.31)	0.40 (NA)	0.51 (0.23)	-0.10 (0.19)
Macular threshold	C1	-0.47 (0.00)	-0.03 (0.50)	-0.74 (0.47)	0.26 (0.37)	-0.24 (0.23)
	C2	0.26 (0.31)	0.13 (0.51)	0.44 (0.28)	-0.60 (0.29)	0.43 (0.64)
	C3	-0.13 (0.30)	0.33 (0.34)	1.24 (NA)	0.74 (0.50)	-0.76 (0.00)
Inner annulus	C1	0.34 (0.13)	-0.27 (0.31)	-0.18 (0.13)	-0.04 (0.25)	-0.36 (0.28)
	C2	-0.43 (0.11)	-0.10 (0.07)	0.07 (0.14)	-0.11 (0.16)	-0.05 (0.29)
	C3	0.44 (0.17)	0.47 (0.18)	0.60 (NA)	0.35 (0.25)	-0.15 (0.13)
Time taken	C1	19.90 (7.50)	-53.10 (86.50)	11.36 (8.25)	27.49 (20.18)	34.27 (10.71)
	C2*	44.42 (14.03)	12.52 (12.64)	-27.46 (17.12)	0.06 (10.77)	-7.70 (18.01)
	C3	-53.82 (19.20)	-44.27 (11.81)	37.12 (NA)	-56.38 (28.50)	-6.38 (26.50)
SF	C1	1.20 (0.20)	1.35 (0.05)	1.02 (0.06)	1.42 (0.42)	1.26 (0.09)
	C2*	1.37 (0.23)	1.43 (0.16)	1.43 (0.12)	1.21 (0.06)	1.13 (0.12)
	C3	1.21 (0.05)	0.93 (0.05)	2.31 (NA)	1.19 (0.28)	0.94 (0.17)

Both the hierarchical statistical model and a simple one-way anova with SNK multiple range test were used to test for differences between menstrual cycle phases in mean change values of MS, macular threshold, inner, middle and outer annuli, the four hemifields, time taken and questions asked, percentage scores of reliability parameters and SF.

Results for the one-way anova with SNK were as follows:

Normally menstruating women (F) (figure 7.3)

- In cycle 1 the mean sensitivity ($F(4,79)=2.45$, $p=0.05$) and sensitivity in the nasal hemifield ($F(4,79)=2.49$, $p=0.05$) were significantly lower in the follicular phase compared to the luteal phase cycle 1, while sensitivity in the inner annulus ($F(4,79)=3.36$, $p=0.014$) was significantly lower in the follicular phase compared with both the luteal and premenstrual phases.

- Sensitivity in the inferior hemifield was significantly higher in the ovulatory compared to the luteal phase in cycle 2 ($F(4,126)=2.75$, $p=0.03$).

- No significant differences were found in cycle 3 at the 5% level.

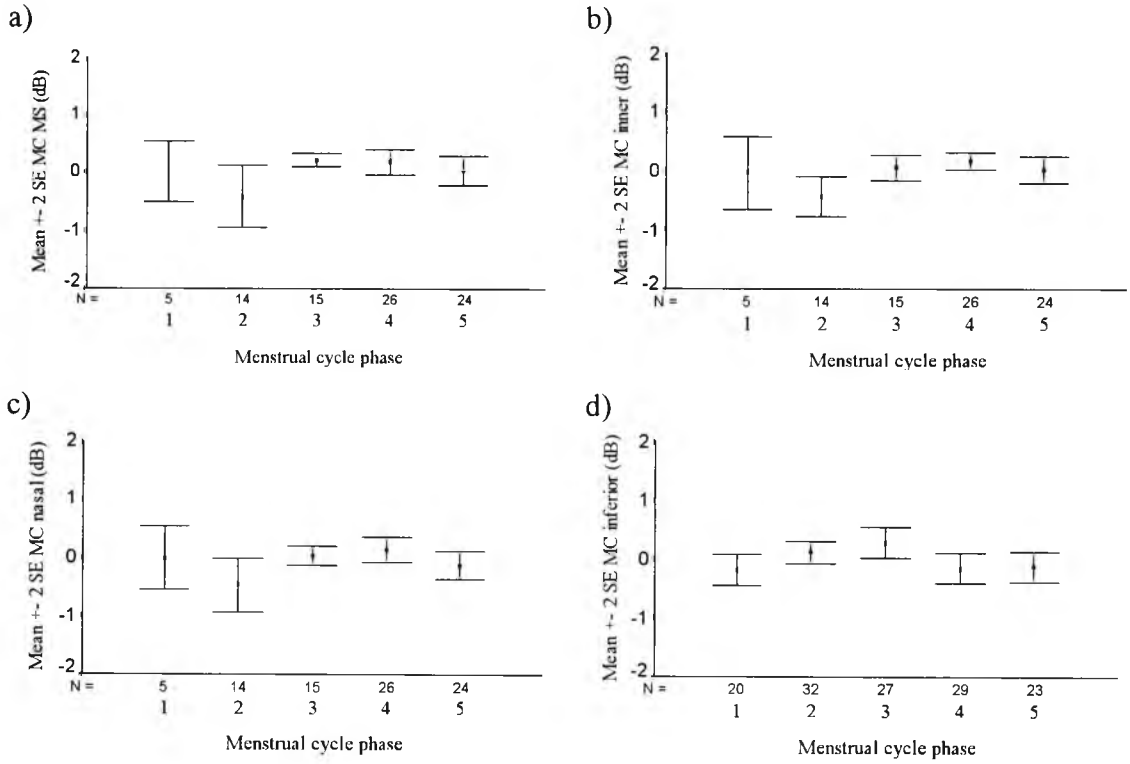


Figure 7.3 Mean change (±2 standard errors) in a) mean sensitivity, b) inner annulus, c) nasal hemifield in cycle 1, and d) inferior hemifield in cycle 2 of the normally menstruating women.

Women taking oral contraceptives (P)

- No significant differences at the 5% level between phases in any variable in any cycle.

Men (M)

- No significant differences at the 5% level across cycle 1 or cycle 3.

- Significant differences in MS (figure 7.4a), all hemifields, middle and outer annuli, time taken (figure 7.4b) and percentage of false negatives across phases of 'cycle' 2. Further statistical details (F values and df) are included in appendix A3.4.5.

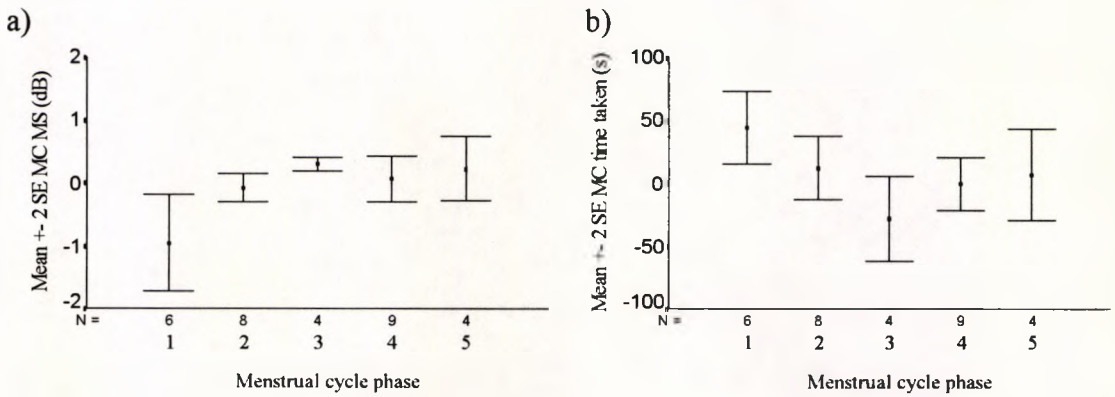


Figure 7.4 Mean change (±2 standard errors) in a) mean sensitivity and b) time taken in 'cycle' 2 of men.

The results in 'cycle' 2 of the men are somewhat unexpected. On closer inspection of individual data it became apparent that one of the male subjects was particularly variable in his responses and contributed several extreme values to the data set. With such small sample sizes these outlying values serve to significantly bias the results. On the removal of this subjects' data and a reanalysis of the remaining data, no significant differences were found between phases. It was assumed therefore that the spurious results of the male subject group were due to this individual.

The heirarchical statistical model yielded much the same results, with no repeatable fluctuations in any variable with menstrual cycle phase.

Time series analysis may be a more appropriate method of analysing data across the menstrual cycle, which is inherently cyclical in nature. The trend in cycle 2, and to a lesser degree in cycle 1, of the F group is for an increase in mean sensitivity around ovulation with lower sensitivity paramenstrually. Although this trend is not significant at the 5% level, there may be an underlying cyclical function to the data.

Exploratory analysis identified the presence of two subjects (one P and one M) in whom the mean sensitivity varied considerably over the study period. As the results of these subjects add noise to the data, and the extreme values may influence the curve fitting, the data for these subjects were removed.

Sine and cosine models with a frequency of 28 days, and a model allowing variable phase in these curves, were fitted across the 84 days encompassing 3 menstrual cycles for all subject groups for MS. In F a cosine curve with a frequency of 28 days significantly fitted the data ($F(1,245)=4.62$, $p=0.03$), indicating an increase in sensitivity mid-cycle with decreases paramenstrually (figure 7.5). None of the models were found to significantly fit the data for the P and M groups at the 5% level. Attempts were made to fit sums of higher frequency sine and cosine waves, but again no significant fits were identified ($p>0.05$).

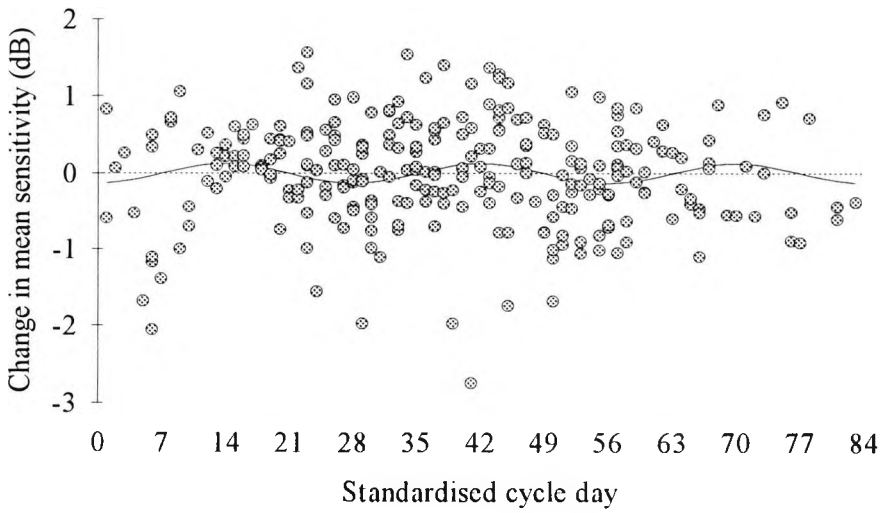


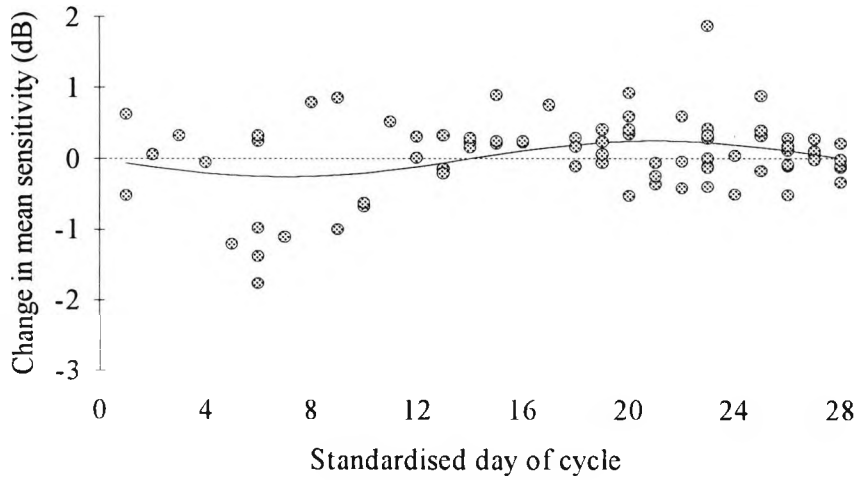
Figure 7.5 Observed change in mean sensitivity over all cycles of normally menstruating women with fitted cosine curve.

Although the cosine fits across the three cycles is significant, inspection of figure 7.5 suggests that this relationship does not account for a high percentage of the variability in the data. Examination of residual sums of squares reveals that only 2% of the variance in the data is explained by a cosine relationship with menstrual cycle day.

To further investigate individual cycles the models were fitted for each cycle separately for each subject group. In cycle 1 of the F group a sine curve was the best significant fitted model ($F(1,65)=6.10$, $p=0.02$) (figure 7.6a). However, this result must be viewed cautiously as there are fewer data points in the first half of the cycle and the spread of the data is generally greater than in the rest of the cycle. In cycle 2 a cosine curve was the best significant fit ($F(1,112)=6.60$, $p=0.01$) (figure 7.6b), indicating an increase in

sensitivity mid-cycle with low points paramenstrually. Again less than 10% of the variability is explained by these curves across either cycle 1 or cycle 2.

a)



b)

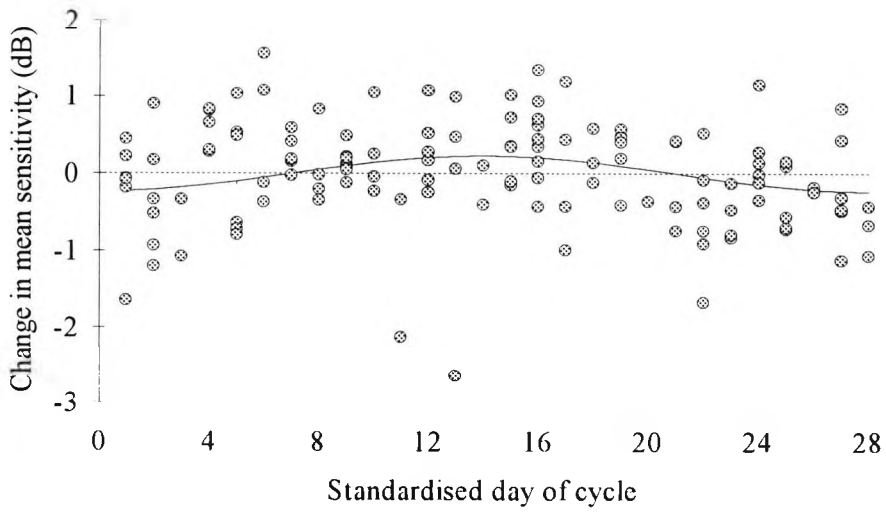


Figure 7.6 Observed change in mean sensitivity (dB) in normally menstruating women with a) fitted sine curve over cycle 1 and b) fitted cosine curve over cycle 2.

A curve of with a frequency of 14 days appeared to significantly fit the data in 'cycle' 2 of the M group ($F(4,16)$, $p=0.04$) (figure 7.7), and explained about 50% of the variance. However, this conclusion must be interpreted with caution as there are only a small number of data points, and this is a probably a spurious result.

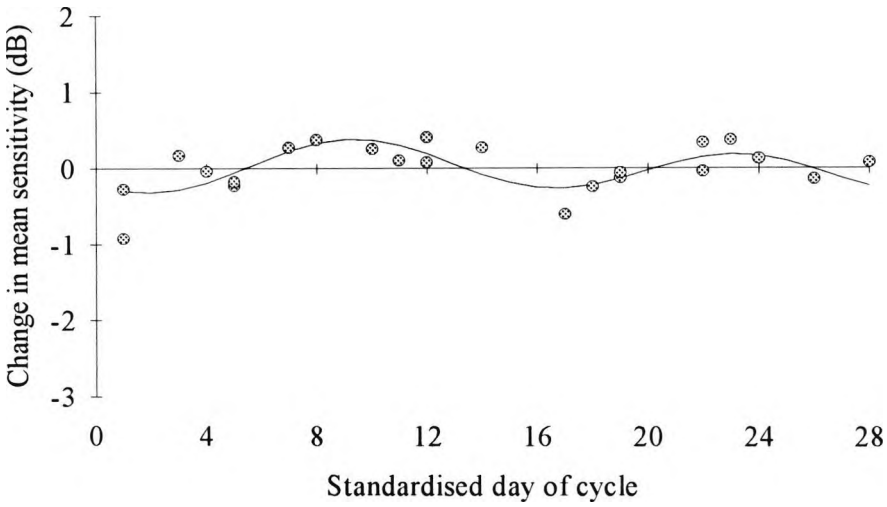


Figure 7.7 Observed change in mean sensitivity over 'cycle' 2 of men with fitted curve.

7.5.2 (ii) Contrast sensitivity

Mean change from baseline values of contrast sensitivity at the five different spatial frequencies were plotted against day of each cycle for all subject groups (appendix 3.4). There was a high degree of inter- and intra-individual variability. A one-way anova and SNK multiple range test was used to test for differences between menstrual cycle phases and identified the following:

Normally menstruating women (F) (figure 7.8)

- Significantly increased contrast sensitivity in the ovulatory phase as compared with the luteal and premenstrual phase at 4cpd ($F(4,25)=2.71$, $p=0.05$) and with all other phases at 0.75cpd ($F(4,25)=4.70$, $p=0.005$) in cycle 1.

- All other comparisons failed to reach significance at the 5% level.

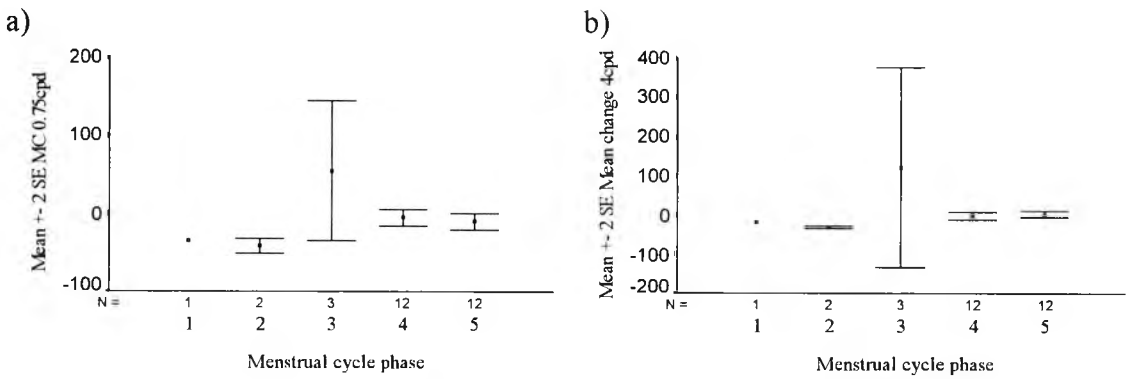


Figure 7.8 Mean change in CSF (±2 standard errors) at a) 0.75cpd and b) 4cpd in cycle 1 of normally menstruating women.

Women taking oral contraceptives (P)

- All comparisons failed to reach significance at the 5% level

Men (M) (figure 7.9)

- Significant difference between phase 4 and phase 2 in CSF at 14cpd in 'cycle' 3 ($F(4,10)=4.3$, $p=0.03$).

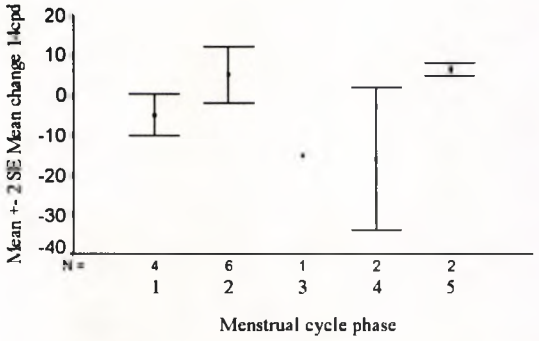


Figure 7.9 Mean change in CSF (±2 standard errors) at 14cpd in 'cycle' 3 of men.

Caution must be taken in the interpretation of the results as the sample sizes associated with these significant differences are very small, particularly in the male subject group.

7.5.2 (iii) Visual acuity

Plots of mean change in logMAR visual acuity at high and low contrast against cycle day for all groups are included in appendix 3.4. One-way anova and SNK were used to test for differences in the change in logMAR visual acuity between menstrual cycle phases. Visual acuity at low contrast was significantly lower (increasingly negative values represent increase in acuity) in the ovulatory phase compared to the premenstrual phase in cycle 2 of the P group ($F(4,56)=3.33$, $p=0.02$) (figure 7.10). All other comparisons failed to reach significance at the 5% level and the heirarchical statistical model failed to identify any repeatable trends in fluctuations in visual acuity across menstrual cycle phase in any subject group.

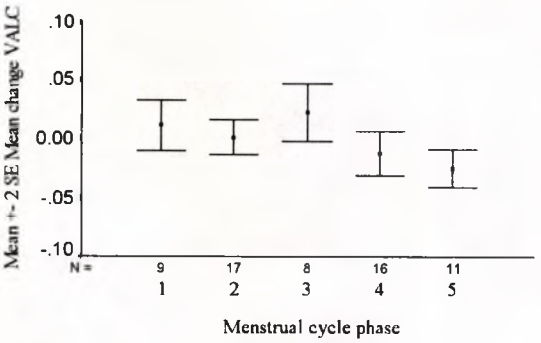


Figure 7.10 Mean change (±2 standard errors) in logMAR low contrast visual acuity in cycle 2 of women taking oral contraceptives.

7.5.3 Pupil diameter

Plots of change in pupil diameter across cycle day for all subject groups are included in appendix 3.4.

The only constant theme in this data was that of a trend for increasing pupil diameter not only across separate cycles in all subject groups, but also across the three cycles. It therefore appeared that pupil diameter increased across the study period as a whole. To investigate this further, the date of each session was numbered, beginning with one on the first day of the study. Change in pupil diameter from baseline values for all subjects was then plotted against this 'date day' to assess changes across the study period (figure 7.11).

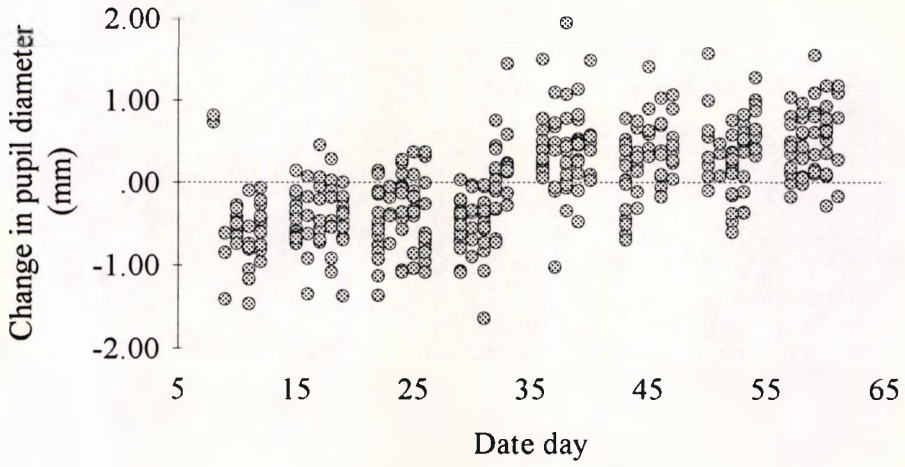


Figure 7.11 Change in pupil diameter across the study for all subjects.

Correlation and regression analysis (table 7.6) identified a significant positive linear relationship between pupil diameter and day of study ($F(1,413)=270.38$, $p<0.0001$), although the R^2 value is low, suggesting a weak correlation. Inspection of the residuals revealed an even scatter of points suggesting that a linear model is appropriate.

On closer inspection of figure 7.11 it appears that rather than a continuous change in pupil diameter across the study, there is an increase about mid-way through the study. Correlation analysis was thus repeated for days up to 32 and again for days beyond 32 (table 7.5). There is no longer any significant linear relationship between study day and pupil size ($p>0.05$) and R^2 values are extremely low.

Table 7.6 Correlation statistics for change in pupil diameter across study in all subjects.

	R^2	*p*-value	gradient
All days	0.4	<0.0001	0.02
Days 1 to 32	0.01	0.1	0.007
Days 33 to 63	0.01	0.07	0.006

Differences in the position of the lens system of the pupillometer would lead to altered magnification, and thus to apparent differences in pupil size. The magnitude of apparent change in pupil size caused by a shift in lens position was investigated by measuring the diameter of a fixed artificial pupil of 5.1mm with the lens focused at infinity and at 1m i.e. in the extremes of lens position. The difference in measured pupil size was 0.9mm. From figure 7.11 it can be seen that the average increase in pupil diameter across the study was around 1mm. The change in pupil diameter mid-way through the study could therefore be due to accidental movement in the lens system of the pupillometer during movement of the instrument at each session to allow CSF measurements.

