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HORMONAL AND EMOTIONAL REGULATION OF MEMORY PROCESSES

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD.) in Pharmacology.

UNIVERSITY OF DUBLIN,
TRINITY COLLEGE.

OCTOBER 2002

DECLARATION

I declare that the work contained in this thesis is entirely my own, except where credit is given in the acknowledgement section.

All subjects participating in the studies gave full and informed consent. The investigations were permitted by approval of the ethics committee of St. James' Hospital and the Federated Dublin Voluntary Hospitals.

This thesis has not been submitted as an exercise for a degree at this or any other University.

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Signed Michelle O'Reilly

Date 30·10·2002

SUMMARY

This thesis comprises two areas of study. The first study examined the effect of the menstrual cycle on Event-Related Potentials (ERPs) and verbal memory, as measured by paragraph recall and paired associates, and mood, as assessed by the Profile of Mood States (POMS) Inventory. The Cambridge Automated Neuropsychological Test Battery (CANTAB) was also deployed to investigate the effect of the menstrual cycle on visual memory and attention. The second study concerned the effect of emotional content of words on recognition memory in terms of age and gender. This was examined using ERPs and behavioural tests (percentage correct and free recall).

Sex hormones and cognition

17 healthy young women, not taking any medication, underwent electrophysiological and behavioural testing at the start and middle of their menstrual cycles. The CANTAB battery was administered to a further 12 young females at the start and middle of their menstrual cycles. Hormone samples were collected to determine the levels of serum oestrogen and progesterone at the time of testing. Plasma oestrogen and progesterone were significantly higher at mid-cycle compared to start-cycle, thus confirming the menstrual cycle phase. The ERP repetition effect, evoked by both direct and indirect memory tasks, was stable across the menstrual cycle. However the P300 and the LPC had greater amplitudes at start-cycle compared to mid-cycle. While recognition accuracy, reaction times, paragraph recall and paired associate test scores did not vary with the cycle, mood as assessed by the POMS inventory was significantly enhanced at mid-cycle relative to start-cycle. No effect of the menstrual cycle on attention and visual memory, as measured by the ID/ED set shift task, the PAL and DMTS tasks, was observed. The electrophysiological findings suggest that while ERP correlates of memory are stable across the menstrual cycle, correlates of

stimulus processing are responsive to hormonal fluctuations throughout the menstrual cycle. The psychometric data results indicate that mood may be sensitive to the menstrual cycle phase.

Emotion and cognition

Much evidence suggests that brain activity is sensitive to the emotional content of words. Results from an emotional word rating study conducted on sixty students revealed that males gave more negative scores to negative words, while females rated positive words more positively. Females rated words as significantly more arousing than males. The effect of emotional content of words on recognition memory in terms of age and gender was investigated via ERPs and behavioural tests (percentage correct and free recall). Nineteen young and eighteen elderly subjects participated in the study. Young females performed significantly better than young males on the percentage correct for the direct, indirect and free recall tasks. This sex difference was pronounced in the elderly group. The elderly group had significantly lower scores in these tasks relative to the young subjects. The free recall data showed a valence effect in the young females, whereby positive words were recalled more than neutral or negative words. No effect of emotional content on these memory tasks was observed in the elderly group. The ERP repetition effect was greater for neutral and positive words than for negative words, though they were not different from each other. This effect was only present in the direct task and in females. Cumulatively, emotional content had consistent effects on emotional response and on recognition memory processes. These findings may reflect the greater processing assigned to negative stimuli. The influence of gender on emotional processing suggests that females have a greater propensity for this negative memory bias. The lack of an emotional memory effect in the elderly may reflect impaired memory function due to the ageing process.

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Dr. Conal Cunningham deserves special thanks for his help and encouragement over the past three years. I would like to express my sincere gratitude to Professor Mike Rowan and Professor Brian Lawlor for their support and advice. I would also like to thank my colleagues in the Mercer's Institute, particularly Nurse Irene Bruce for collecting blood samples and Dr. Robert Coen for advice on neuropsychological testing. I am very grateful to Leigh Carolan for helping me with the ERP testing, recruiting elderly participants and for keeping my spirits up over the past year. The support of Richard Roche and Nicola Porter from the Psychology Department in Trinity College is also much appreciated. I would like to thank Cathal Walsh (Statistics Department) for his statistical help and advice.