It may be argued that measurements of pupil diameter over the first half of the study are more accurate, and thus this data alone was used for a subsequent investigation into fluctuations in pupil size with the menstrual cycle. One-way anova failed to identify any significant differences in change in pupil diameter across menstrual cycle phase at the 5% level in any subject group in any cycle.

7.5.4 Questionnaire

In order to investigate overall levels of symptom reporting in the different subject groups, mean scores for the symptoms abdominal pain, backache, irritability, mood swings, an overall positive mood (well being + happy) and an overall pain score (abdominal pain + backache + general aches and pains + headache) were calculated for each subject group (table 7.7).

Table 7.7 Means (standard error) of symptom scores for all subject groups, where * $p<0.001$ significant difference across subject group.

	F	P	M
Abdominal pain*	1.46 (0.04)	1.73 (0.08)	1.05 (0.04)
Backache	1.36 (0.03)	1.44 (0.06)	1.32 (0.07)
Irritability	2.11 (0.05)	2.20 (0.10)	2.20 (0.12)
Mood swings*	1.74 (0.05)	1.83 (0.08)	2.20 (0.12)
Pain*	6.35 (0.10)	7.05 (0.22)	5.64 (0.22)
Positive moods*	10.98 (0.12)	10.76 (0.21)	12.05 (0.32)

A non-parametric one-way anova test (Kruskal-Wallis) identified significant differences in mean symptom scores between subject groups in abdominal pain (χ^2=48.62, df=2, $p<0.001$), mood swings (χ^2=21.32, df=2, $p<0.001$), overall pain (χ^2=31.22, df=2, $p<0.001$) and positive moods (χ^2=20.98, df=2, $p<0.001$). Post-hoc two sample Mann-Whitney U tests were then used in an attempt to identify where these differences lay (Altman 1991). The results were as follows:

- Abdominal pain was significantly greater in both F (Z=-6.086, $p<0.0001$) and P (Z=-7.011, $p<0.0001$) compared to M, and greater in P (Z=-2.45, p=0.01) compared to F.
- Mood swings were significantly greater in M compared to P (Z=-3.826, $p<0.0001$) and F(Z=-4.487, $p<0.0001$) .
- Overall pain scores were greater in F (Z=-5.451, $p<0.0001$) and P (Z=-4.927, $p<0.0001$) than in M.
- Overall positive mood scores were greater in M compared to either F (Z=-4.164$p<0.0001$) or P (Z=-4.551, $p<0.0001$).

For investigation into symptom patterns across the menstrual cycle, change in symptom scores from individuals' baseline scores were calculated for the symptoms of abdominal pain, backache, irritability, mood swings and positive mood score for investigation into fluctuations across the menstrual cycle. Mean values for each menstrual cycle phase in each cycle for all groups were calculated (tables 7.8 to 7.10). Graphical examples are shown in figures 7.12 to 7.14. Plots of mean change in scores of abdominal pain, backache, irritability, mood swings and overall positive mood across standardised cycle day for each subject group are included in appendix A3.4.

Table 7.8 Means (SE) for change in symptom scores across menstrual cycle phase for normally menstruating women, where * $p<0.05$ significant difference in scores across cycle phase, where C1 to C3 represent cycles 1 to 3 respectively.

		Menstrual cycle phase				
		Menstrual	Follicular	Ovulatory	Luteal	Premenstrual
Abdominal pain	C1*	1.05 (0.44)	-0.29 (0.12)	-0.38 (0.06)	-0.18 (0.06)	-0.14 (0.08)
	C2*	0.89 (0.21)	-0.05 (0.09)	-0.19 (0.09)	-0.04 (0.11)	-0.17 (0.08)
	C3*	0.83 (0.24)	0.04 (0.17)	-0.26 (0.09)	-0.17 (0.10)	-0.65 (0.24)
Backache	C1*	0.34 (0.30)	-0.16 (0.10)	-0.25 (0.09)	-0.18 (0.06)	0.05 (0.08)
	C2*	0.86 (0.17)	-0.04 (0.06)	-0.25 (0.05)	-0.09 (0.06)	-0.13 (0.08)
	C3*	0.23 (0.14)	-0.12 (0.09)	-0.08 (0.09)	-0.05 (0.12)	0.76 (0.52)
Mood swings	C1*	0.22 (0.30)	-0.38 (0.14)	-0.05 (0.14)	0.15 (0.10)	0.16 (0.16)
	C2	0.15 (0.12)	0.11 (0.11)	0.00 (0.10)	-0.19 (0.07)	-0.01 (0.11)
	C3	-0.06 (0.13)	0.00 (0.13)	-0.04 (0.21)	-0.29 (0.23)	0.32 (0.72)
Positive mood	C1*	-1.15 (0.93)	1.06 (0.38)	-0.52 (0.37)	-0.19 (0.25)	0.16 (0.27)
	C2	-0.47 (0.31)	-0.05 (0.22)	-0.08 (0.22)	-0.03 (0.25)	0.22 (0.29)
	C3	0.19 (0.24)	0.17 (0.37)	1.22 (0.69)	-0.39 (0.43)	0.20 (0.70)
Irritability	C1*	-0.40 (0.31)	-0.33 (0.23)	-0.35 (0.16)	0.10 (0.15)	0.39 (0.15)
	C2	0.16 (0.18)	-0.22 (0.12)	0.12 (0.14)	0.21 (0.14)	-0.15 (0.14)
	C3	-0.10 (0.17)	0.08 (0.19)	-0.38 (0.22)	0.34 (0.28)	-0.58 (0.49)

Table 7.9 Means (SE) for change in symptom scores across menstrual cycle phase for women taking oral contraceptives, where * $p<0.05$ significant difference in scores across cycle phase, where C1 to C3 represent cycles 1 to 3 respectively.

		Menstrual cycle phase				
		Menstrual	Follicular	Ovulatory	Luteal	Premenstrual
Abdominal pain	C1*	1.24 (0.44)	-0.38 (0.10)	-0.70 (0.10)	-0.56 (0.10)	0.29 (0.28)
	C2*	1.29 (0.33)	-0.17 (0.17)	-0.68 (0.10)	-0.15 (0.21)	0.44 (0.35)
	C3*	2.05 (0.72)	-0.55 (0.34)	0.18 (0.37)	-0.62 (NA)	
Backache	C1*	1.24 (0.40)	-0.28 (0.09)	0.11 (0.21)	-0.21 (0.14)	-0.21 (0.14)
	C2*	0.74 (0.20)	0.11 (0.16)	-0.41 (0.12)	-0.12 (0.09)	-0.02 (0.07)
	C3	0.06 (0.17)	-0.03 (0.35)	-0.62 (0.00)	-0.62 (NA)	
Mood swings	C1	0.44 (0.39)	0.26 (0.28)	0.31 (0.31)	-0.33 (0.17)	-0.30 (0.20)
	C2	0.07 (0.27)	-0.17 (0.21)	-0.23 (0.25)	0.11 (0.22)	0.59 (0.21)
	C3	0.15 (0.39)	-0.56 (0.25)	0.14 (0.80)	-0.66 (NA)	
Positive mood	C1	0.30 (0.64)	0.39 (0.62)	1.25 (0.58)	1.00 (0.50)	-0.51 (0.44)
	C2*	-0.46 (0.51)	-1.10 (0.46)	0.22 (0.54)	0.31 (0.45)	-2.06 (0.60)
	C3*	-0.83 (0.55)	1.97 (0.68)	1.82 (0.49)	4.02 (NA)	
Irritability	C1	0.14 (0.32)	0.22 (0.27)	-0.20 (0.25)	-0.42 (0.17)	0.29 (0.30)
	C2	0.45 (0.28)	-0.37 (0.22)	0.09 (0.28)	0.00 (0.24)	0.44 (0.25)
	C3	-0.24 (0.33)	-0.15 (0.38)	0.31 (0.51)	-1.29 (NA)	

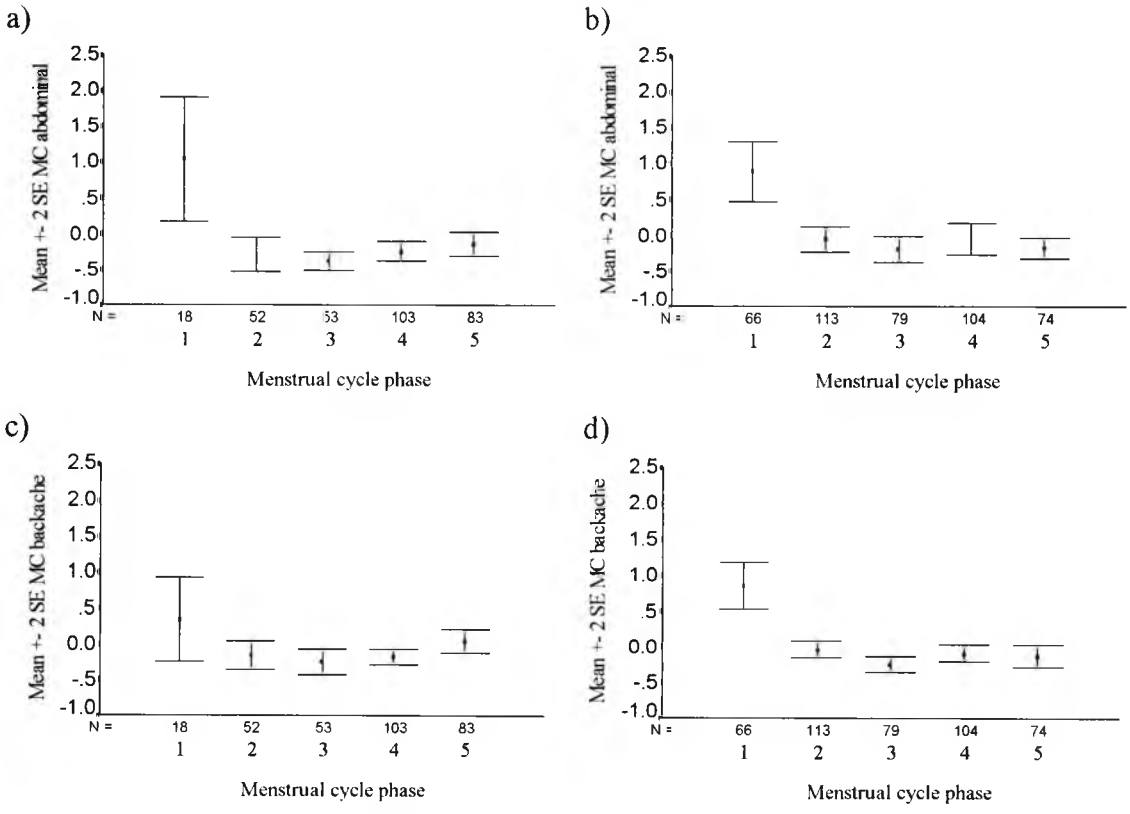
Table 7.10 Means (SE) for change in symptom scores across 'menstrual cycle' phase for men , where * $p<0.05$ significant difference in scores across 'cycle' phase, where C1 to C3 represent 'cycles' 1 to 3 respectively.

		Menstrual cycle phase				
		Menstrual	Follicular	Ovulatory	Luteal	Premenstrual
Abdominal pain	C1	-0.17 (0.00)	-0.11 (0.03)	-0.04 (0.02)	-0.05 (0.02)	0.05 (0.11)
	C2	-0.06 (0.02)	0.23 (0.28)	-0.06 (0.02)	-0.05 (0.01)	0.11 (0.13)
	C3	-0.02 (0.01)	-0.03 (0.10)	-0.07 (0.00)	-0.07 (0.00)	-0.07 (0.00)
Backache	C1	-1.06 (0.33)	0.13 (0.55)	0.39 (0.32)	0.24 (0.20)	0.29 (0.19)
	C2	0.24 (0.31)	-0.20 (0.10)	-0.24 (0.16)	-0.19 (0.08)	-0.05 (0.02)
	C3	-0.05 (0.02)	-0.03 (0.02)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Mood swings	C1	-1.21 (0.67)	0.08 (0.62)	0.41 (0.25)	-0.07 (0.10)	0.17 (0.22)
	C2	0.35 (0.26)	-0.01 (0.12)	0.12 (0.24)	-0.27 (0.16)	-0.13 (0.16)
	C3	0.07 (0.22)	-0.28 (0.14)	-0.19 (0.51)	-0.08 (0.36)	0.71 (0.50)
Positive mood	C1	0.80 (1.53)	-1.38 (0.91)	-0.90 (0.42)	-0.30 (0.46)	0.86 (0.61)
	C2	0.25 (0.52)	0.37 (0.48)	0.10 (0.69)	1.07 (0.47)	-0.33 (0.63)
	C3*	-1.76 (0.39)	0.30 (0.46)	1.45 (1.39)	-1.89 (0.96)	-1.25 (2.50)
Irritability	C1	-0.87 (0.88)	0.20 (0.62)	-0.05 (0.20)	0.09 (0.26)	-0.17 (0.32)
	C2	0.07 (0.18)	0.07 (0.24)	0.44 (0.40)	-0.32 (0.19)	-0.21 (0.11)
	C3	0.41 (0.29)	-0.13 (0.22)	-0.62 (0.68)	0.12 (0.74)	0.48 (0.50)

One-way anova with SNK multiple range test identified the following:

For women with normal menstrual cycles (table 7.8 and figure 7.12):

- Abdominal pain was greater in the menstrual phase than in all other phases cycle 1 ($F(4,304)=11.48$, $p<0.0001$), cycle 2 ($F(4,431)=12.60$, $p<0.0001$) and cycle 3 ($F(4,318)=6.13$, $p<0.0001$).
- Backache was greater in the menstrual phase compared to follicular, ovulatory and luteal phases in cycle 1 ($F(4,304)=3.38$, $p=0.01$) and to all other phases in cycle 2 ($F(4,431)=23.8$, $p<0.0001$). Backache was also greater in the premenstrual phase compared with the follicular, ovulatory and luteal phases in cycle 3 ($F(4,138)=3.04$, $p=0.02$).
- Mood swings were greater in the luteal and premenstrual phase compared with the follicular phase in cycle 1 ($F(4,304)=2.74$, $p=0.03$).
- Irritability was greater in the premenstrual phase compared with the follicular and ovulatory phases in cycle 1 alone ($F(4,304)=3.45$, $p=0.008$).
- Positive mood scores were greater in the follicular phase compared to the menstrual, ovulatory and luteal phases in cycle 1 alone ($F(4,304)=3.58$, $p=0.007$).



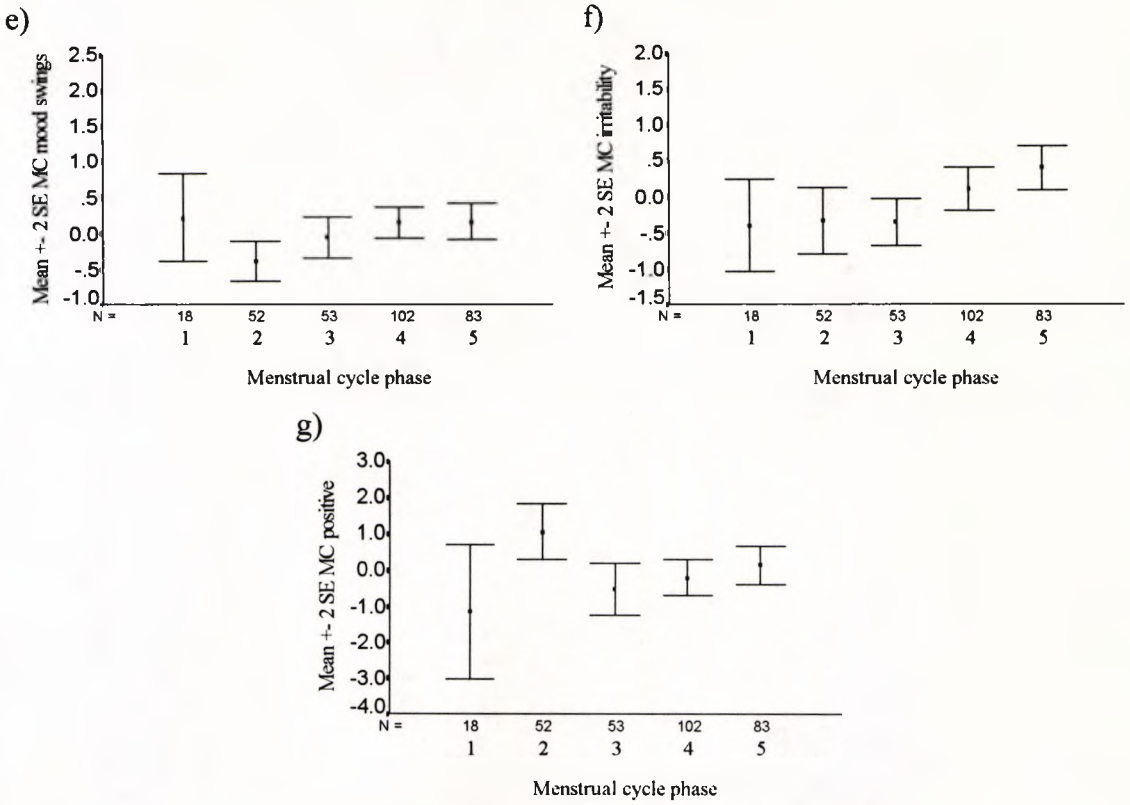


Figure 7.12 Means (± 2 standard errors) of mean change in abdominal pain across a) cycle 1 and b) cycle 2, in backache across c) cycle 1 and d) cycle 2, and in e) mood swings, f) irritability and g) overall positive mood score across cycle 1 in normally menstruating women.

For women taking oral contraceptives (table 7.9 and figure 7.13):

- Abdominal pain was greater in the menstrual compared with all other phases in cycles 1 ($F(4,157)=11.59$, $p<0.0001$) and 2 ($F(4,202)=9.51$, $p<0.0001$), and in the premenstrual phase compared with follicular, ovulatory and luteal in cycle 1, and to the ovulatory phase in cycle 2. In cycle 3 abdominal pain was greater in the menstrual compared with the follicular phase ($F(3,30)=4.57$, $p=0.009$).
- Backache was greater in the menstrual phase compared with all other phases in cycles 1 ($F(4,157)=8.07$, $p<0.0001$) and 2 ($F(4,202)=8.15$, $p<0.0001$), and in the follicular phase compared with all other phases in cycle 2.
- Overall positive mood scores were greater in the ovulatory and luteal phases than in the premenstrual phase in cycle 2 ($F(4,202)=3.44$, $p=0.009$) and in the ovulatory and follicular phases compared to the menstrual phase in cycle 3 ($F(3,30)=4.58$, $p=0.008$).

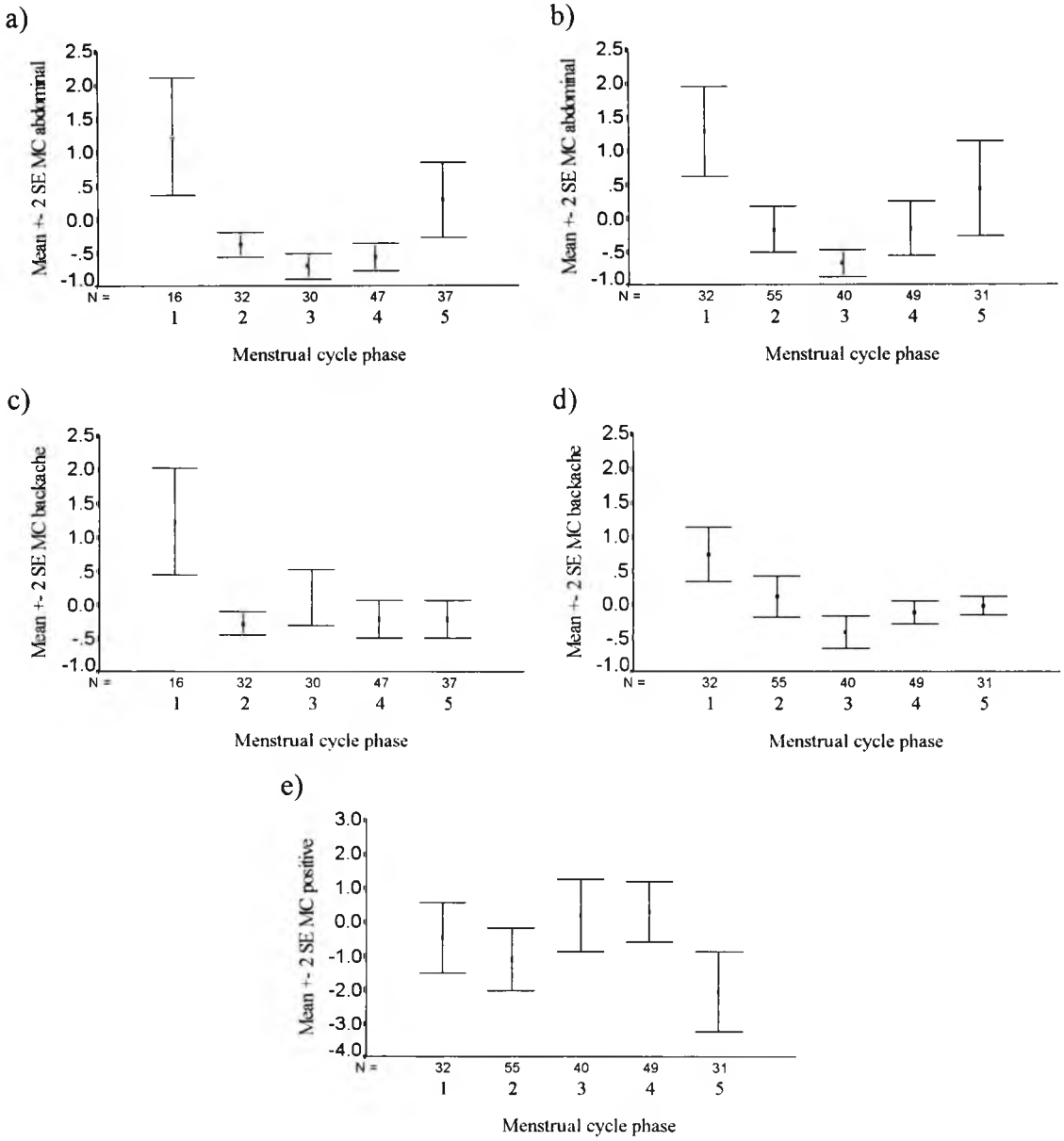


Figure 7.13 Means (±2 standard errors) of mean change in abdominal pain across a) cycle 1 and b) cycle 2, in backache across c) cycle 1 and d) cycle 2, and in overall positive mood score across cycle 2 in women taking oral contraceptives.

For men (table 7.10 and figure 7.14):

- Positive mood scores were greater in the 'follicular' and 'ovulatory' phases compared with the 'menstrual' phase in cycle 3 ($F(4,37)=3.6$, $p=0.002$).

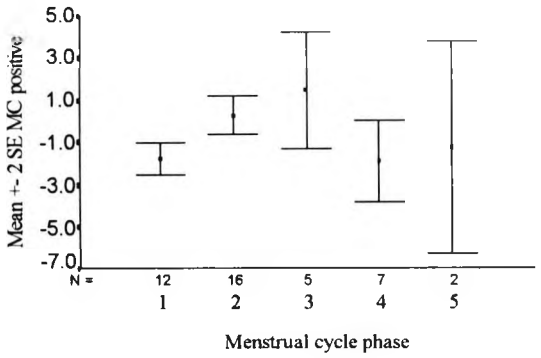


Figure 7.14 Means (±2 standard errors) of mean change in overall positive mood score over 'cycle' 3 in men.

In order to test for instrument stability, i.e. the systematic increase or decrease in symptom reporting over the study period, each subject's days of taking part in the study were coded beginning with day one of inclusion into the study for each individual. Data was then divided into phases of 10 days duration. One-way anova with SNK multiple range test failed to identify any significant differences at the 5% level across time in symptom scores of abdominal pain, backache, irritability, mood swings and overall positive mood score.

7.5.4 Symptomatology and performance

It has been suggested that changes in moods and physical symptoms across the menstrual cycle may be correlated to performance measures (e.g. DeMarchi and Tong 1972). In order to investigate this an overall pain score was computed, together with change from baseline values as before, and a heirarchical anova model was fitted to the data. The number of cigarettes smoked, overall pain score, positive score, mood swings, and irritability were introduced into the model as potential explanatory variables for change in MS and SF of the visual field. No significant correlation between any symptom or behaviour score and either MS or SF were identified.

Symptoms of mood have been shown to fluctuate with day of the week (e.g. Englander et al 1986; McFarlane et al 1988; Mansfield et al 1989), and performance may also change with the day on which the test was undertaken. Thus day of the week was also introduced as an explanatory variable for MS and SF in the statistical model. Again, no significant relationship was found.

7.6 Discussion

7.6.1 Visual performance

Visual Fields

Overall global indices, mean sensitivities of different field regions, and both the time taken and number of questions asked were stable across all three subject groups (table 7.2). This suggests that there are no sex differences, or differences between normally cycling women and those taking OCs, in the results of visual fields as assessed by automated perimetry. In all groups, MS decreased with increasing eccentricity in accordance with previous work (Wild et al 1986, 1987; Wood et al 1986, 1988a; Goldstick and Weinreb 1987; Heuer et al 1989; Flanagan et al 1991; Zulauf 1994) with an overall rate of decline of between -0.15 and -0.18dB per degree. This rate of loss is slightly less than the previously reported range of -0.22dB to -0.44dB per degree over the central 30^{o} (Brenton and Argus 1987; Heuer et al 1989; Zulauf 1994). A possible explanation for this difference lies in the different age ranges of the subjects used, with all the previous studies using older subjects than the present study. Steepening of the perimetric profile is known to occur with increasing age (e.g. Jaffe et al 1986) and hence the rate of decline per degree of eccentricity is likely to be greater in older subject groups.

Mean MD for each subject group ranged between -0.91dB and -1.87dB suggesting reduced threshold sensitivities compared to the normative age-matched subject sample of the HFA. This replicates the result found in the pilot study and reported elsewhere (e.g. Rudnicka 1994) and the same arguments apply (see section 6.5.1). Other global indices are similar to those reported elsewhere for normal subjects for the central 30^{o} field (table 6.8).

Both a simple anova procedure and a heirarchical statistical model failed to demonstrate any repeatable significant differences in any visual field index between menstrual cycle phases across all three cycles.

Significant differences were identified between cycle phases in cycle 1 with MS, and sensitivity of the nasal hemifield and inner annulus being lower in the follicular compared with the luteal phase. In cycle 2 sensitivity in the inferior hemifield is significantly higher in the ovulatory phase compared to the luteal phase. Of note is that the configurations with significant differences include those in which variability might be expected to be lower, as variability increases both with eccentricity (e.g. Heijl et al 1987d, 1989b) and in the superior field (e.g. Katz and Sommer 1986). These differences may be due to real

sensitivity changes associated with the menstrual cycle, to changes in criterion levels across the cycle, to chance fluctuations or to statistical artefacts.

If the changes are directly associated with the menstrual cycle they may be due to the effects of fluctuating hormone levels either on the CNS, or directly upon ocular parameters (Gandelman 1983), or due to some other variable e.g. emotional or physical state. Without direct measurement, the levels of circulating hormones in each cycle phase are not known, and even with this knowledge, a direct causal relationship between hormones and performance can not be assumed. In cycle 1 the sample sizes, particularly in the early phases, are small, thus limiting the conclusions that may be drawn. In cycle 2 where the greatest amount of data was collected and is available for analysis, the trend is for an increase in sensitivity around ovulation, with decreases paramenstrually, although significant differences were only found between the ovulatory and luteal phases. Increases in threshold levels of visual sensitivity around ovulation would be consistent with the general arousal theory of the effects of ovulation on behaviour (Kopell et al 1969). An increase in sensitivity around ovulation has also been reported in previous studies with other visual tasks of TFFT (e.g. Wong and Tong 1974) and dark-adapted visual detection (e.g. Diamond et al 1972), whilst decreases in sensitivity paramenstrually have also been reported in TFFT (e.g. Kopell et al 1969).

It has been suggested that decreases in visual sensitivity paramenstrually may be due to generalised increases in water retention leading to corneal oedema (Ward et al 1978). However, these authors did not attempt to assess corneal oedema and although there is a small body of work assessing corneal parameters across the menstrual cycle, there is insufficient conclusive evidence suggesting a significant increase in corneal oedema paramenstrually.

Curve fitting techniques identified a significant cosine cyclical fluctuation in MS across the three menstrual cycles as a whole in normally menstruating women. Individual cycles also demonstrated significant cyclical change, with a significant sine relationship in cycle 1 and a cosine in cycle 2 of the normally cycling women. The sine fit in cycle 1 must be viewed with some caution however, as there are fewer data points in the first half of the cycle. The cosine relationship with a 28 day phase over the three cycles together, and in cycle 2 alone, i.e. the cycle with the most data, supports a conclusion of increase in sensitivity around ovulation with low points occurring menstrually and premenstrually. There is therefore evidence in favour of an effect of the menstrual cycle on MS, however, only about 2% of the variance in MS is explained by menstrual cycle day, with other factors influencing sensitivity to a greater degree. A curve with a frequency of 14 days explaining 50% of the variance in 'cycle' 2 of the men is likely to be spurious due to the small number of data points available.

The difference between the peak mean sensitivity mid-cycle, or in the ovulatory phase and the lowest points paramenstrually is actually less than 0.5dB. It has been suggested that a change in sensitivity of at least 4dB is required before any clinical change in sensitivity can be detected (Werner et al 1987; Hoskins et al 1988). Hence it is unlikely that any fluctuation in sensitivity across the menstrual cycle is clinically significant.

Automated perimetry is a highly criterion dependent test, and as such, apparent changes in sensitivity may be due to alterations in a subjects' criterion levels at different phases of the menstrual cycle rather than a true sensitivity change, i.e. a woman may become more cautious in certain phases of the cycle. Previous studies have reported both changes in criterion levels (DeMarchi and Tong 1970; Wong and Tong 1974) and in sensitivity (Braier and Asso 1980) across the menstrual cycle using criterion-free methods for finding threshold. It is impossible to separate criterion and true sensitivity change in automated perimetry, although masking of the study may have minimised any menstrual cycle related criterion changes due to stereotypical beliefs of patterns in performance levels across the cycle.

It was proposed that the presence of a fluctuation in visual field performance across the menstrual cycle could potentially confound the interpretation of automated perimetric results, particularly where repeated assessment is necessary e.g. in glaucoma patients and suspects. As any fluctuation that may be associated with the menstrual cycle is in the order of 0.5dB, it is highly unlikely that this would be sufficient to lead to misinterpretation of the results of automated perimetry. Additionally other global indices and reliability parameters were not found to fluctuate significantly with menstrual cycle phase.

Contrast Sensitivity

High spatial frequencies are affected by optical aberrations and are thus highly correlated to visual acuity (Moseley and Hill 1994). Contrast sensitivity may be reduced at low and intermediate spatial frequencies, even though visual acuity is normal (Arden 1988). Defects in CSF at low spatial frequencies are due to either neurological causes or to scattering in the visual pathway, with simple optical aberrations not affecting these frequencies (Arden 1988). Differences between responses at different spatial frequencies may therefore aid in the identification of the locus of any change within the visual system across the menstrual cycle.

No repeatable fluctuations in CSF at any of five different spatial frequencies were identified across the menstrual cycle. In cycle 1 of the normally menstruating women CSF at 0.75cpd and 4cpd was higher in the ovulatory phase than in the rest of the cycle.

Confidence limits for CSF measurement were generally wide, and varied between different spatial frequencies (table 7.1), suggesting an overall poor level of repeatability in this test. Fatigue effects may have influenced the data as CSF was always the last subjective task to be performed. Both the poor repeatability and the small sample sizes mean that any conclusions must be drawn cautiously. It appears unlikely that CSF at these spatial frequencies is generally increased in all women around ovulation, but it may be that some individuals do demonstrate this sort of fluctuation and this is being highlighted by the small sample sizes.

The results of the present study fail to support previous reports where increases in contrast sensitivity have been found in the post-ovulatory phase (Dunn and Ross 1985), and at several points across the menstrual cycle (Johnson and Petersik 1987). However, both studies limited data collection to one menstrual cycle and subjects were aware of the study focus. Differences in the method of finding threshold may also contribute to these differences.

Visual acuity

The 95% confidence limits for the Bailey-Lovie high and low contrast charts were found to be approximately ±0.1 log units i.e. a subject's acuity must change by at least one line of letters for the change to be considered clinically significant at the 95% probability level. This is a somewhat better repeatability than the previously reported ±2 lines for high contrast charts (Reeves et al 1991; Lovie-Kitchin 1988). However, all subjects included in the present study had Snellen visual acuities of at least 6/6 and low refractive errors, whilst those in the previous studies had a much wider range of acuities and refractive errors, and this may explain the differences found. In support of this, Elliott and Sheridan (1988) have reported repeatabilities of ±0.2 (2 lines) and ±0.07 (3.5 letters) in normal subjects with uncorrected and corrected refractive errors between ±6.00DS respectively, using similar logMAR letter charts.

No significant fluctuation in visual acuity at high or low contrast was found across the menstrual cycle of normally menstruating women. Low contrast VA was significantly worse in the ovulatory phase compared to the premenstrual phase in cycle 2 of the P group. However, the difference between the peak VA and lowest point is 0.05 log units. This is well within the repeatability found for the chart and is therefore not a clinically significant change.

Despite the use of two different versions for the high and low contrast letter charts, there was still a tendency for subjects to memorise the letters, with subjects having to read the charts up to eight times each. For the assessment of VA in this type of longitudinal study

the use of many more charts with different letters, or the random projection presentation of letters would be recommended. However, the usefulness of measuring visual acuity across the menstrual cycle using optotypes is questionable as changes in acuity are unlikely to be greater than a line of letters (usually 5 letters) and thus within the confidence limits of the instrument, i.e. menstrual cycle variations are not discernible from long-term fluctuations.

7.6.2 Pupil diameter

Instrument error mid-way through the study caused an apparent increase in pupil diameter. Data from the first half of the study was analysed with respect to the menstrual cycle. There was no significant change in pupil diameter across the menstrual cycle in any subject group. This supports the conclusion of Barris et al (1980) who found no change in pupil diameter across the ovulatory phase of normally menstruating women. It is also in agreement with an increasing number of reports that have failed to identify appreciable alterations in ANS arousal states across the menstrual cycle as measured by EDA (e.g. Kopell et al 1969; Zimmerman and Parlee 1973; Strauss et al 1983) and HR (Doty et al 1981; Ussher and Wilding 1991).

7.6.3 Questionnaire

There were large inter-individual variations in symptom reporting throughout the study, and overall levels of reporting differed between subject groups for different symptoms. Women in general complained of more pain, particularly abdominal pain, than men, with women taking OCs reporting more abdominal pain than women with normal cycles. This difference between men and women is not unexpected as the questionnaire was intended to tap menstrual cycle related symptomatology and thus these physical symptoms would be expected to be greater in women. It is more difficult to explain the difference between women taking OCs and those with normal cycles. It has been suggested that the use of oral contraceptives may reduce physical symptoms associated with the menstrual cycle, in particular 'period-like pain' (e.g. Wilcoxon et al 1976; Bancroft 1993), however, this study fails to support these reports, finding greater reports of pain in women taking OCs. With small subject sample sizes the responses of single individuals may significantly bias the results and this is a possible explanation.

Of additional interest is that men overall report both more mood swings and a greater degree of positive moods (well-being and happiness) than either female group. No differences were found between groups for irritability and backache. These results support in part previous reports where, across the study in general, fluctuations in mood experienced by women were found to be no greater than those by men (e.g. Wilcoxon et

al 1976) and adds weight to the argument that women do not experience generally greater emotional instability than men.

Repeatable patterns of fluctuation were found across the menstrual cycle in pain, particularly abdominal pain, for all women, both with or without the use of OC (figures 7.12 to 7.13). Pain increased significantly in the menstrual phase compared with other phases for all women. This pattern of change in pain across the menstrual cycle is concurrent with previous reports (e.g. Slade 1984; Beck et al 1990). Subjects were unaware of the purpose of the study, and in particular of the saliency of the menstrual cycle, and hence it is unlikely that this pattern is due to the reporting of stereotypical beliefs about menstrual cycle symptomatology. Of interest is that in women taking OCs abdominal pain is also a feature of the premenstrual phase.

In cycle 1 of the normally menstruating women there are significant fluctuations in mood swings, irritability and overall positive mood across menstrual cycle phase (table 7.8 and figure 7.12). These trends follow the recognised stereotypical pattern of increases in negative mood premenstrually and in positive mood intermenstrually. Although this pattern was repeated in some of the symptoms in other cycles, and in some cycles of those women taking oral contraceptives, it was not consistent across all the symptoms and the differences were not significant at the 5% level. These differences between cycles may be explained by varying symptom patterns in separate cycles of the same individual, and serve to highlight the necessity of collecting data over more than one cycle. External factors such as stressful life experiences may also influence menstrual symptomatology (Wilcoxon et al 1976; Woods et al 1985) in a particular cycle. Another explanation may be the presence of an order effect, such that subjects reported their symptoms more accurately at the start of the study i.e. in cycle 1, before a degree of instrument deterioration, perhaps born of a boredom effect, took place. However, an investigation into the stability of symptom reporting revealed no alteration of ratings with time. The subject group consisted of young, healthy, normally menstruating women and other studies (Lahmeyer et al 1982; Baisden and Gibson 1975; Markum 1976; Ward et al 1978; Slade 1981,1984; Dye and Hindmarsh 1991), including the pilot study in this thesis (section 6.4.2), have reported few changes in emotional symptoms across the menstrual cycle in similar subject groups. The overall conclusion must therefore be of no repeatable trend in fluctuation in symptoms of mood swings, irritability, or in positive moods across the menstrual cycle in either female subject group.

Significant differences between phases were also identified in symptom scores of overall positive mood in the male control group in 'cycle' 3. This is likely to be due to chance variations which are more apparent in small sample sizes where extreme responses from individuals may bias the results considerably. As can be seen from figure 7.14 the sample

sizes for the male subject group for cycle 3 are particularly small. Additionally by chance 5% of comparisons will be significant and this unexpected result may be due to a type I error.

Changes in self-reported moods and behaviour may be also related to fluctuations in visual performance. Mean sensitivity and SF of the visual field were not found to be significantly correlated with scores of number of cigarettes smoked, overall pain score, positive mood, mood swings and irritability in this study. This is in agreement with previous work that failed to find an association between CFFT performance and symptomatology (Dye 1989). Visual field performance was also found to be independent of day of the week.

7.6.4 General discussion

Overall, few repeatable significant differences were identified in visual performance as measured by automated perimetric assessment of the visual field, contrast sensitivity and visual acuity, across all of three consecutive menstrual cycles. There is some evidence to suggest a menstrual cycle related fluctuation in the mean sensitivity of the visual field, with an increase in sensitivity mid-cycle and decreases in the premenstrual and menstrual phases, with a significant cosine relationship found across the 84 days comprising all three cycles. However, any conclusions must be drawn cautiously. There was a large degree of inter- and intra-subject variability and only around 2% of the variability in MS could be explained by this cosine relationship with menstrual cycle day. Additionally the change in MS across the cycle was in the order of 0.5dB and is therefore well within normal limits, and would not be considered clinically significant. This degree of fluctuation is also unlikely to lead to the misinterpretation in the assessment of the results of automated perimetry for pathological field change.

There were no repeatable fluctuations in visual performance across the menstrual cycle in either control group. Women taking oral contraceptive preparations do experience a 'menstrual cycle', albeit pharmacologically controlled, and thus experience different hormone levels to normally cycling women. Early studies of visual performance across the menstrual cycle using women on OCs as control subjects have generally reported no change in performance for these women compared to cycle related fluctuations in women with normal cycles (Wong and Tong 1974; Lanfair and Smith 1974; Friedman and Meares 1978; Becker et al 1982). However, more recent work has identified similar patterns of change in visual performance across the menstrual cycle in these two groups (Dye 1989, 1991). Dye suggests that the high proportion of women in the study using triphasic preparations, and thus experiencing hormonal fluctuations, may explain the similarity in performance patterns between the OC users and normally cycling women.

In the present study three women were taking triphasic and five were taking combined OCs. Attempts were not made to analyse the results of these subjects separately as there would be insufficient data in each group to allow any firm conclusions to be drawn.

The failure in this study to identify a generalised fluctuation in visual performance with the menstrual cycle does not necessarily imply that this type of effect does not exist. There is considerable lack of agreement in the results of previous studies assessing different visual performance measures across the menstrual cycle (see section 1.4 and table 1.2), and it has been suggested that fluctuations in visual sensitivity across the menstrual cycle are task specific (Ward et al 1978; Scher et al 1985), with some tasks failing to demonstrate changes across the cycle, while others demonstrate peaks in sensitivity in different phases.

There may also be a small number of women whose behaviour may be 'consistently and markedly' affected by hormonal variations across the menstrual cycle (Sommer 1980). In a generalised study, the responses of these individuals may be masked by those of the majority in whom no change in performance is apparent.

Female subjects in this study were selected for their reported normal regular 28 day menstrual cycles. Subjects were also young, predominantly nulliparous and all were university students. This biases the subject population toward the 'normal' menstrual cycle experience and is far from a typical section of the general female population. Also subjects were not screened for PMS or menstrual symptomatology. It may be that older or parous women, women with more irregular cycles, or those with higher levels of emotional or physical symptomatology fluctuations across the cycle may in some way be more likely to experience menstrual cycle fluctuations in visual performance. This study did not address this issue. Indeed Strauss and Appelt (1983 p.219) have commented that 'it is doubtful that a representative sample can be defined with respect to the menstrual cycle'.

Although the sample size used in this study is much larger than that of most studies in this area (see table 1.2), it is still relatively small, and whilst a larger sample would have improved the design, practical constraints were a limiting factor.

In agreement with the pilot study (Chapter 6) different patterns of fluctuation in visual performance are found across individual menstrual cycles. This again highlights the necessity of taking data over at least two cycles before any conclusions can be drawn. Indeed, if the results from one cycle alone had been presented the overall conclusions would be quite different. The majority of previous studies on visual performance measures across the menstrual cycle have reported data from one cycle alone (table 1.2),

and it may be argued this is insufficient data from which to draw conclusions about menstrual cycle fluctuations in these parameters.

7.7 Summary

There is some evidence to suggest that there is a statistically significant fluctuation in mean sensitivity of the central visual field, with an increase in sensitivity mid-cycle and decrease paramenstrually. However, the maximum fluctuation due to this relationship is in the order of 0.5dB, and hence this is not a clinically significant change in visual field sensitivity.

Overall there appears to be insufficient evidence to reject the null hypothesis of no change in contrast sensitivity, visual acuity or pupil diameter across the menstrual cycle.

Whilst self-report measures of physical symptoms, e.g. abdominal pain, fluctuated across menstrual cycle phase and were generally increased paramenstrually in all women, changes in emotional symptoms, e.g. mood swings and irritability, were not associated with menstrual cycle phase. Women in general did not report any more emotional symptoms than men.

Fluctuations in visual field performance were not significantly correlated with changes in mood, physical symptoms, number of cigarettes smoked, or with the day of week.

CHAPTER 8

Conclusions and future work

8.1 Conclusions

Threshold visual sensitivity as measured by research-based tools has been reported to fluctuate over the menstrual cycle (section 1.4). However, in this study using predominantly clinical methods, there was little evidence for a repeatable clinically significant fluctuation in the visual field as measured by automated perimetry, sine-wave grating contrast sensitivity, visual acuity at high and low contrast, or in pupil diameter across the normal menstrual cycle. It therefore appears unlikely that fluctuations in visual performance are a contributory factor for the changes in accident rates reported with menstrual cycle phase.

There is some evidence for a statistically significant fluctuation in mean sensitivity in the visual field across the menstrual cycle in normally menstruating women, with an increase mid-cycle and decrease paramenstrually. However, only a small proportion of the variability in sensitivity is explained by menstrual cycle day, and the fluctuation is well within normal limits and is not of clinical significance. Additionally a greater proportion of the variance was explained by a curve fitted to one of the 'cycles' in the men, and although likely to be a spurious result, highlights the lack of firm conclusions that can be drawn. This is a positive result for women in general, and fails to support popular theories of a debilitation in performance paramenstrually.

The different patterns of fluctuation in performance measures found across individual menstrual cycles in the present studies highlight the necessity of taking data over at least two cycles before any conclusions can be drawn.

The young, normally menstruating women who comprised the study groups prospectively reported few significant fluctuations in symptomatology across the menstrual cycle. Physical symptoms, e.g. abdominal pain, were generally increased paramenstrually, but changes in emotional symptoms, e.g. mood swings and irritability, were not associated with menstrual cycle phase. Women in general did not report any more emotional symptoms than men.

Self-reported levels of mood and physical state, the number of cigarettes smoked and the day of the week on which the tests were carried out did not appear to significantly influence visual performance in this sample of subjects.

8.2 Future work

From the results of the curve-fitting techniques there may be reason to suspect that there is a fluctuation in mean sensitivity of the visual field across the normal menstrual cycle that follows a cosine curve, with a peak mid-cycle and low points paramenstrually. However, much larger subject samples followed over several menstrual cycles, with the continued use of control groups, are necessary before any firm conclusions can be drawn. Of particular interest would be the use of different subject groups, comprising a more generally representative sample of the female population as a whole. These subjects might include older and/or parous women, those experiencing menstrual cycle related emotional and/or physical symptom changes and women with irregular cycles. Other groups of women with different hormonal fluctuations, e.g. women taking hormone replacement therapies or those taking different OC preparations (i.e. triphasic and combined), would also provide additional scope for further study.

Despite a reasonable body of research on both visual and ocular physiological changes across the menstrual cycle, little work has examined these in conjunction with each other. Useful information may be obtained from studies combining both visual performance measures and objective measures of ocular parameters, and investigating the strength of any relationships between them. In particular it has been suggested that corneal oedema may be the locus of change for the decrease in visual detection sensitivity found premenstrually (Ward et al 1978). There is evidence to suggest that the cornea may be an oestrogen sensitive tissue and the examination of corneal parameters in conjunction with measurement of visual sensitivity may allow some hypothesis about the locus of any change in visual thresholds with the menstrual cycle within the visual system.

Future work in this area might also include direct measurement of hormone levels, not only to detect accurately whether a cycle is ovulatory, but also to allow further discussion into the relationship between visual performance and hormonal fluctuations across the cycle.

Changes in criterion levels may complicate the interpretation of results of menstrual cycle related study, and clinical tests in particular are highly criterion dependent. Further use of criterion-free measurement techniques, e.g. the use of forced-choice methods, for

finding threshold may elicit more useful information about any fluctuations in visual performance across the cycle.

There is still no one standard methodology for menstrual cycle research. This area of research is fraught with complicating factors to be taken into consideration in the planning of such a study. It is time consuming, and practical and logistical constraints are often a limiting factor in study design. However, it is useful and worthwhile research, that continues to provide information about the effect of the normal menstrual cycle, and other gynaecological states, on women's performance and on central nervous system activity. The publication of an increasing number of 'negative' results, and of fluctuations in performance being within normal limits, may also help to dispel the myths and stereotypical views of a substantial fall in performance levels paramenstrually.

APPENDICES

Appendix A1 Menstrual Distress Questionnaire

A1.1 Form T

Name _____ Today's Date _____

The following is a list of common symptoms and feelings. For each item check the box for the category that best describes your experience today. Even if none of the categories is exactly correct, choose the one that best describes your experience. Please be sure to check one box for each item. Remember to fill in your name and today's date in the spaces at the top of this page.

	None	Present Mild	Present Moderate	Present Strong	Present Severe
	0	1	2	3	4
1. Muscle stiffness	☐	☐	☐	☐	☐
2. Weight gain	☐	☐	☐	☐	☐
3. Dizziness, faintness	☐	☐	☐	☐	☐
4. Loneliness	☐	☐	☐	☐	☐
5. Headache	☐	☐	☐	☐	☐
6. Skin blemish or disorder . . .	☐	☐	☐	☐	☐
7. Cold sweats	☐	☐	☐	☐	☐
8. Anxiety	☐	☐	☐	☐	☐
9. Mood swings	☐	☐	☐	☐	☐
10. Cramps	☐	☐	☐	☐	☐
11. Painful or tender breasts . .	☐	☐	☐	☐	☐
12. Nausea, vomiting	☐	☐	☐	☐	☐
13. Crying	☐	☐	☐	☐	☐
14. Backache	☐	☐	☐	☐	☐
15. Swelling (breasts, abdomen) .	☐	☐	☐	☐	☐
16. Hot flashes	☐	☐	☐	☐	☐
17. Irritability	☐	☐	☐	☐	☐
18. Tension	☐	☐	☐	☐	☐
19. Fatigue	☐	☐	☐	☐	☐
20. Feeling sad or blue	☐	☐	☐	☐	☐
21. General aches and pains . . .	☐	☐	☐	☐	☐
22. Restlessness	☐	☐	☐	☐	☐

		None 0	Present Mild 1	Present Moderate 2	Present Strong 3	Present Severe 4
23.	Insomnia	☐	☐	☐	☐	☐
24.	Poor school or work performance	☐	☐	☐	☐	☐
25.	Affectionate	☐	☐	☐	☐	☐
26.	Feelings of suffocation	☐	☐	☐	☐	☐
27.	Forgetfulness	☐	☐	☐	☐	☐
28.	Take naps, stay in bed	☐	☐	☐	☐	☐
29.	Orderliness	☐	☐	☐	☐	☐
30.	Chest pains	☐	☐	☐	☐	☐
31.	Confusion	☐	☐	☐	☐	☐
32.	Poor judgment	☐	☐	☐	☐	☐
33.	Stay at home	☐	☐	☐	☐	☐
34.	Excitement	☐	☐	☐	☐	☐
35.	Ringing in the ears	☐	☐	☐	☐	☐
36.	Difficulty concentrating	☐	☐	☐	☐	☐
37.	Avoid social activities	☐	☐	☐	☐	☐
38.	Feelings of well-being	☐	☐	☐	☐	☐
39.	Heart pounding	☐	☐	☐	☐	☐
40.	Distractable	☐	☐	☐	☐	☐
41.	Decreased efficiency	☐	☐	☐	☐	☐
42.	Bursts of energy, activity	☐	☐	☐	☐	☐
43.	Numbness, tingling	☐	☐	☐	☐	☐
44.	Minor accidents	☐	☐	☐	☐	☐
45.	Blind spots, fuzzy vision	☐	☐	☐	☐	☐
46.	Poor motor coordination	☐	☐	☐	☐	☐
47.	Increased appetite	☐	☐	☐	☐	☐
48.	Do you have your period (menstrual flow) today?	☐ Yes		☐ No		

A1.2 Form C

Menstrual Distress Questionnaire

Form C

Name _____ Marital Status _____

Age _____ Number of children _____

Today's Date _____ Occupation _____

Write the approximate dates of your most recent menstrual period (flow) in the space marked "A" below. Then write the dates of the menstrual period which preceded the most recent one in the space marked "D".

previous menstrual flow			most recent flow
from _____	other times during most recent cycle	four days before most recent flow	from _____
to _____			to _____
D	C	B	A

On the next two pages is a list of symptoms that women sometimes experience. Please describe your experience of each of these symptoms during the three time periods listed below:

Col. 1 during your most recent menstrual flow (the dates shown in area A on the diagram above),

Col. 2 during the four days before your most recent menstrual flow (area B on the diagram),

Col. 3 during the remainder of your most recent menstrual cycle (area C).

Note: The answers you put in columns 1, 2, and 3 should be accurate for your experience during your most recent menstrual cycle. Please do not report your general experience. Also, please report any experience of these symptoms whether or not they seem to you to be related to your menstrual cycle.

For each answer choose the category that best describes your experience of that symptom during that time. Write the number of that category in the space provided. Even if none of the categories is exactly correct, choose the one that best describes your experience. Do not leave any blank spaces.

Descriptive Categories

0 - No experience of symptom
1 - Present, mild
2 - Present, moderate
3 - Present, strong
4 - Present, severe

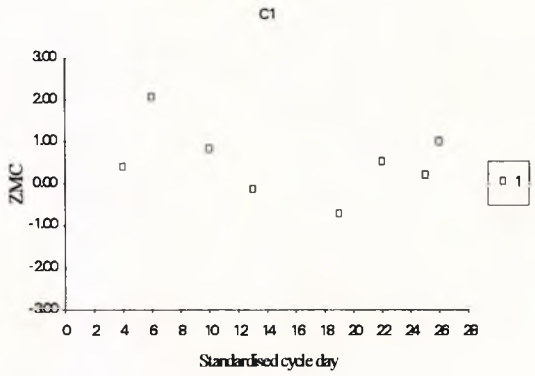
	1 Most recent flow (A)	2 Four days before (B)	3 Remainder of cycle (C)
1. Muscle stiffness	___	___	___
2. Weight gain	___	___	___
3. Dizziness, faintness	___	___	___
4. Loneliness	___	___	___
5. Headache	___	___	___
6. Skin blemish or disorder	___	___	___
7. Cold sweats	___	___	___
8. Anxiety	___	___	___
9. Mood swings	___	___	___
10. Cramps	___	___	___
11. Painful or tender breasts	___	___	___
12. Nausea, vomiting	___	___	___
13. Crying	___	___	___
14. Backache	___	___	___
15. Swelling (breasts, abdomen)	___	___	___
16. Hot flashes	___	___	___
17. Irritability	___	___	___
18. Tension	___	___	___
19. Fatigue	___	___	___
20. Feeling sad or blue	___	___	___
21. General aches and pains	___	___	___
22. Restlessness	___	___	___

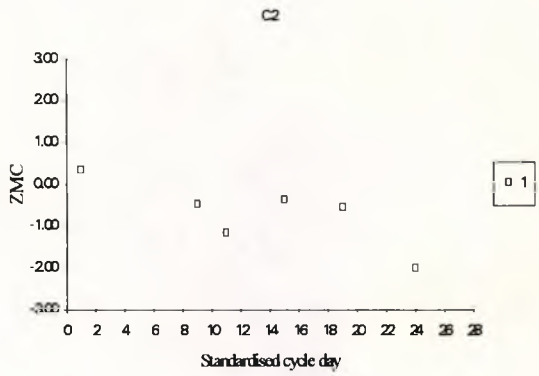
		1 Most recent flow (A)	2 Four days before (B)	3 Remainder of cycle (C)
23.	Insomnia	___	___	___
24.	Poor school or work performance	___	___	___
25.	Affectionate	___	___	___
26.	Feelings of suffocation	___	___	___
27.	Forgetfulness	___	___	___
28.	Take naps, stay in bed	___	___	___
29.	Orderliness	___	___	___
30.	Chest pains	___	___	___
31.	Confusion	___	___	___
32.	Poor judgment	___	___	___
33.	Stay at home	___	___	___
34.	Excitement	___	___	___
35.	Ringing in the ears	___	___	___
36.	Difficulty concentrating	___	___	___
37.	Avoid social activities	___	___	___
38.	Feelings of well-being	___	___	___
39.	Heart pounding	___	___	___
40.	Distractable	___	___	___
41.	Decreased efficiency	___	___	___
42.	Bursts of energy, activity	___	___	___
43.	Numbness, tingling	___	___	___
44.	Minor accidents	___	___	___
45.	Blind spots, fuzzy vision	___	___	___
46.	Poor motor coordination	___	___	___
47.	Increased appetite	___	___	___

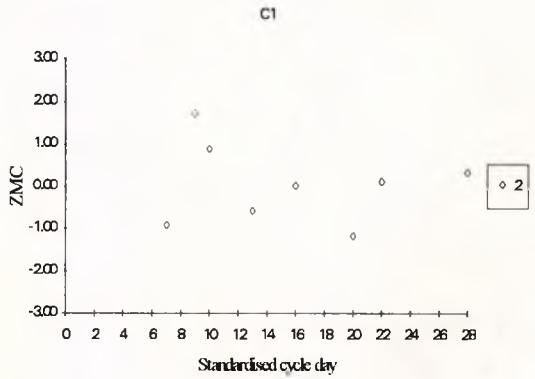
In what ways, if any, was your most recent menstrual cycle unusual?

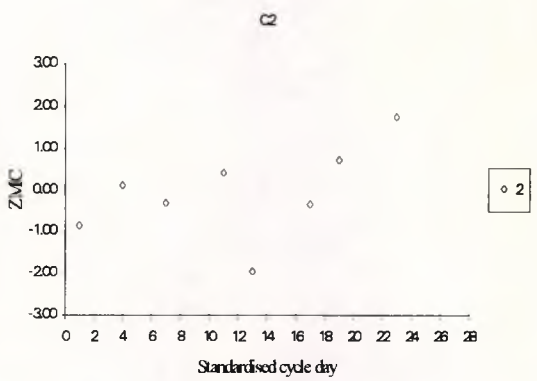
Appendix A2 Individual plots of ZMC against cycle phase

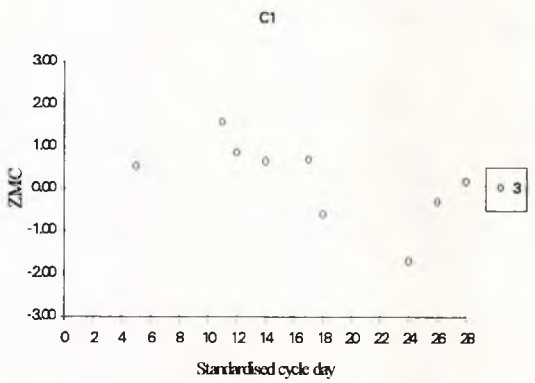
A2.1 Central 30-2

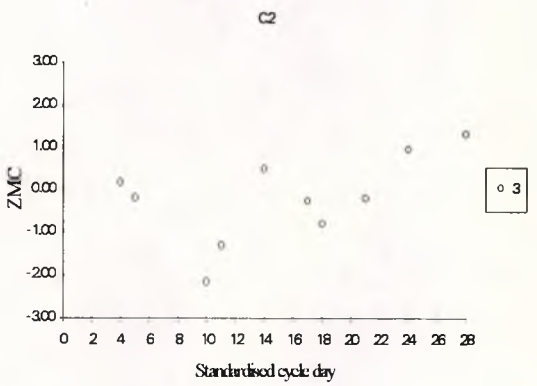


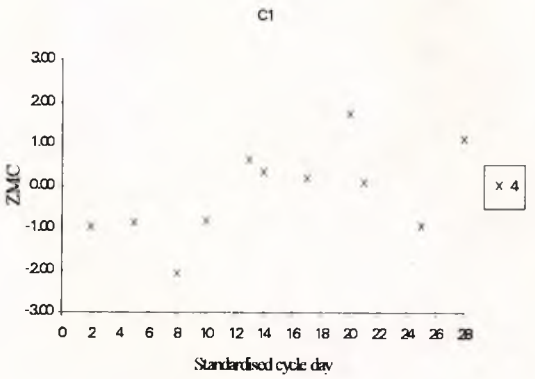


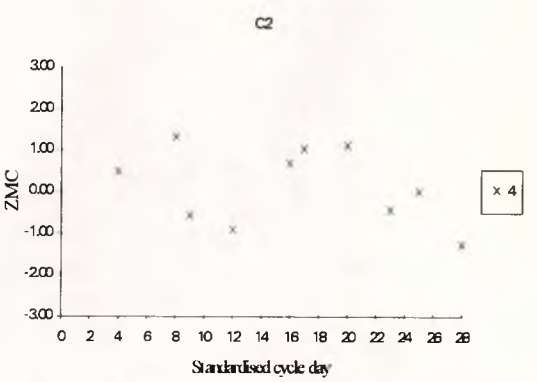


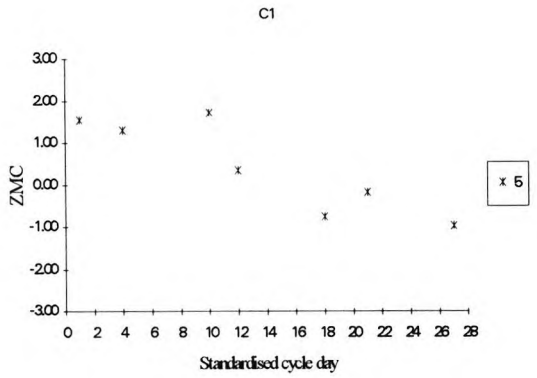








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Standardised cycle day
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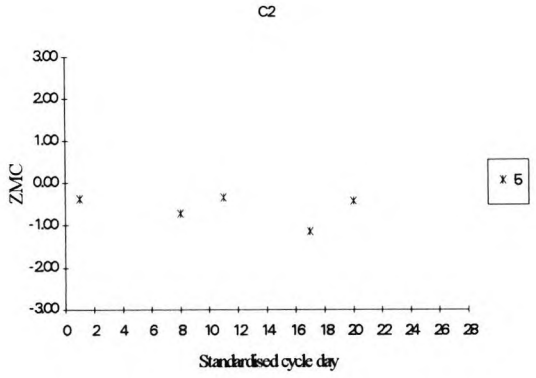
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Standardised cycle day
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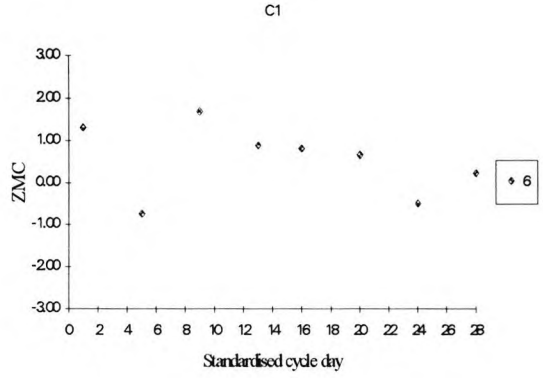
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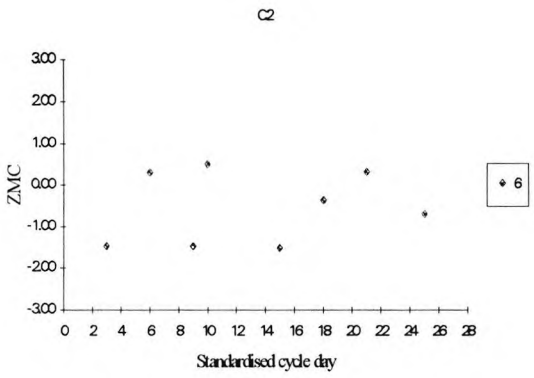
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Standardised cycle day
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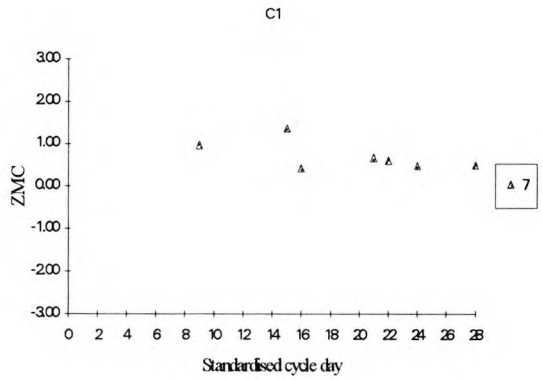
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Standardised cycle day
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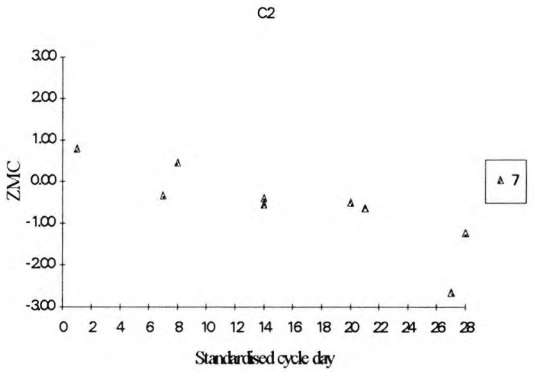
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Standardised cycle day
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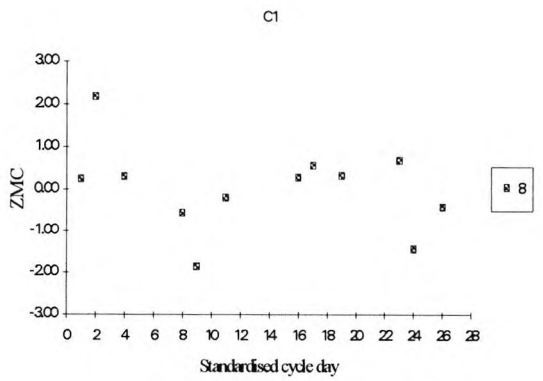
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Standardised cycle day
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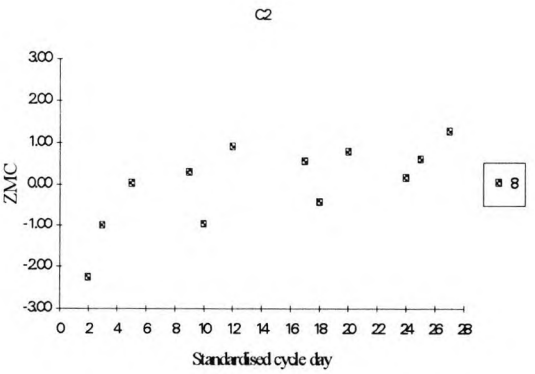
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0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Standardised cycle day
8

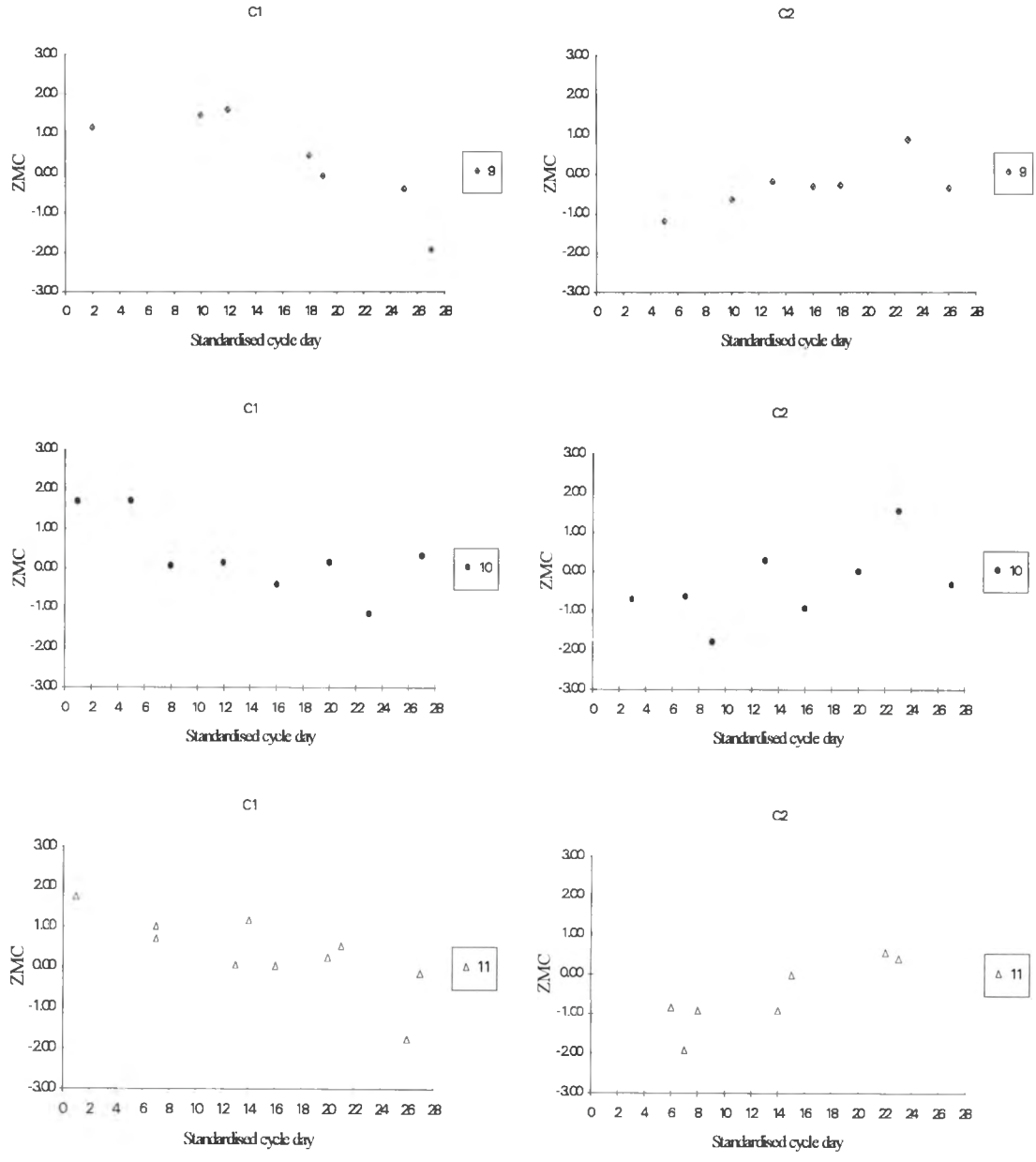
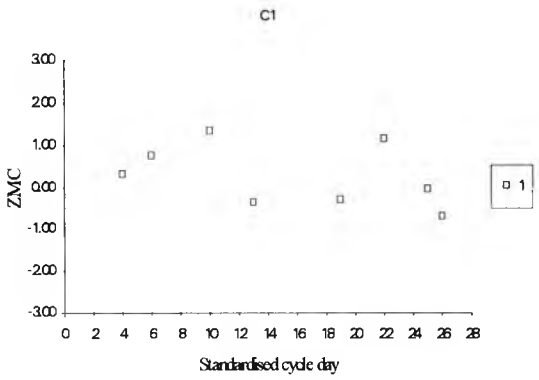
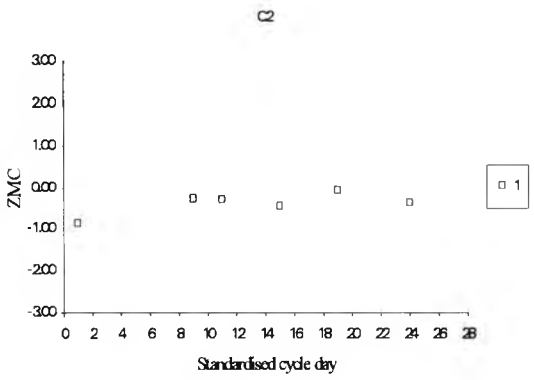
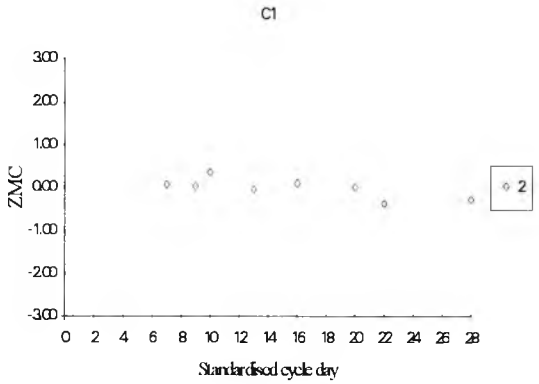


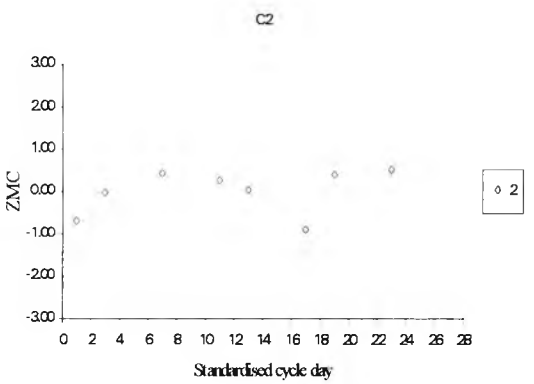
Figure A2.1 ZMC against standardised cycle day for individual subjects for the central field.

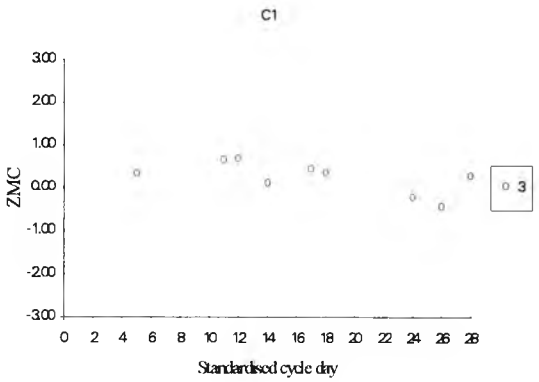
A2.2 Peripheral 30/60-2

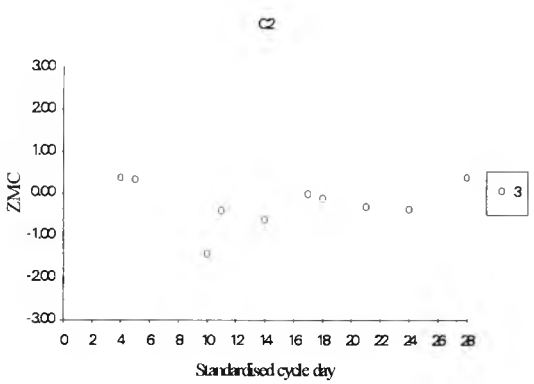


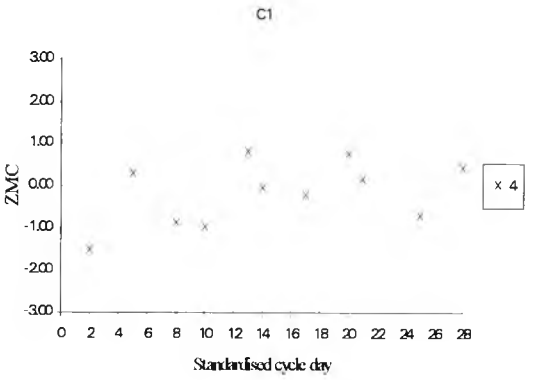


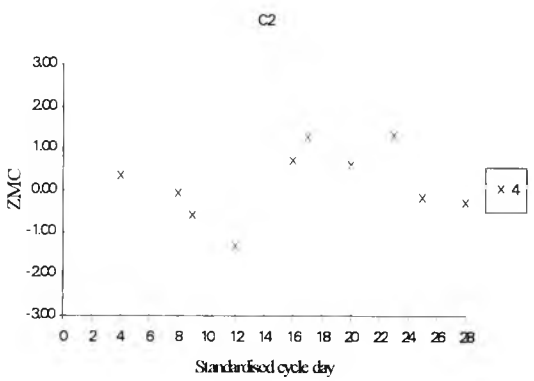


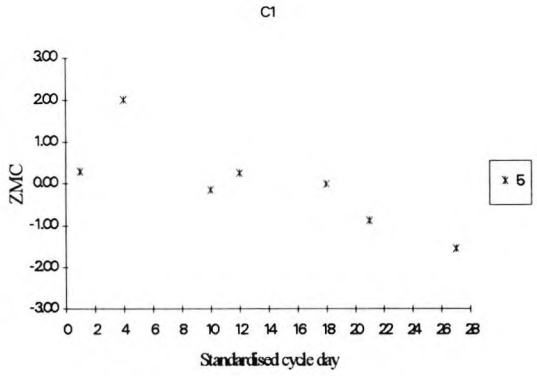








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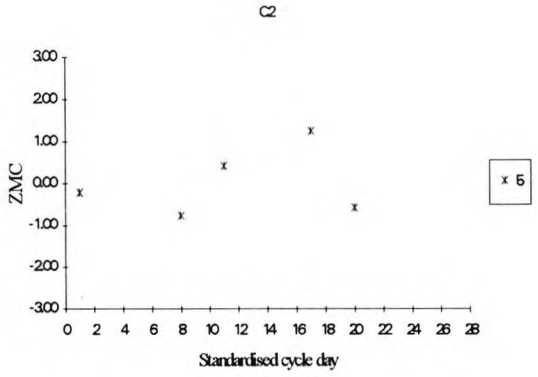
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Standardised cycle day
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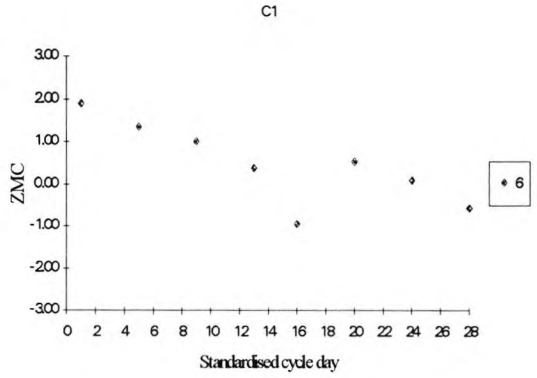
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Standardised cycle day
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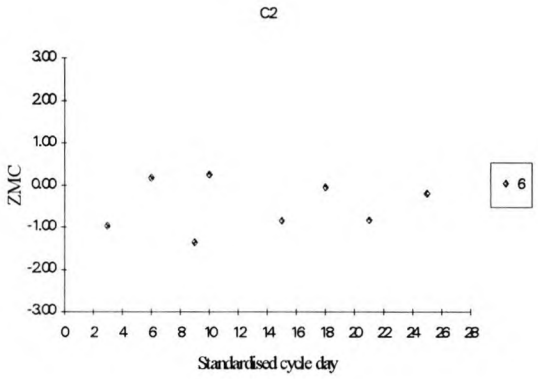
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Standardised cycle day
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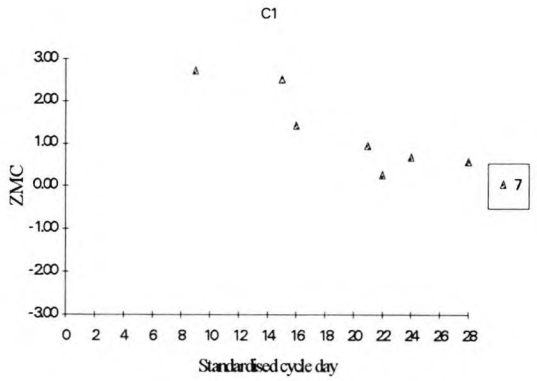
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Standardised cycle day
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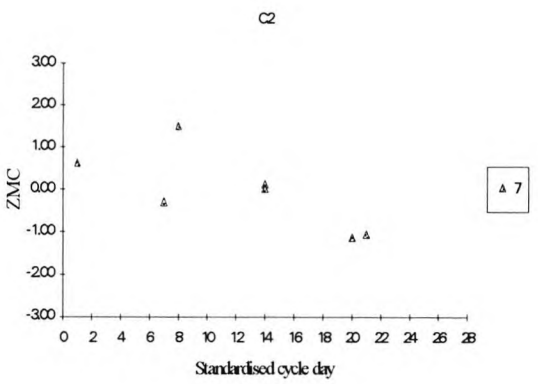
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0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Standardised cycle day
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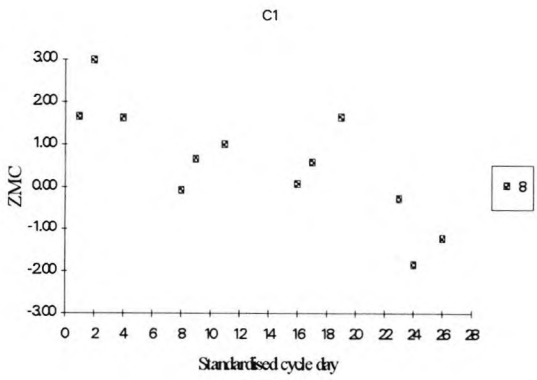
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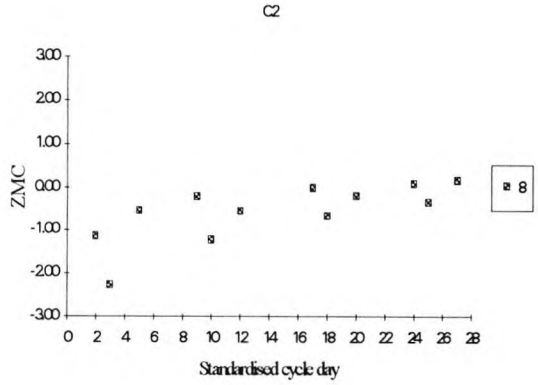
-3.00
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Standardised cycle day
8


C2
ZMC
3.00
2.00
1.00
0.00
-1.00
-2.00
-3.00
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Standardised cycle day
8

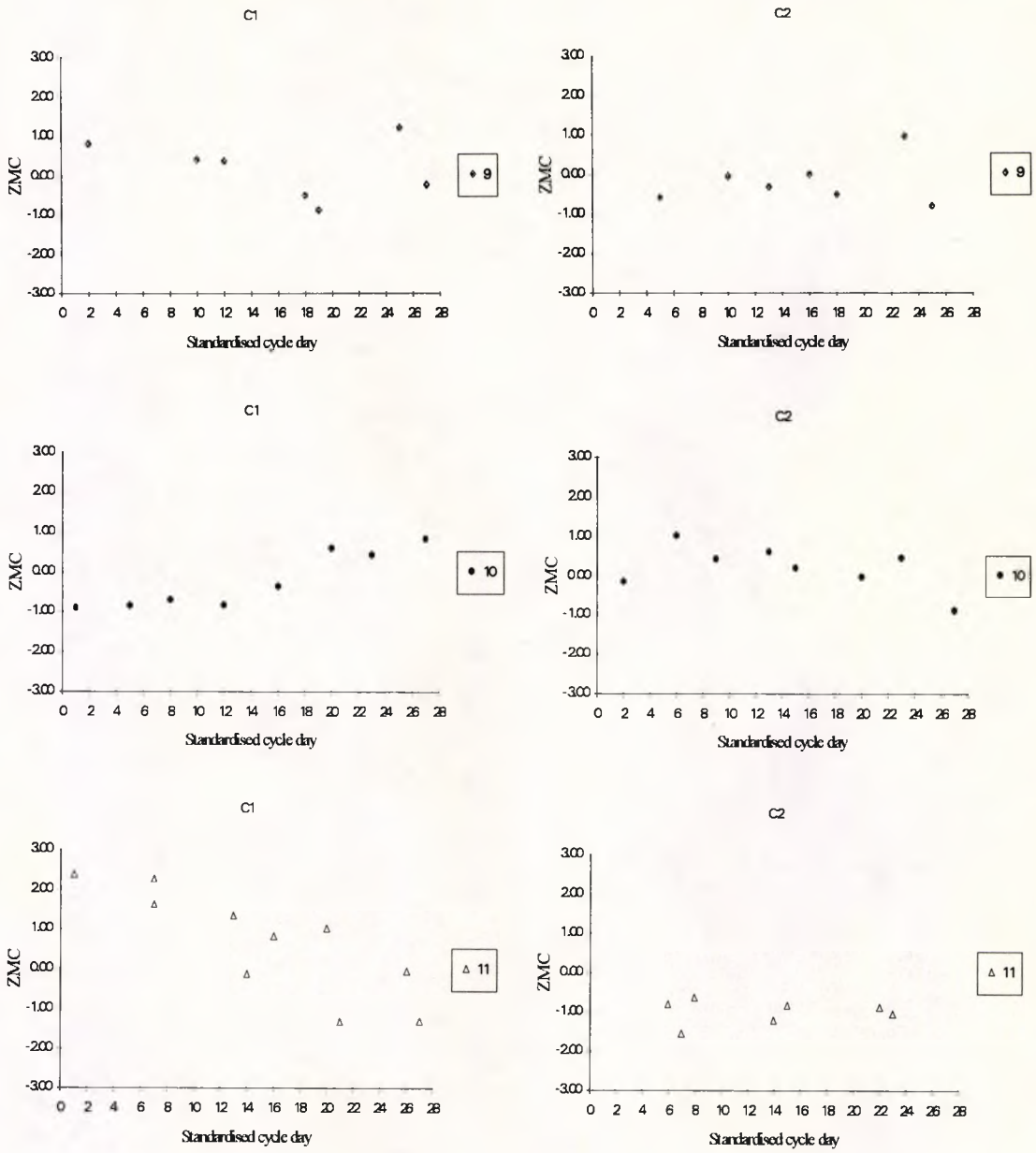


Figure A2.2 ZMC against standardised cycle day for individual subjects for the peripheral field

A2.3 Statistics

Table A2.1 Statistics for paired two sample *t*-tests between cycle 2 and Moos' (1985) normative data (table 6.6).

MDQ factor scale	Menstrual cycle phase	p value	*t* distribution	df
Pain	Menstrual	<0.05	1.688	407
Negative Affect	Menstrual	<0.05	2.854	407
Impaired Concentration	Menstrual	<0.05	3.322	407
Behaviour Change	Menstrual	<0.05	4.997	407
	Intermenstrual	<0.05	2.129	408
	Premenstrual	<0.05	2.807	405
Arousal	Intermenstrual	<0.05	2.616	408
	Premenstrual	<0.05	4.146	405

Table A2.2 Statistics for paired two sample *t*-tests between MDQ form C and Moos' (1985) normative data (table 6.7), where df = 2390.

	Menstrual cycle phase					
	Menstrual		Intermenstrual		Premenstrual	
MDQ factor scale	*t*	p value	*t*	p value	*t*	p value
Pain	5.436	<0.001	2.150	<0.02	2.688	<0.01
Water Retention	4.547	<0.001	2.037	<0.05	4.514	<0.001
Autonomic Reaction	4.333	<0.001	2.297	<0.05	2.990	<0.01
Negative Affect	5.999	<0.001	6.460	<0.001	6.553	<0.001
Impaired Concentration	10.17	<0.001	5.652	<0.001	7.042	<0.001
Behaviour Change	6.193	<0.001	5.673	<0.001	8.046	<0.001
Arousal	ns	ns	4.796	<0.001	4.134	<0.001
Control	3.58	<0.001	2.792	<0.01	5.005	<0.001

Table A2.3 Statistics for paired two sample *t*-tests between MDQ form C and cycle 2 of form T (table 6.7).

	Menstrual cycle phase					
	Menstrual			Premenstrual		
MDQ factor scale	*t*	p value	df	*t*	p value	df
Pain	-4.01	0.003	9			
Water Retention	-2.32	0.05	9	-3.23	0.01	7
Autonomic Reaction						
Negative Affect				-3.70	0.008	7
Impaired Concentration				-2.31	0.05	7
Control	-2.31	0.05	9			

Appendix A3 Main study

A3.1 General Questionnaire

OPTOMETRY AND VISUAL SCIENCE DEPT, CITY UNIVERSITY

Please answer as many parts of the questionnaire as you are able.
All information will be treated as strictly confidential.
Thank you for your co-operation.

* Circle as applicable

NAME_____ SEX * male / female DOB / /

STATUS * married or cohabiting / single NUMBER OF CHILDREN _____

GROUP (optometry students only) * A B C D E

1) GRADE YOUR GENERAL HEALTH * very good / good / fair / poor

2) ARE YOU TAKING ANY MEDICATION PRESCRIBED BY A DOCTOR? * yes / no
IF YES, PLEASE LIST

3) ARE YOU TAKING ANY OVER THE COUNTER/PHARMACY MEDICATION? * yes / no
IF YES, PLEASE LIST

4) DO YOU SUFFER FROM HEADACHES OR MIGRAINES? * yes / no
IF YES, COMMENT ON FREQUENCY, INTENSITY AND MEDICATION TAKEN

5) DO YOU HAVE ANY HISTORY OF PSYCHIATRIC DISORDERS? * yes / no
IF YES, PLEASE DESCRIBE BRIEFLY

6) HAVE YOU HAD ANY OPERATIONS OR MAJOR ILLNESSES? * yes / no
IF YES, PLEASE LIST

7) DO YOU SUFFER FROM DIABETES? * yes / no

8) HOW MANY CIGARETTES DO YOU SMOKE A DAY?
_____

9) HOW MANY UNITS OF ALCOHOL DO YOU CONSUME EACH WEEK?
_____
(1 unit = 1 glass wine, 1 spirit measure, half a pint of beer)

Females only

1) IS YOUR MENSTRUAL CYCLE REGULAR? * yes / no
IF YES, WHAT IS THE AVERAGE LENGTH IN DAYS ?_____
IF NO, PLEASE COMMENT

2) DO YOU SUFFER FROM PREMENSTRUAL SYMPTOMS?
* always / sometimes / never
HAVE YOU EVER HAD TREATMENT FOR PREMENSTRUAL SYMPTOMS? * yes / no
IF YES, PLEASE COMMENT

Males and females

1) DO YOU REQUIRE ANY OPTICAL CORRECTION? * yes / no
IF YES, DO YOU KNOW WHAT THE PRESCRIPTION IS? (please make a note of it below if you do)

2) DO YOU WEAR CONTACT LENSES? *yes / no
IF YES, WHICH TYPE? (eg. daily wear soft, gas permeable, hard etc.)

HOW MANY HOURS A DAY DO YOU WEAR
THEM?_____

HOW MANY MONTHS/YEARS HAVE YOU WORN THEM FOR?_____

3) HAVE YOU EVER HAD ANY SURGICAL OPERATIONS ON YOUR EYES? * yes / no
IF YES, LIST

4) HAVE YOU EVER HAD ANY ORTHOPTIC TREATMENT? (eg. patching of one eye, eye exercises) * yes / no
IF YES, PLEASE COMMENT

5) HAVE YOU EVER HAD ANY EYE INFECTIONS OR DISEASE OF THE EYE? * yes / no
IF YES, PLEASE COMMENT

6) IS THERE ANY HISTORY OF EYE PROBLEMS IN THE FAMILY? (eg. glaucoma, squints, 'lazy eyes', blindness) * yes / no
IF YES, PLEASE COMMENT

A3.2 Daily Questionnaire

SECTION 1
To be completed each morning

Name Date / / Day of week (circle) M/T/W/Th/F/S/Su

Oral temperature (oCelsius) Pulse rate (over 15s)

SECTION 2
To be completed in the evening

How many of each of the following have you had over the past 24hrs?

Units of alcohol (1 unit = 1/2 pint beer, 1 glass wine, 1 spirit measure)	0	1-2	3-4	5-6	7 or over
Cigarettes	0	1-5	6-10	11-15	16 or over
Caffeinated drinks (eg coffee, tea, coke)	0	1-3	4-6	7 or over	
Units of exercise (1 unit = 1/2 hour)	0	1-2	3-4	5 or over	

Hours of sleep < 6 6-9 >10

Have you taken any medication today? YES/NO
If yes, please list

(females only) Do you have your period (menstrual flow) today? YES/NO

Please rate the degree to which you have experienced the following symptoms over the past 24hrs using a scale of 0 - 8
0 represents complete absence and 8 extremely severe presence of symptom.

Headache	Depression
General aches and pains	Irritability
Backache	Poor academic/work performance
Abdominal pain	Difficulty concentrating
Lethargy/tiredness	Accidents
Dizziness/faintness	Happy
Cold sweats	Feelings of well-being
Nausea	Skin disorder
Vomiting	Blind spots, fuzzy vision
Insomnia	Mood swings

Please record any specific illnesses, life events (eg holiday, marriage, bereavement) and any work or personal increases in stress over the page.

A3.3 Repeatability

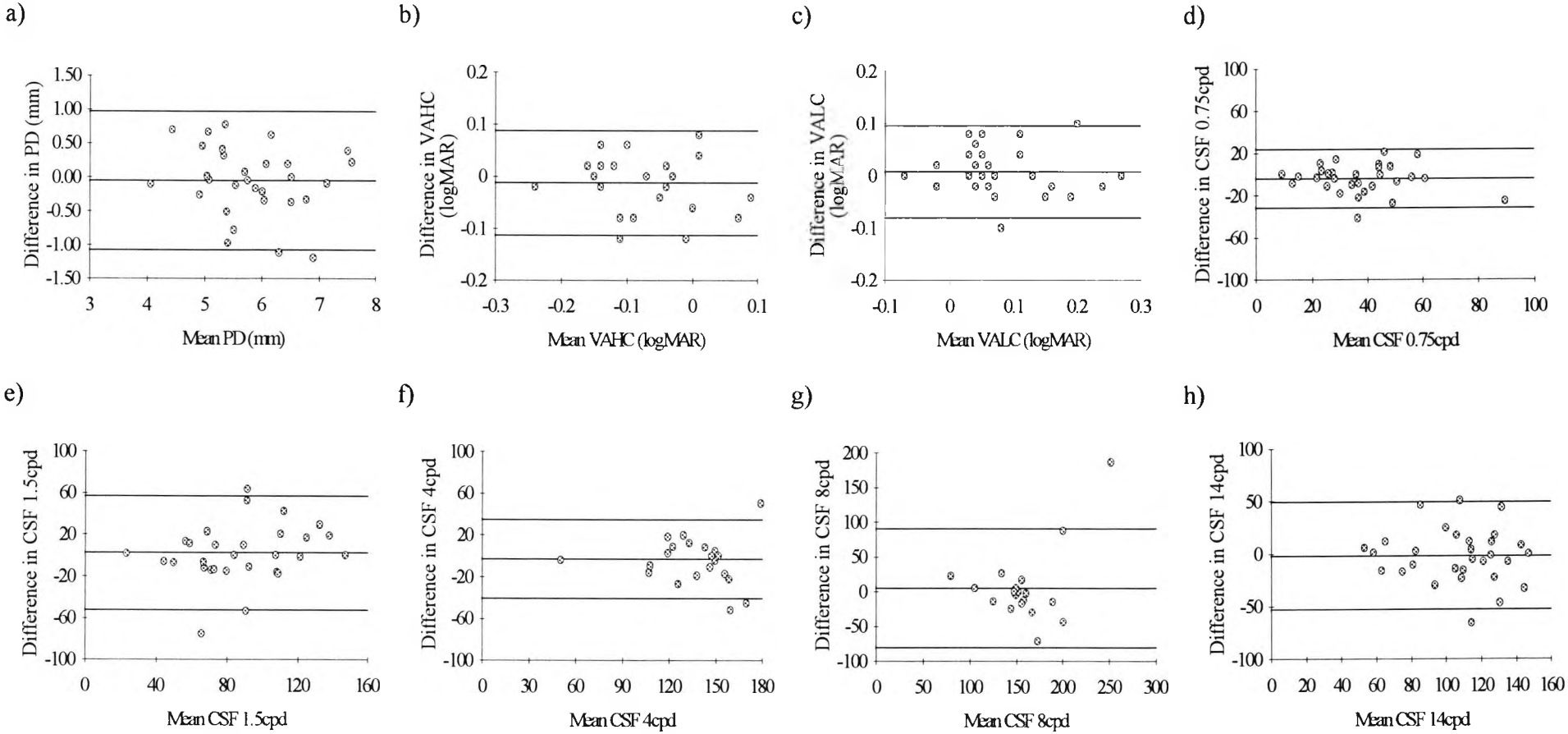


Figure A3.1 Differences between paired values for sessions 1 and 2 plotted against their means for a) pupil diameter (PD), b) high contrast logMAR acuity (VAHC), c) low contrast logMAR acuity (VALC), and contrast sensitivity function (CSF) at d) 0.75cpd, e) 1.5cpd, f) 4cpd, g) 8cpd and h) 14cpd. Horizontal lines represent the mean difference and 95% confidence limits.

A3.4 Mean change in visual performance across cycle day

A3.4.1 Visual field

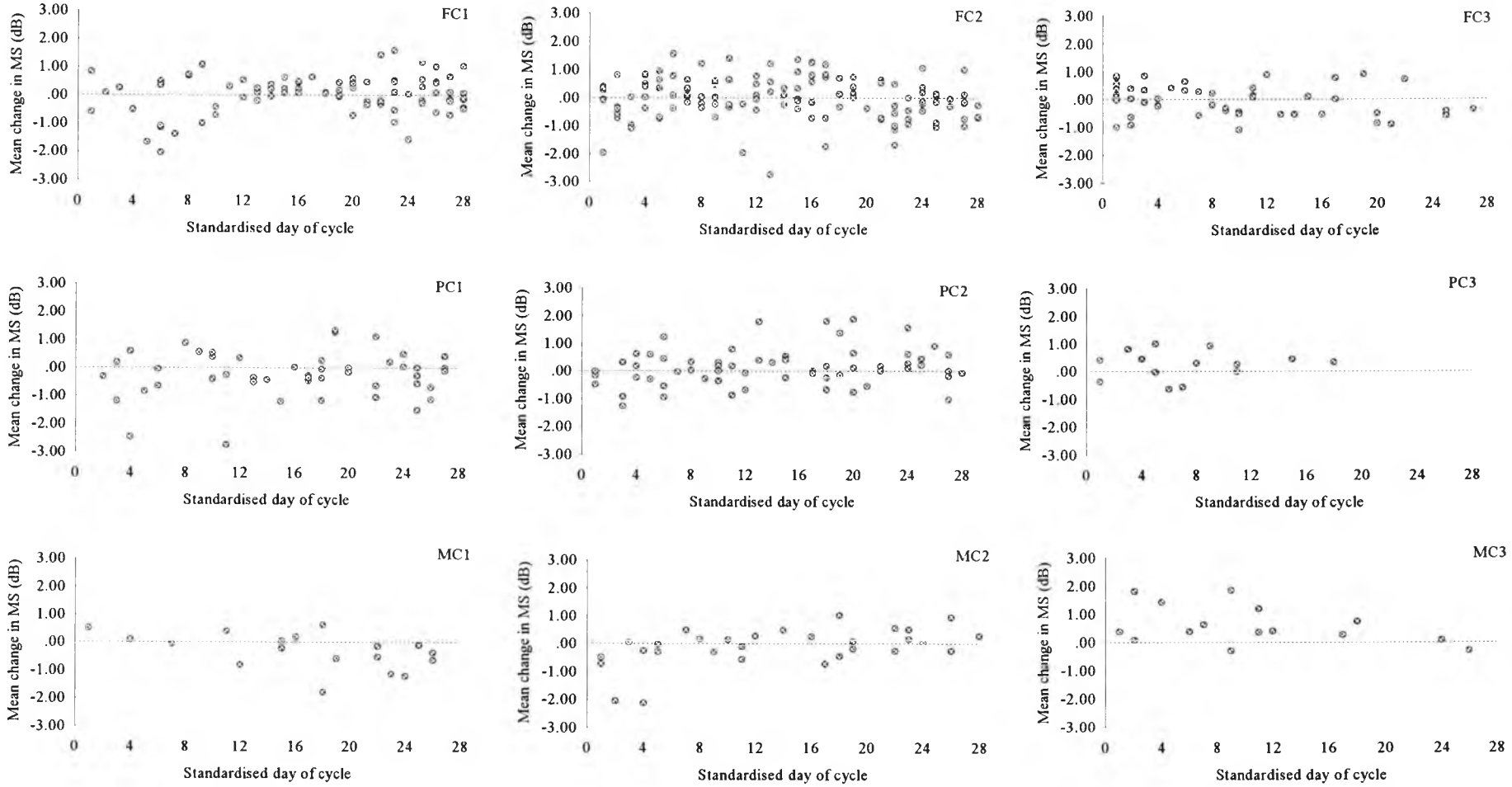


Figure A3.2 Mean change in mean sensitivity of 24-2 HFA plot across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

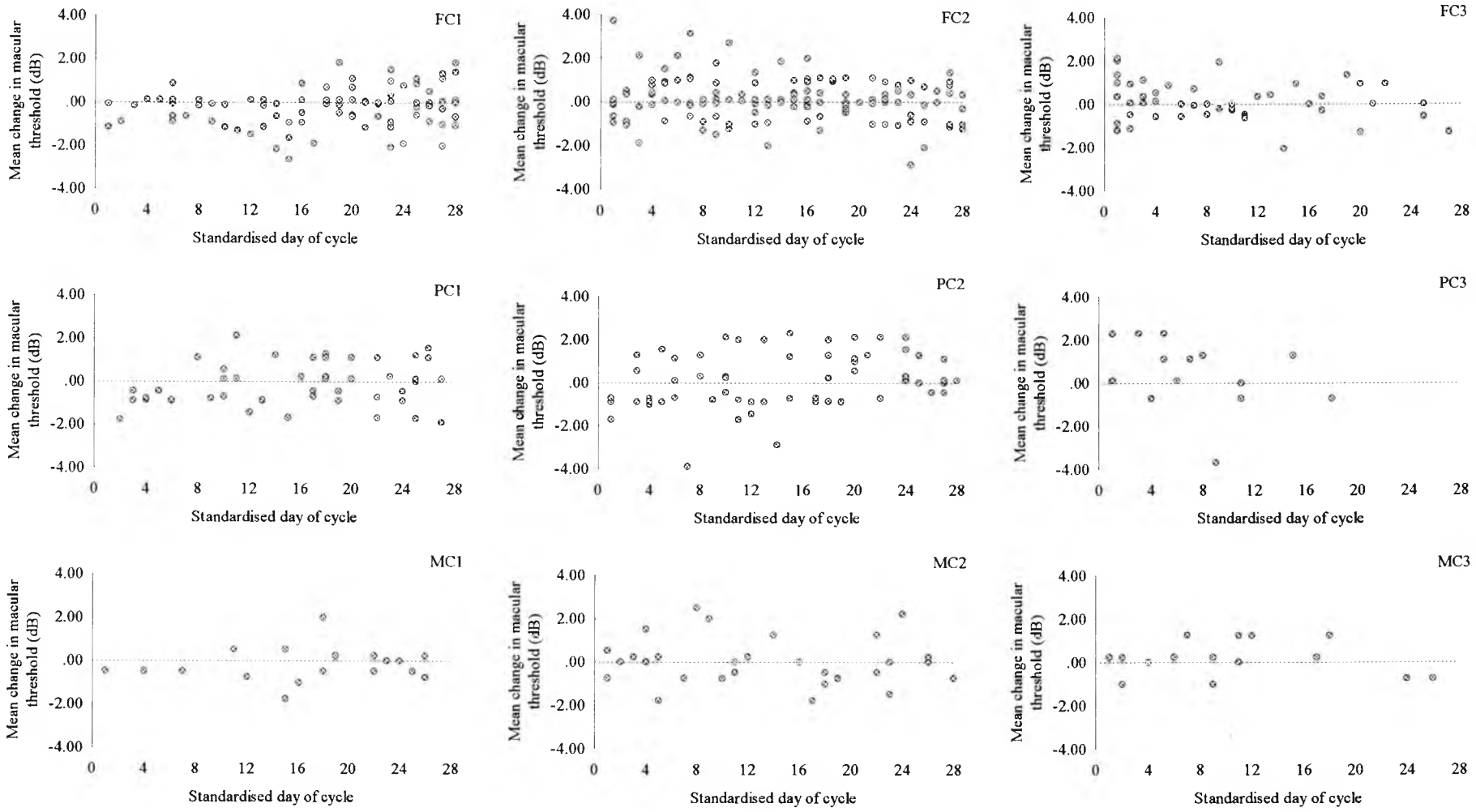


Figure A3.3 Mean change in macular threshold across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

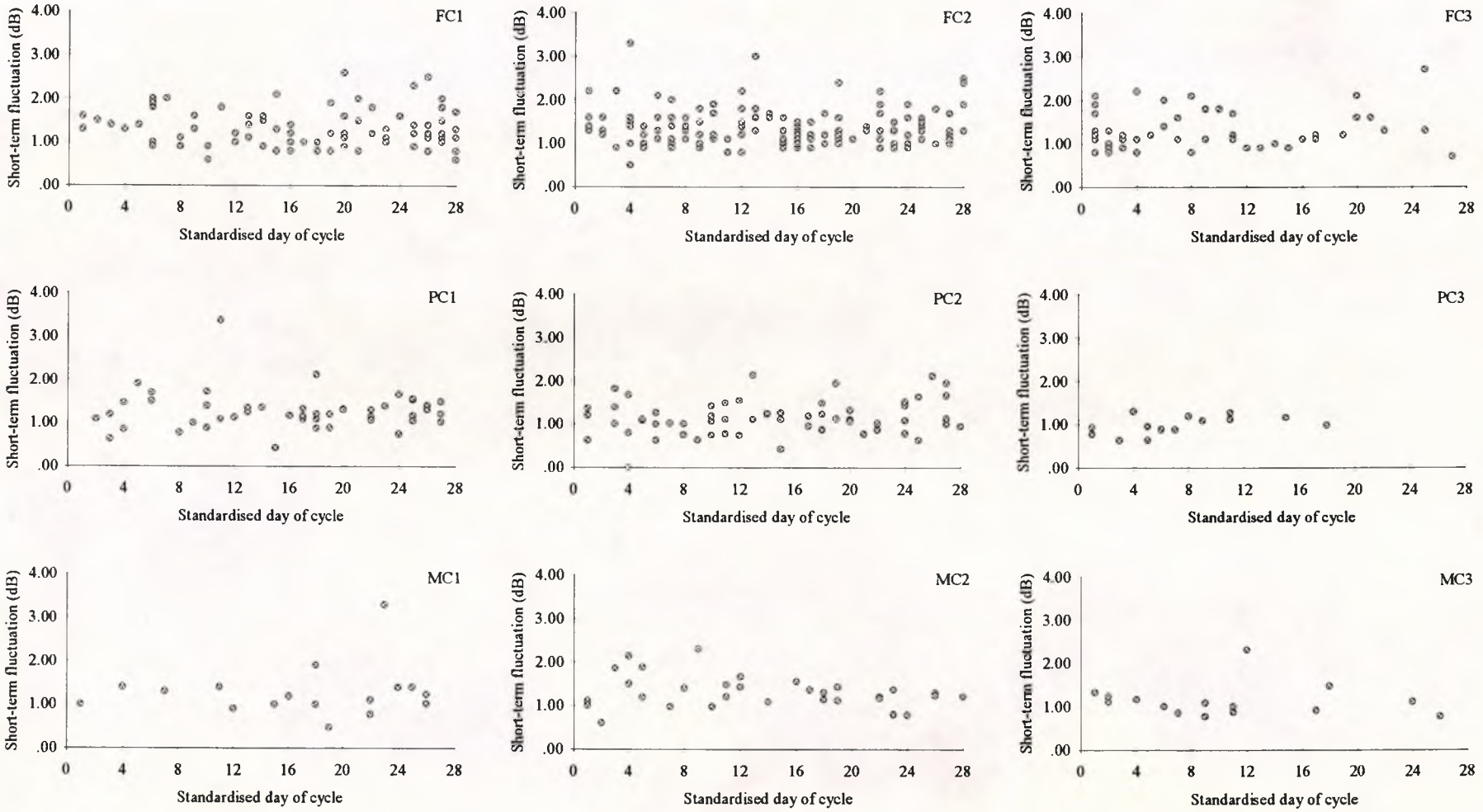


Figure A3.4 Mean change in short-term fluctuation in 24-2 HFA plot across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

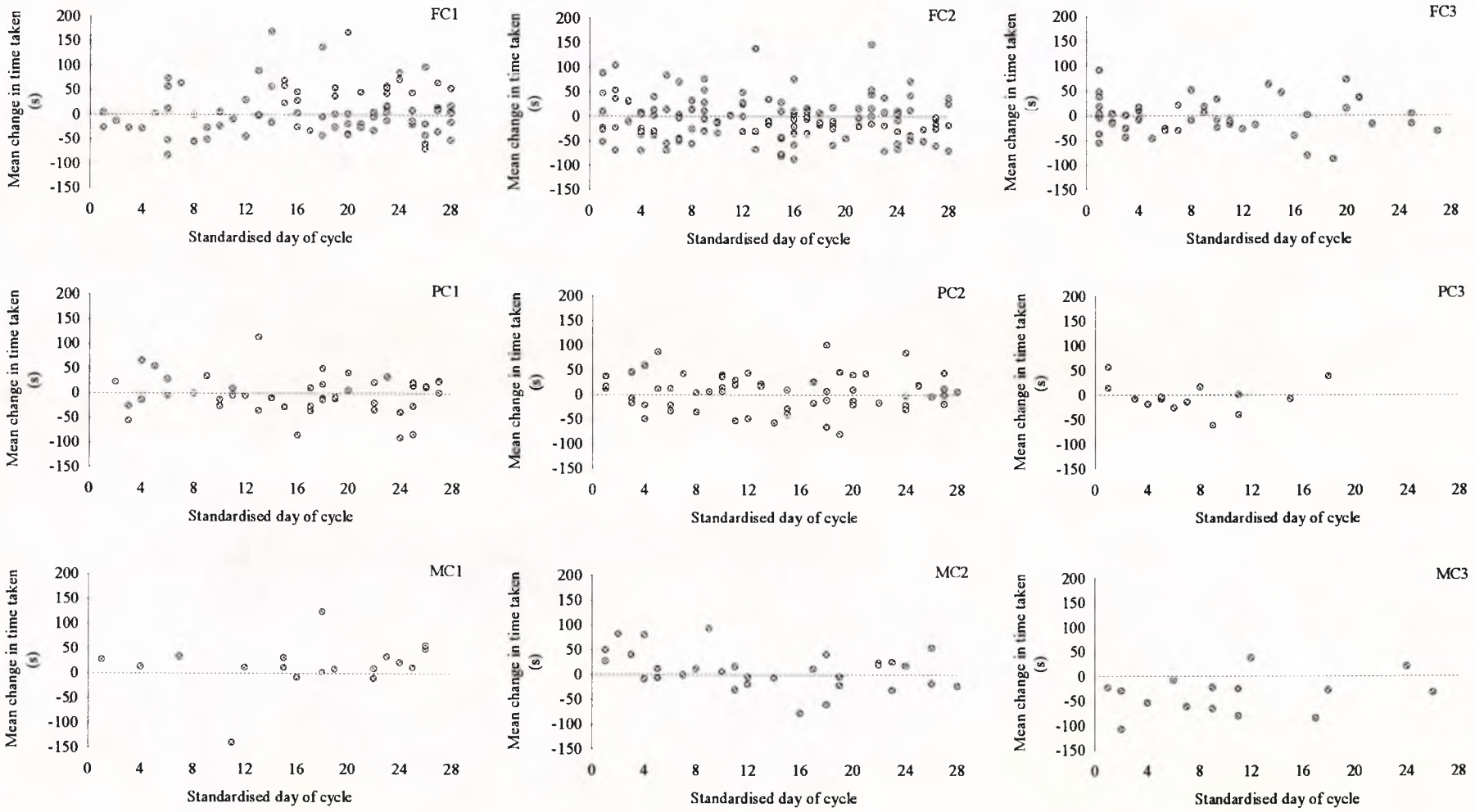


Figure A3.5 Mean change in time taken for 24-2 HFA plot across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

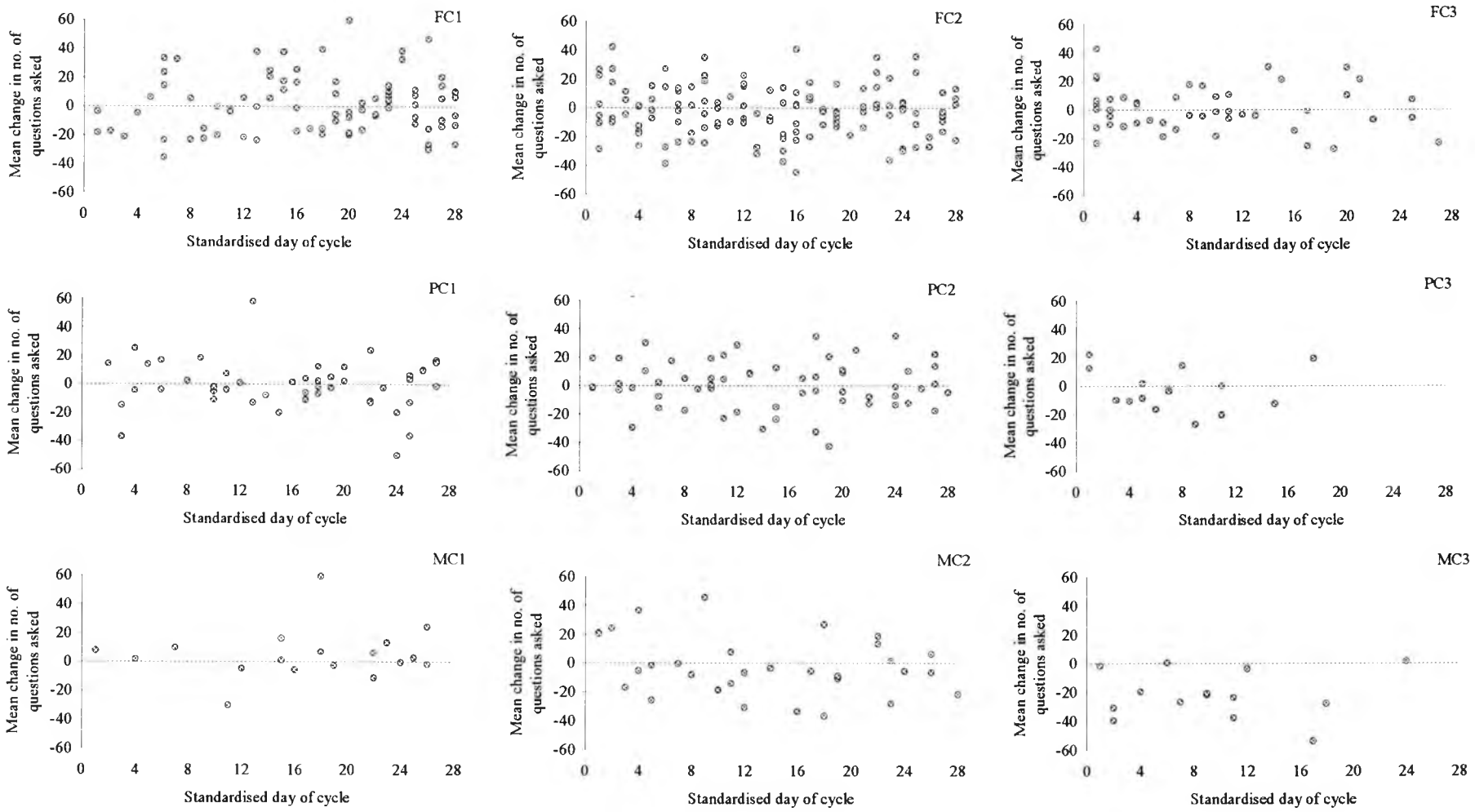


Figure A3.6 Mean change in number of questions asked for 24-2 HFA plot across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

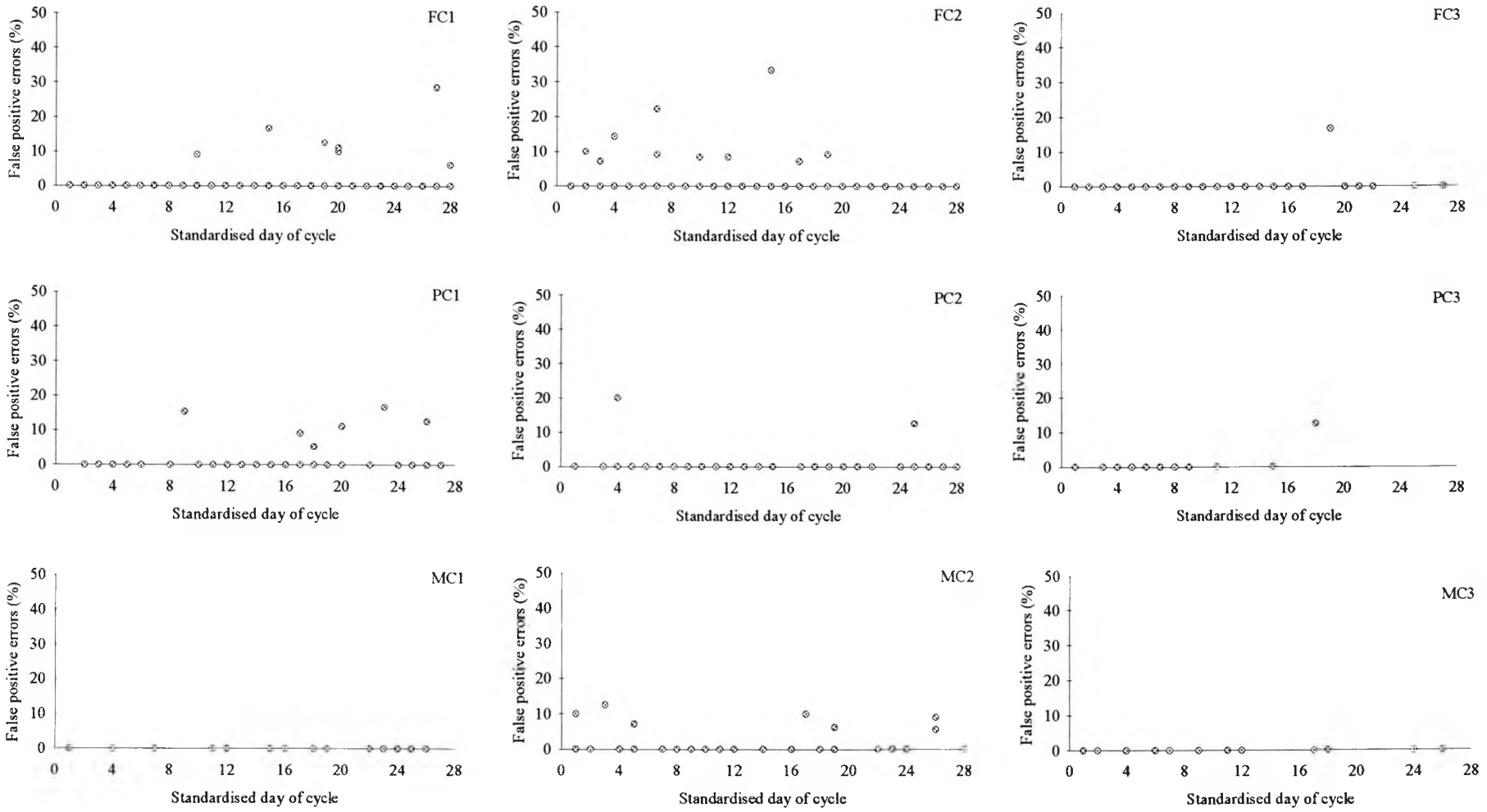


Figure A3.7 Percentage of false positive errors across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

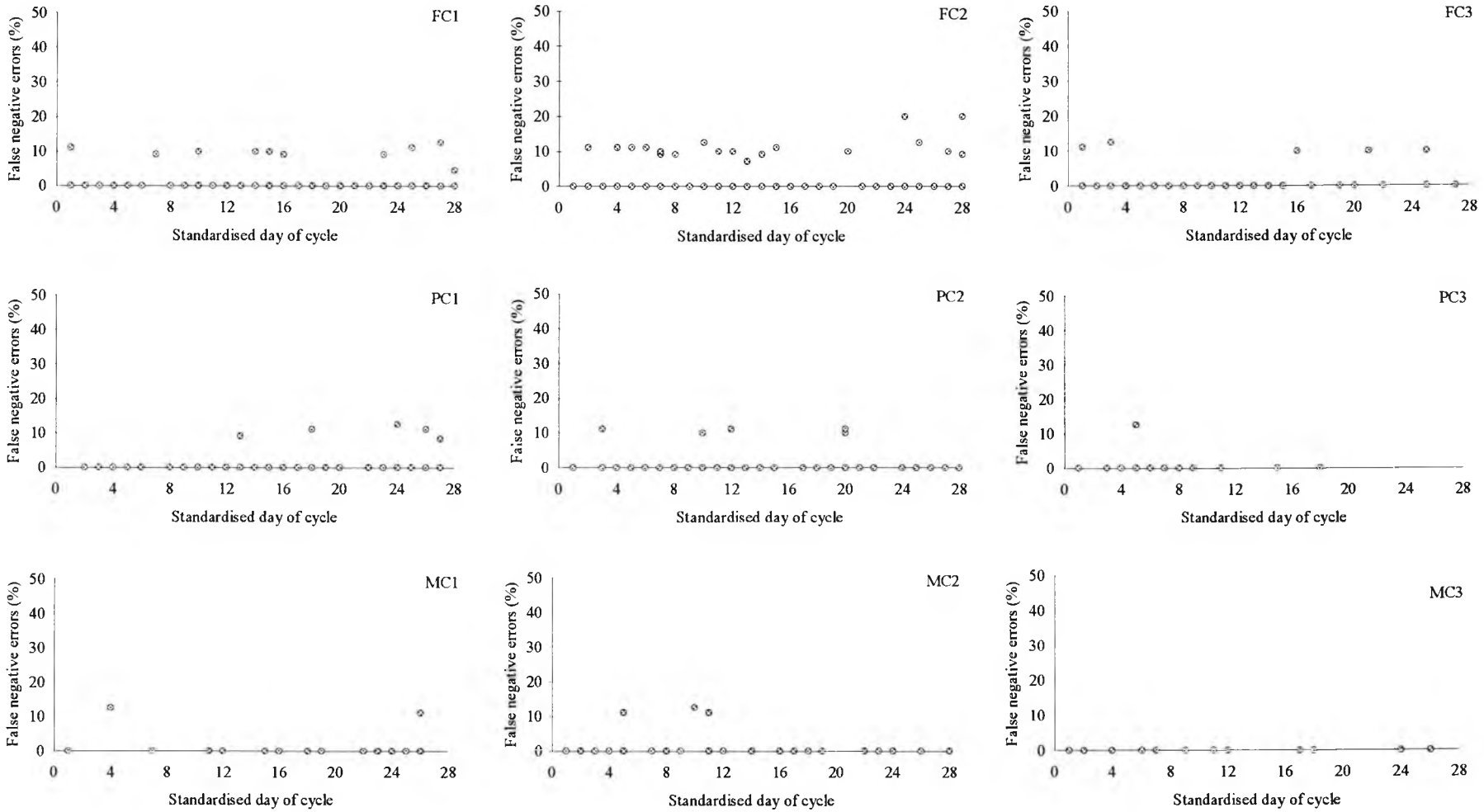


Figure A3.8 Percentage of false negative errors across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

A3.4.2 Contrast sensitivity

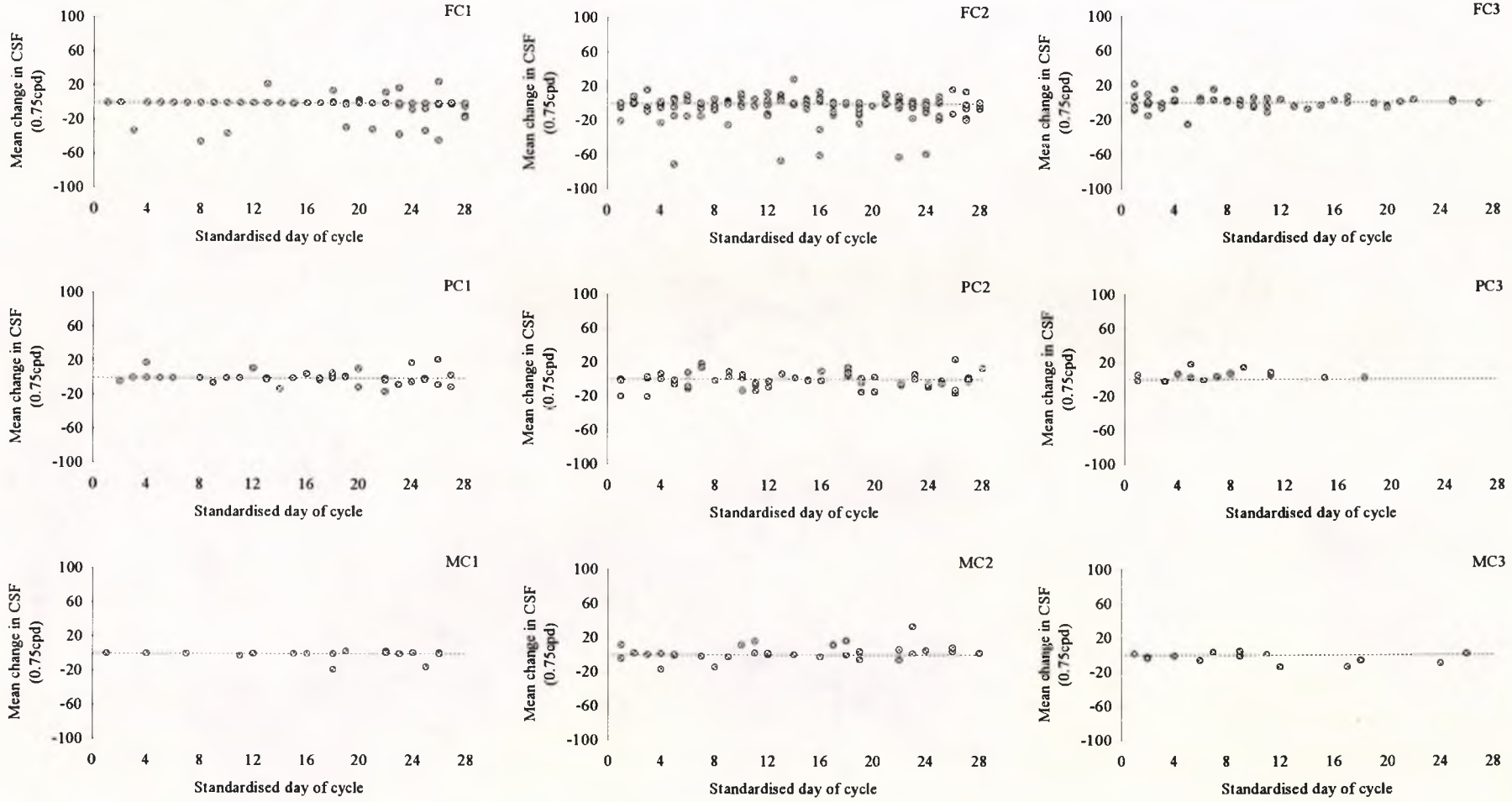


Figure A3.9 Mean change in CSF (0.75cpd) across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

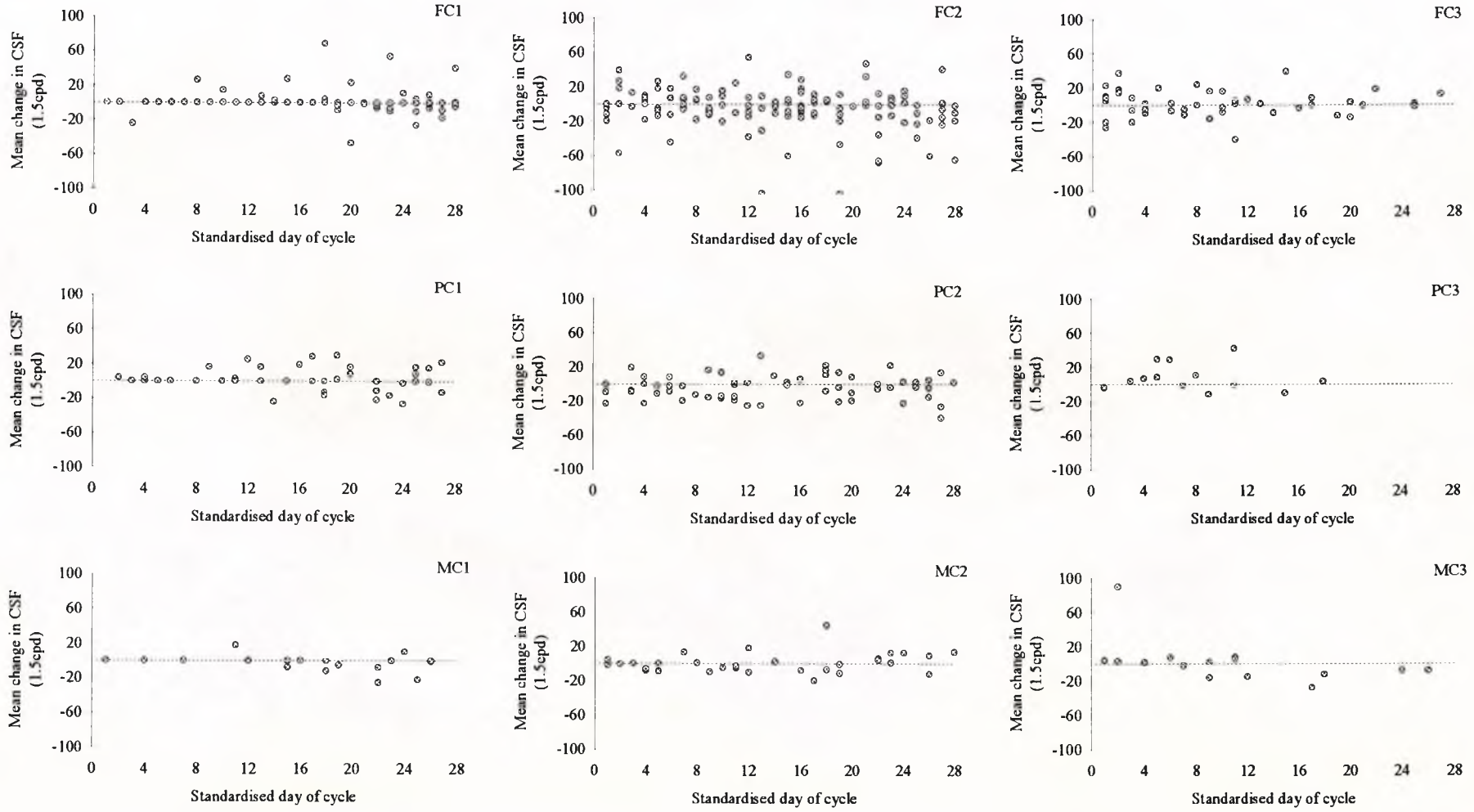


Figure A3.10 Mean change in CSF (1.50cpd) across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

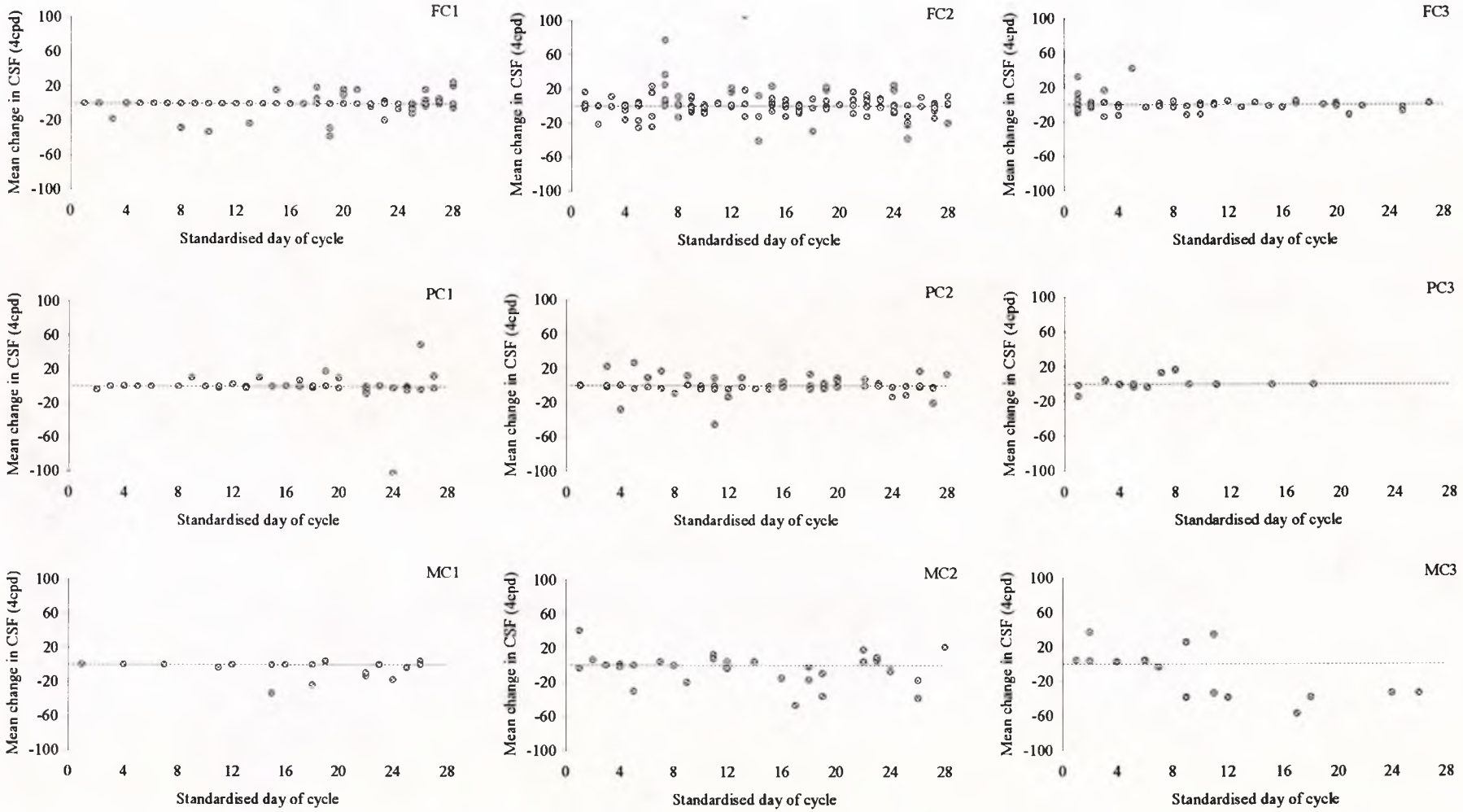


Figure A3.11 Mean change in CSF (4cpd) across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

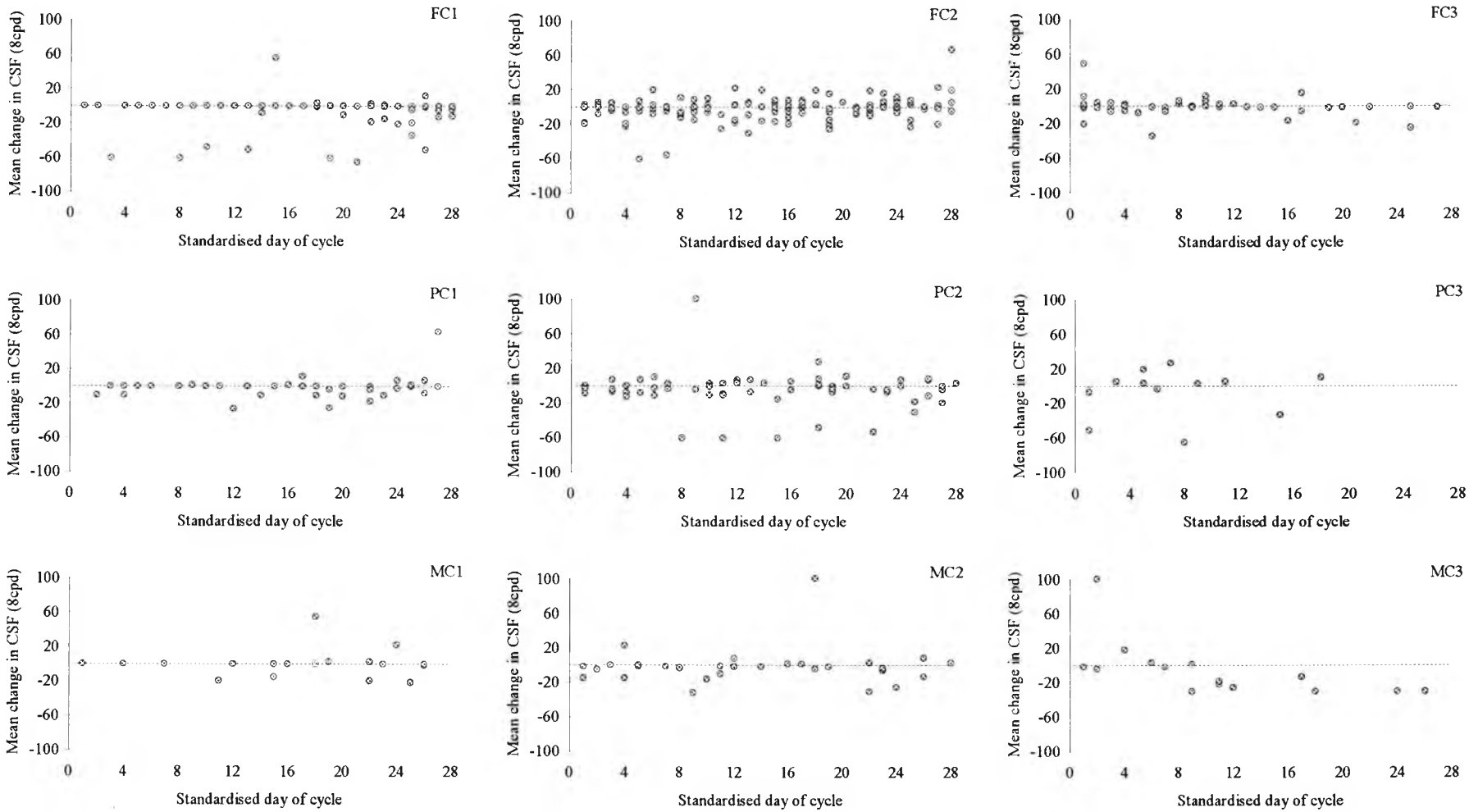


Figure A3.12 Mean change in CSF (8cpd) across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

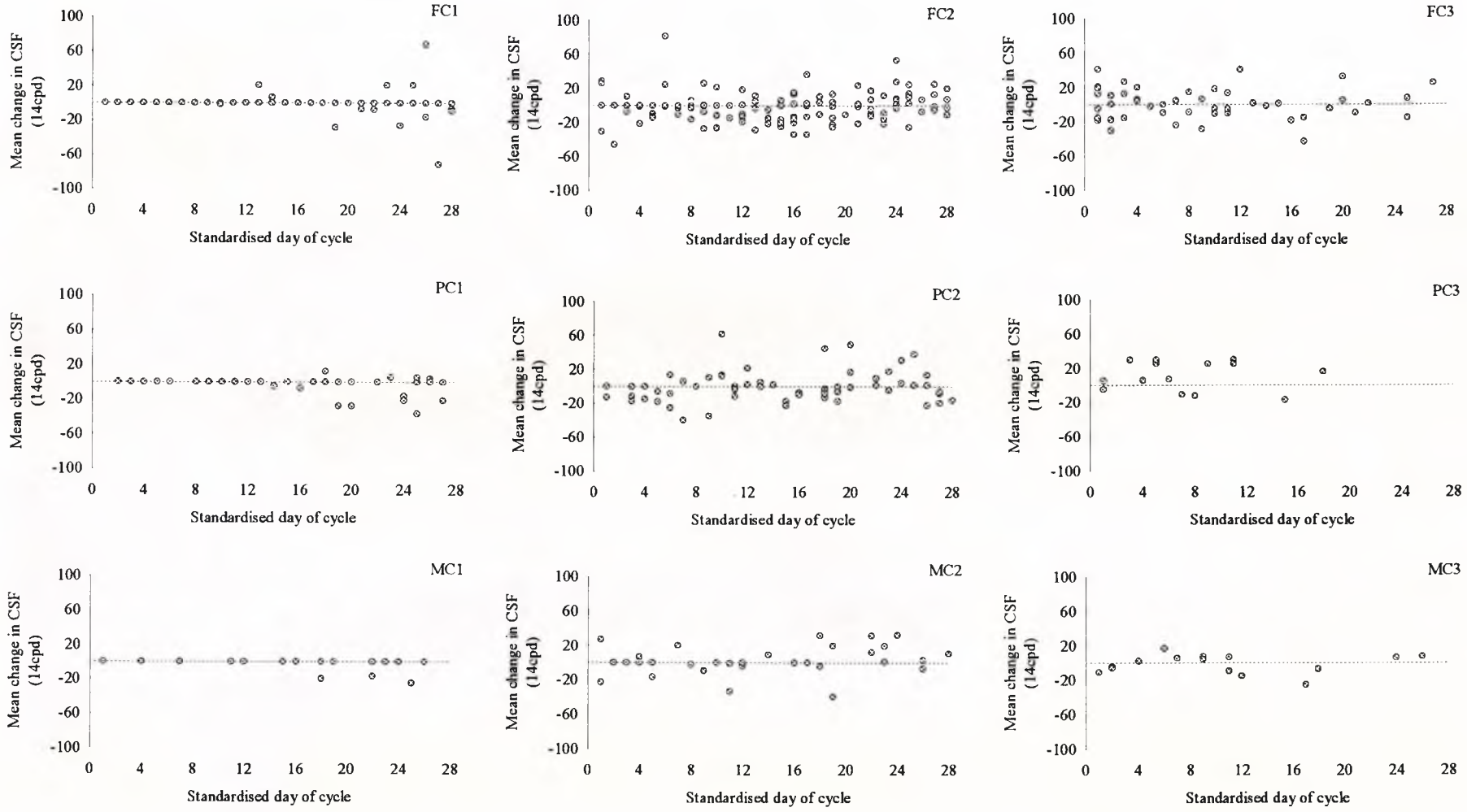


Figure A3.13 Mean change in CSF (14cpd) across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

A3.4.3 Visual acuity

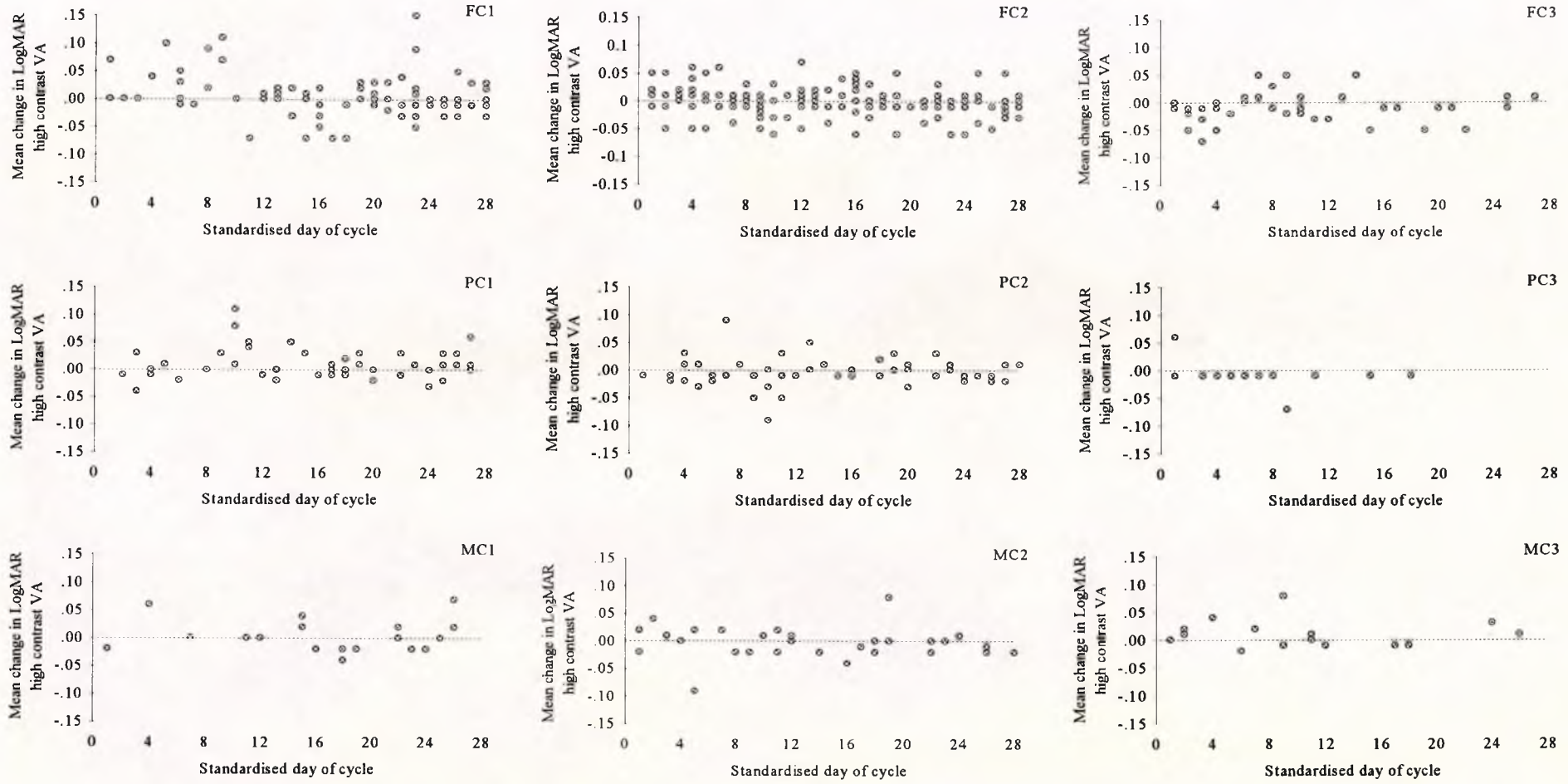


Figure A3.14 Mean change in LogMAR high contrast visual acuity across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

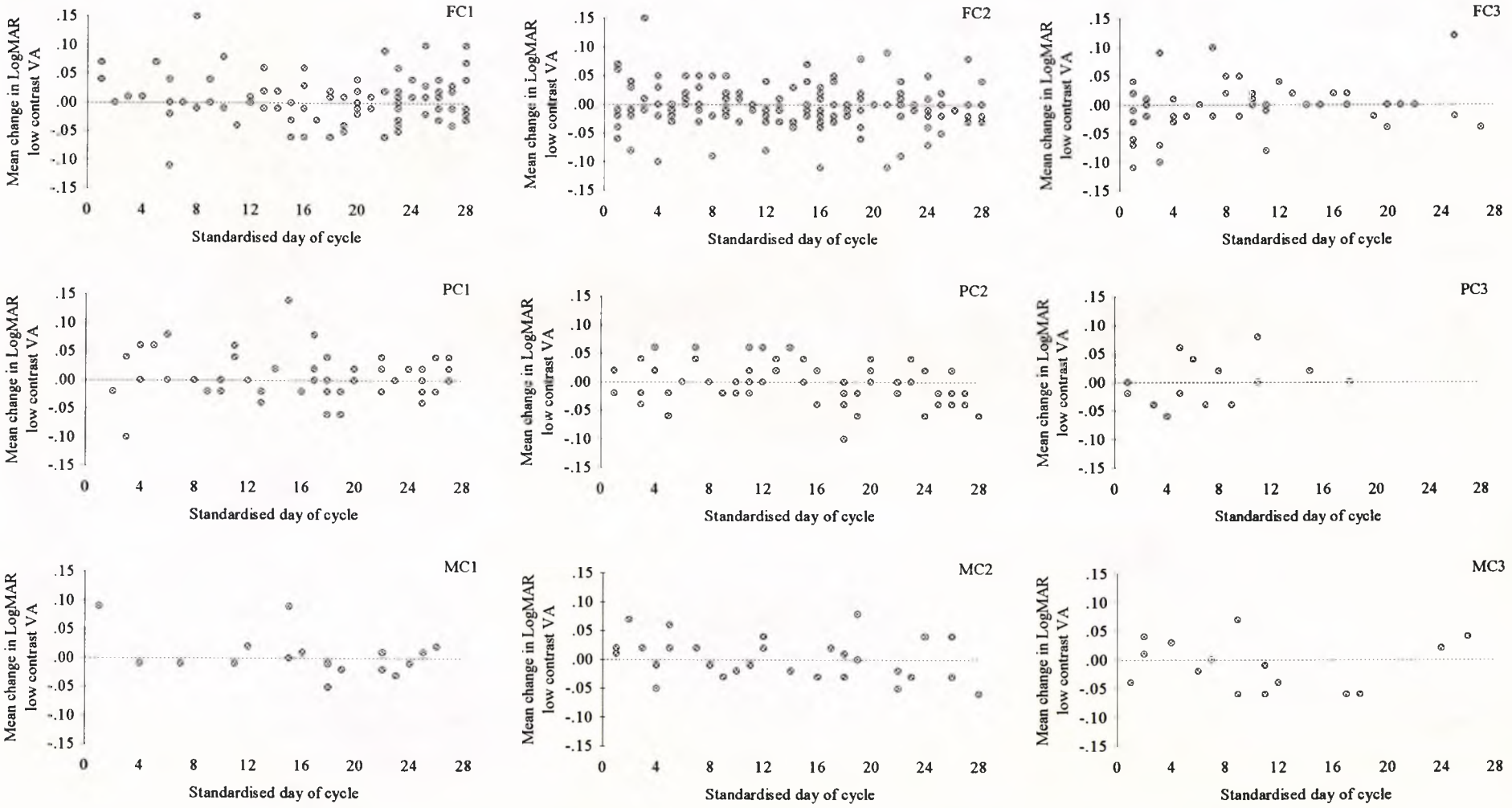


Figure A3.15 Mean change in LogMAR low contrast visual acuity across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

A3.4.4 Pupil diameter

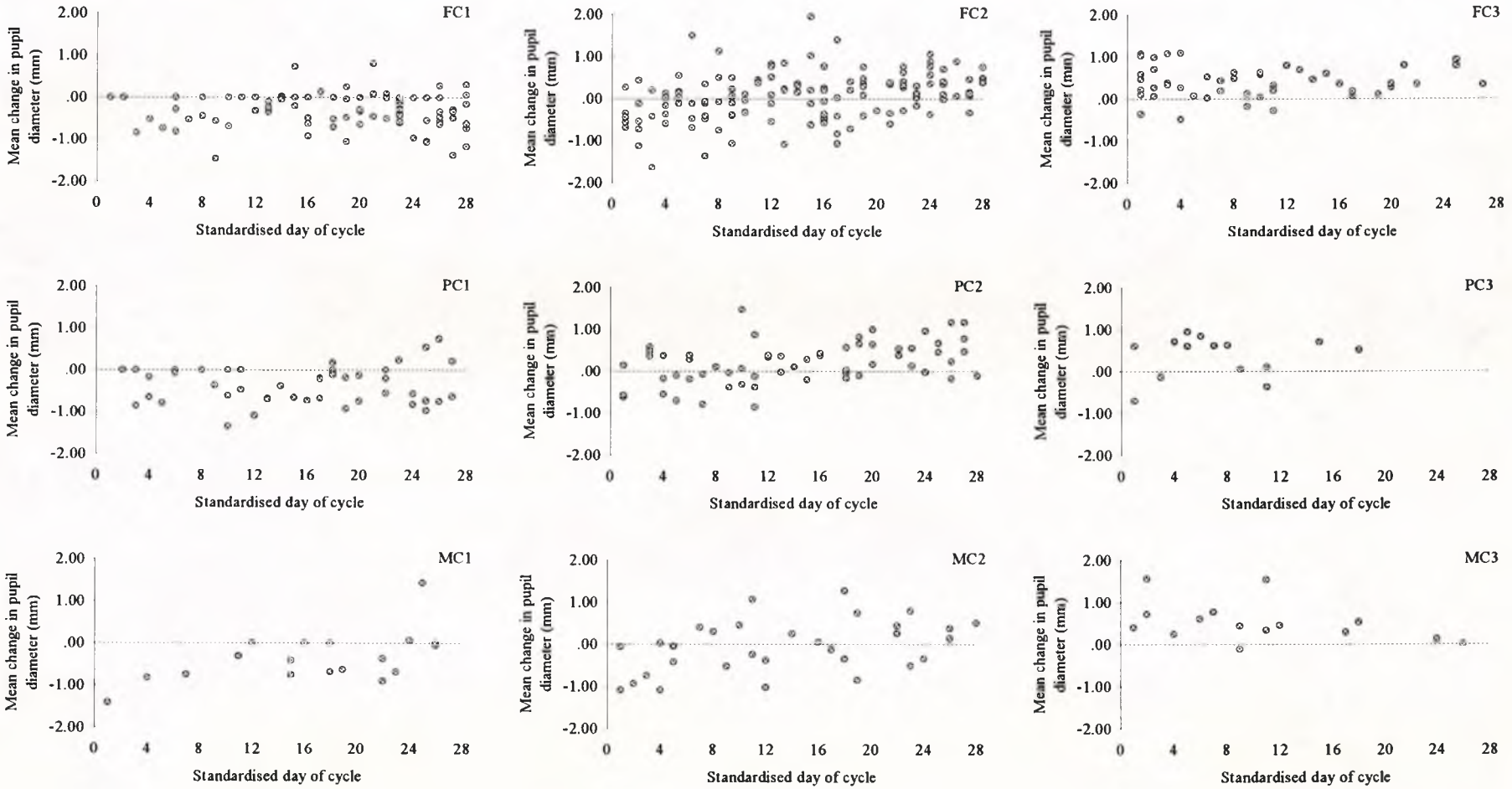


Figure A3.16 Mean change pupil diameter (mm) across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

A3.4.5 Statistics

Table A3.1 Statistics from oneway anova for differences between 'cycle' phases in visual field parameters in 'cycle' 2 of men.

	F distribution	df	p value
Mean sensitivity	4.45	4,26	0.007
Nasal hemifield	4.01	4,26	0.005
Inferior hemifield	3.35	4,26	0.02
Superior hemifield	3.62	4,26	0.02
Temporal hemifield	3.82	4,26	0.01
Outer annulus	3.03	4,26	0.04
Middle annulus	3.73	4,26	0.02
Time taken	2.90	4,26	0.04
FN errors	2.88	4,26	0.04

A3.5 Mean change in symptom scores across cycle day

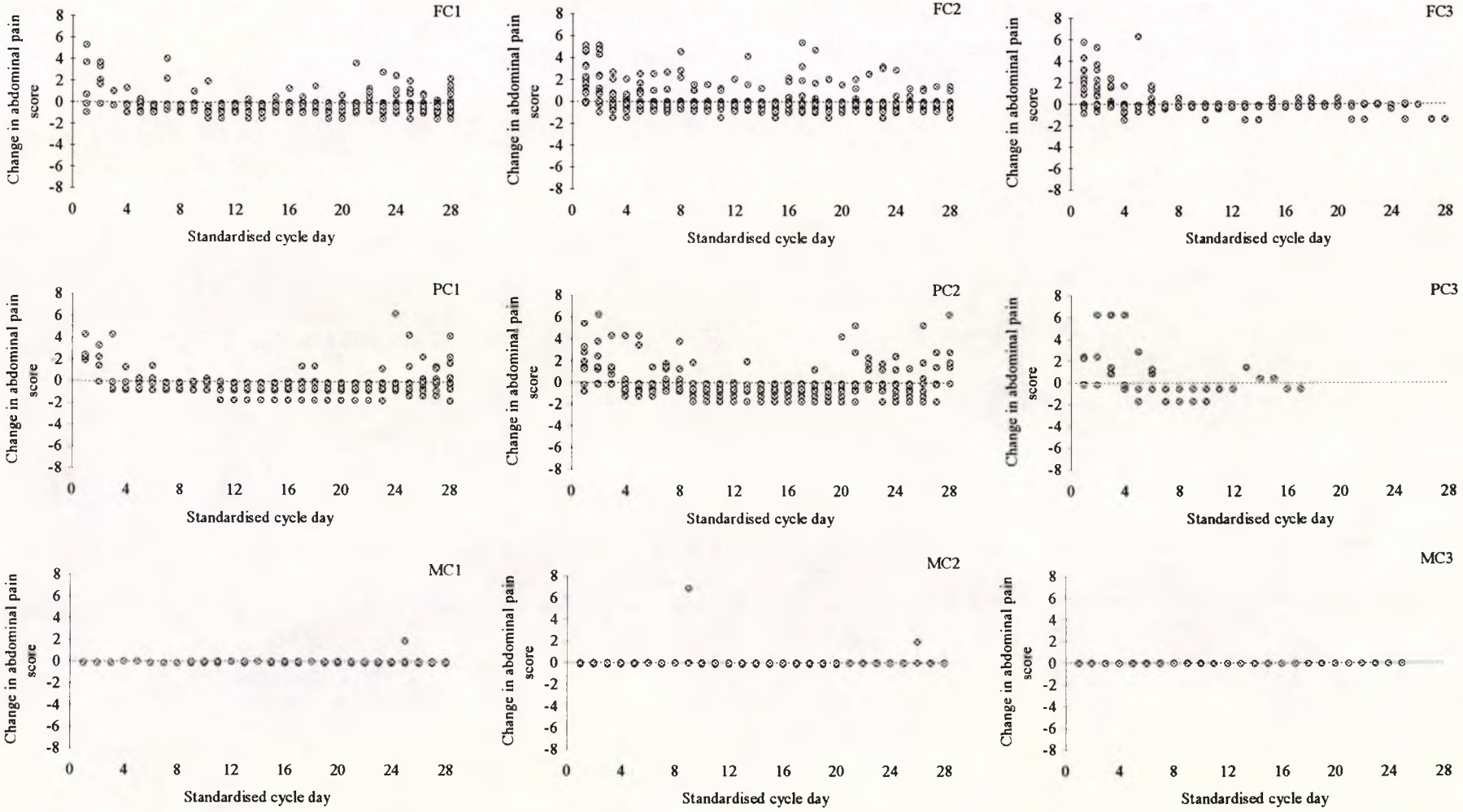


Figure A3.17 Mean change in abdominal pain scores across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

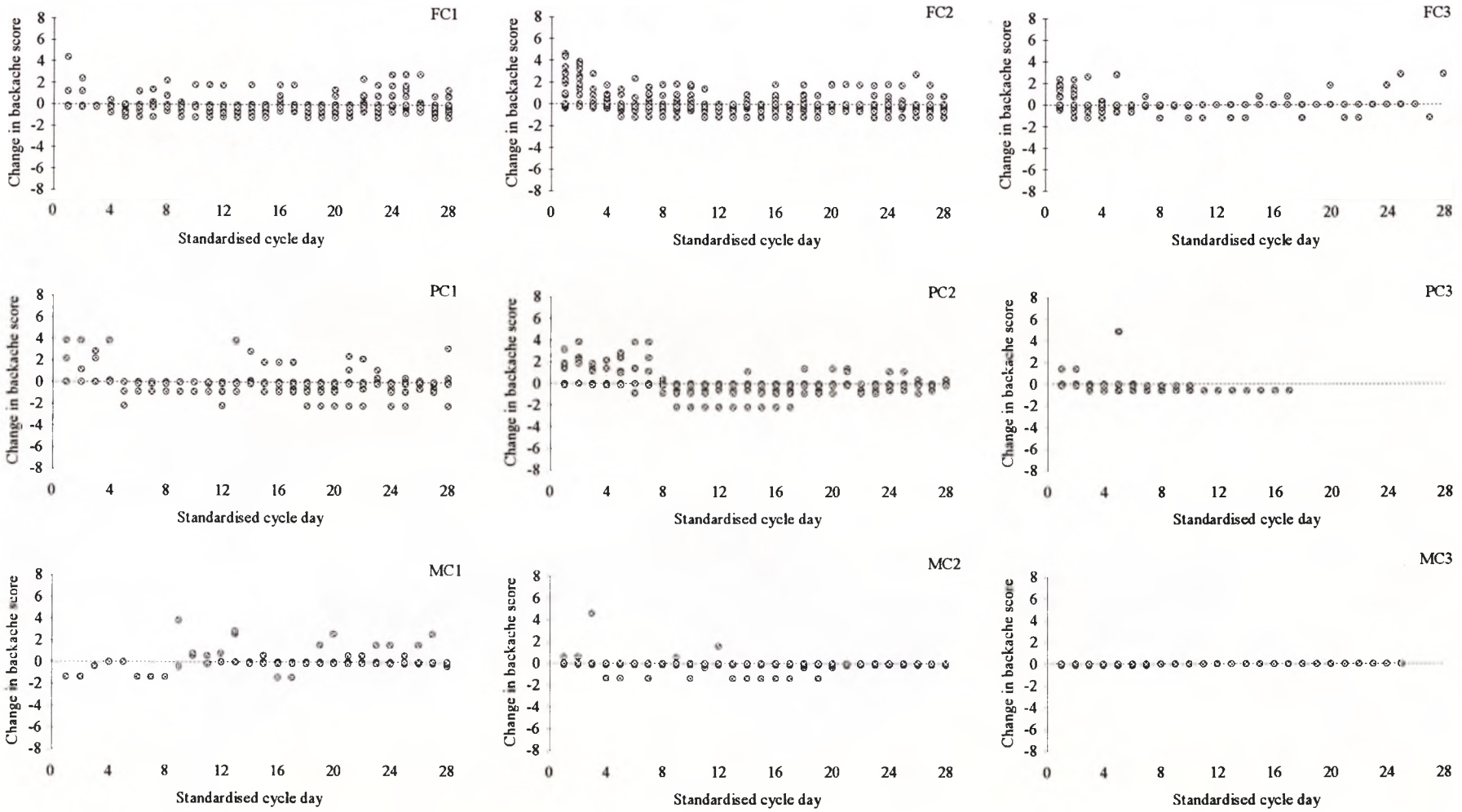


Figure A3.18 Mean change in backache scores across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

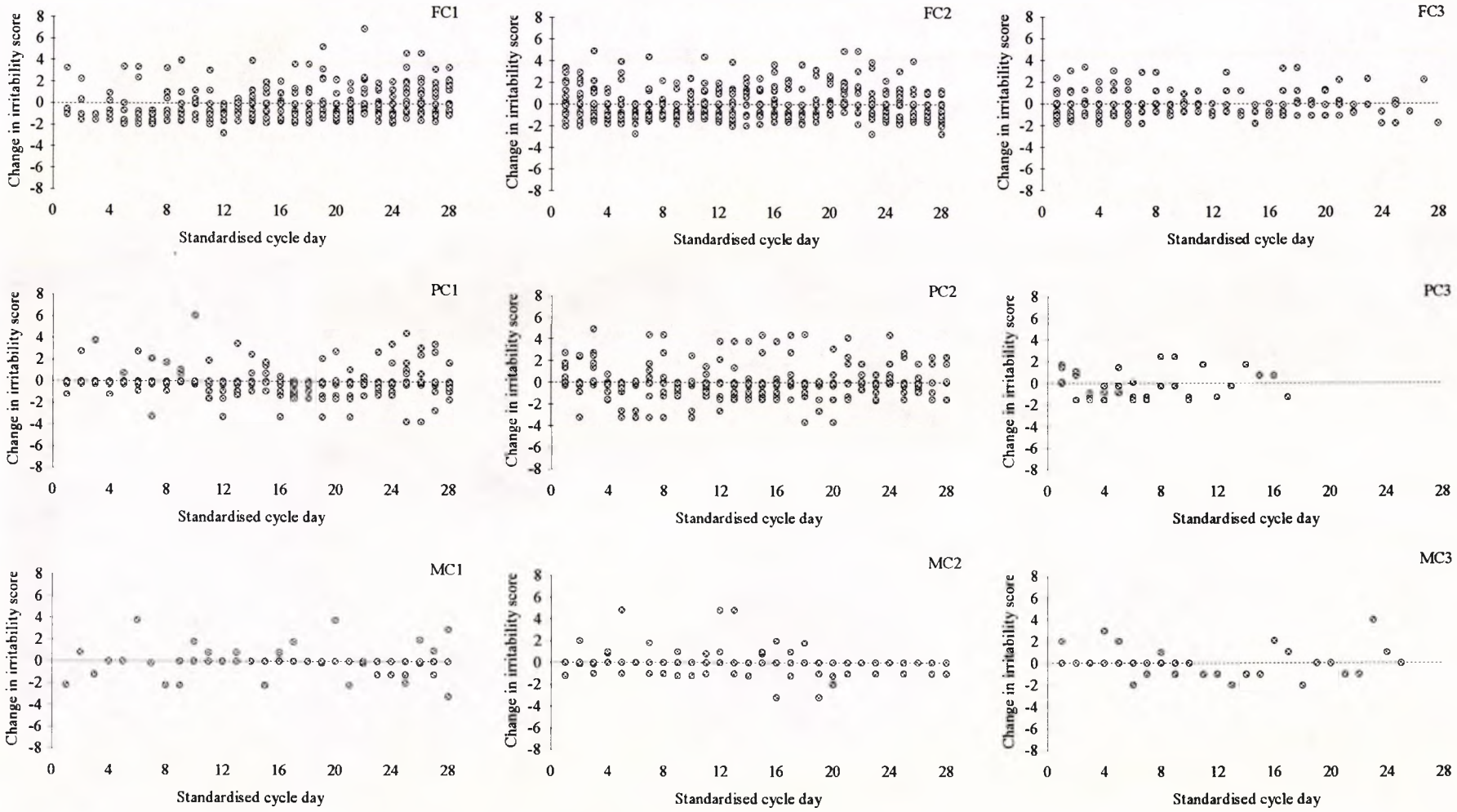


Figure A3.19 Mean change in irritability scores across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

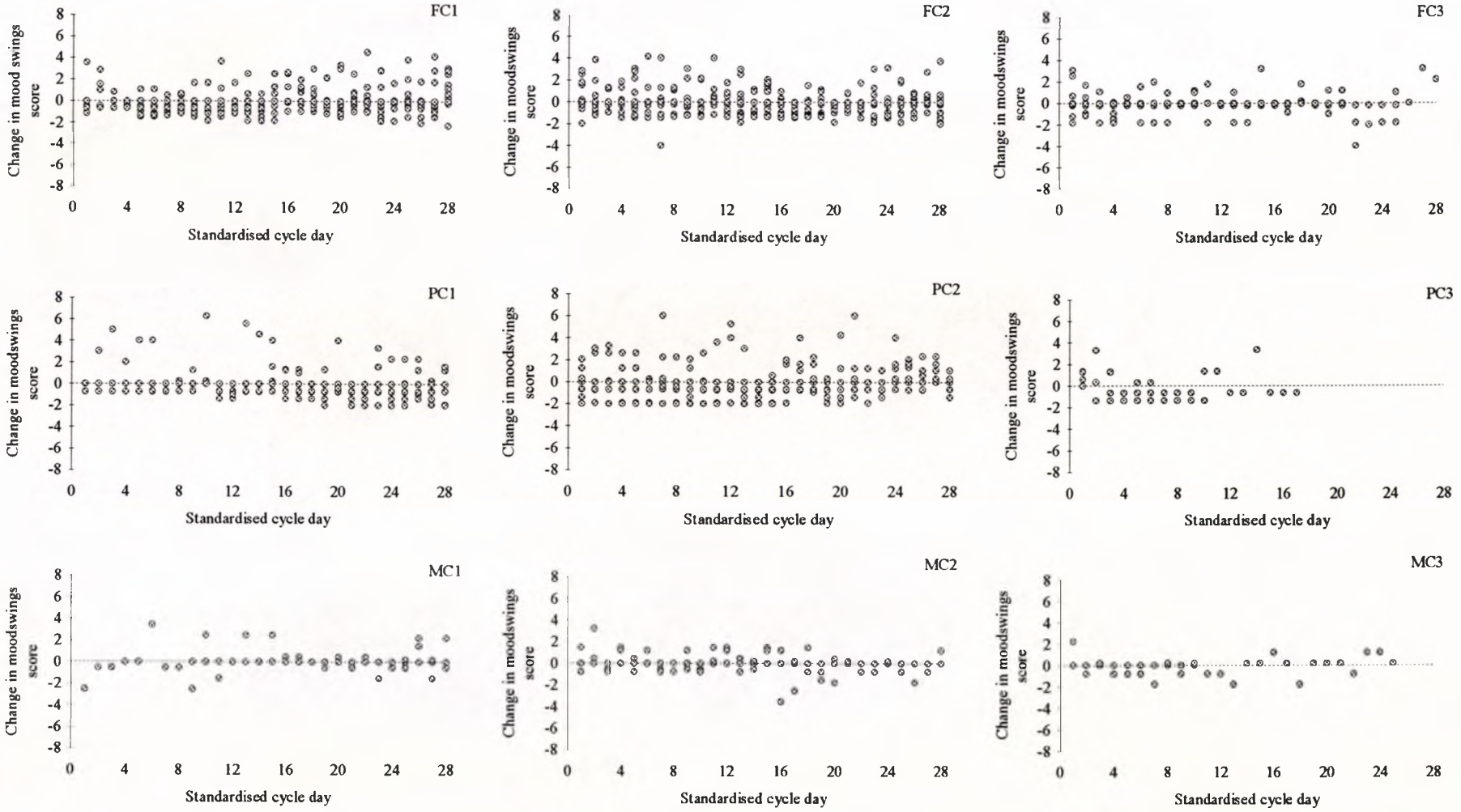


Figure A3.20 Mean change in mood swings scores across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

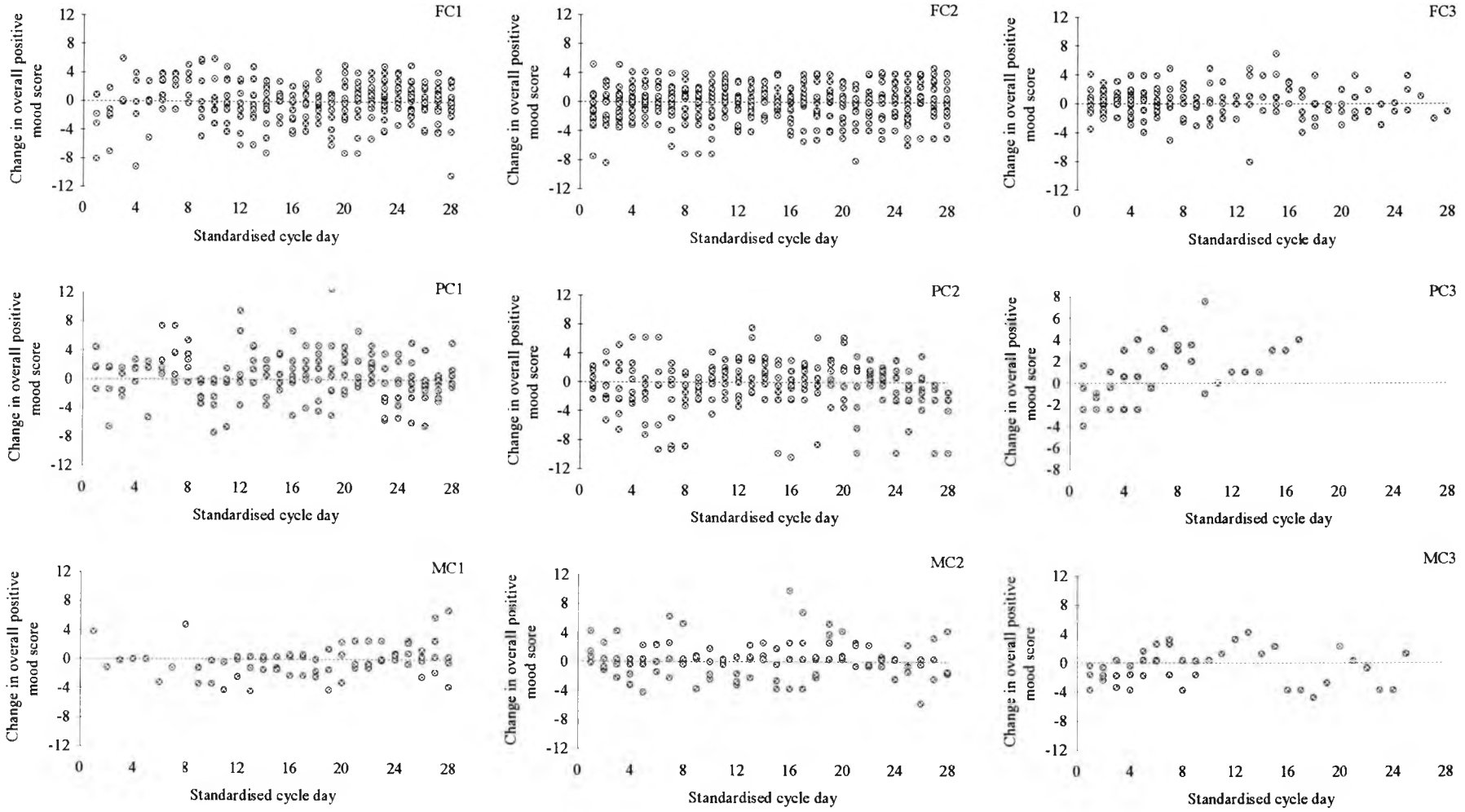


Figure A3.21 Mean change in overall positive mood scores across cycles 1 to 3 in normally menstruating women (FC1-FC3), women taking oral contraceptives (PC1-PC3) and men (MC1-MC3).

Appendix A4 Supporting publications

Refereed Papers

Guttridge, N.M., Allen, P.M., Rudnicka, A.R., Edgar, D.F., Renshaw, A.E. (1991). Influence of learning on the peripheral field as assessed by automated perimetry. In *Perimetry Update 1990/1991* (Eds R.P. Mills and A. Heijl), Kugler and Ghedini, Amsterdam, pp 567-575.

Guttridge, N.M. (1994). Changes in ocular and visual variables during the menstrual cycle. *Ophthal Physiol Opt* **14**: 38-48.

Refereed Conference Abstracts

Guttridge, N.M., Edgar, D.F. and Crabb, D.P. (1992).
Invest Ophthalmol Vis Sci (suppl) **33**:

Guttridge, N.M. and Edgar, D.F. (1994). The effect of the menstrual cycle on visual performance. *Invest Ophthalmol Vis Sci (suppl)* **35**: 1752.

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Åsman, P. (1992). Computer-assisted interpretation of visual fields in glaucoma. *Acta Ophthalmol* **70** (suppl 206):1-47.

Asso, D. and Beech, H.R. (1975). Susceptibility to the acquisition of a conditioned response in relation to the menstrual cycle. *J Psychosom Res* **19**: 337-344.

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