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I would like to dedicate this to my Aunt Tess Kilcullen, who will always be a source of inspiration to me.

Table of Contents

Chapter 2 - Sex Hormones and Cognition: Background

Chapter 3 - Sex Hormones and Cognition - Methods

Chapter 6 - Emotion and Cognition: Background

Chapter 7 - Emotion and Cognition - Methodology

Appendices

List of Tables

List of Figures

List of Abbreviations

ABR - Auditory Evoked Potential

AD – Alzheimer's Disease

ANEW – Affective Norms for English Words

BAER – Basal Auditory Evoked Potential

CANTAB – Cambridge Automated Neuropsychological Test Battery

CNV – Cognitive Negative Variation

DMTS – Delayed Matching to Sample

EEG – Electroencephalogram

EPSP - Excitatory Post-Synaptic Potential

ERP - Event-Related Potential

fMRI – functional magnetic resonance imaging

HRT – Hormone Replacement Therapy

ID/ED – Intra-Dimensional/Extra-Dimensional

IPSP - Inhibitory Post-Synaptic Potential

LPC – Late Positive Component

PAL – Paired Associate Learning

PD – Parkinson's Disease

PET – Positron Emission Tomography

POMS – Profile of Mood States

rCBF - regional Cerebral Blood Flow

VEP – Visual Evoked Potential

Chapter 1

Event-related Brain Potentials (ERPs) and Memory

1.1 Introduction

The study of event-related brain potentials (ERPs) has, along with functional neuroimaging, become one of the primary research tools in the field of neuroscience and neuropsychology. Event-related potentials are a unique investigative tool in that they allow the time-course of cognitive processing to be pinpointed with millisecond accuracy. The employment of ERPs as a research method is appropriate to the aims of this thesis, namely the examination of the effects of hormonal fluctuations across the menstrual cycle and emotional processing on cognition in general, and memory in particular. The ERP technique provides an objective method of analysing multiple memory systems in the human brain and offers insights into brain function at a qualitative (site of brain activity) and quantitative (magnitude of brain activity) level.

1.2 Historical background

The credit for the discovery of the EEG, a devise that can record electrical potential differences between different parts of the brain, lies with Richard Caton, a physician from Liverpool. By the late 1800s, scientists were able to demonstrate for the first time that stimulation of certain parts of the cortex caused activation of specific muscle groups. Whether any connection existed between external stimuli and possible electrical activity in the brain was still unknown. In the course of his studies, Caton observed continuous fluctuations in electrical potential when two electrodes were attached to the exposed cerebral hemispheres of rabbits and monkeys (Caton, 1875). Furthermore, he demonstrated that this oscillation of potential was present in the stimulated animal and that it was unrelated to cardiac or respiratory rhythms. This electrical potential was biological in nature as it varied in response to hypoxia and

anaesthesia and was abolished by death. Caton also observed electrical potential change elicited by peripheral stimulation. Thus, this second discovery represents the beginning of sensory evoked potentials.

Such findings were pursued by Adolf Beck, a Polish physiologist and more prominently by Hans Berger, a German neuropsychiatrist now known as the father of encephalography. He recorded the first human trace in 1924 and named the electrical activity from the scalp "Das Elektrenkephalogram", now known as the electroencephalogram or "EEG". Its two principal components were named alpha and beta. However Berger's work was viewed with scepticism and it was not until a scientific demonstration to the British Physiological Society in 1934 in Cambridge that the EEG became widely accepted. Further work by Berger in the 1930s clearly demonstrated that the EEG was intrinsically cerebral in origin, and not due to cerebral pulsations, cerebral blood flow, skeletal or eye movement artifact or the electrical properties of the skin.

In 1939, Davis carried out a study on changes in the EEG due to a sensory stimulus i.e. the evoked potential. In a study titled "A Summation Technique for Detecting Small Signals in a Large Irregular Background", Dawson demonstrated evoked potentials to electrical stimulation of the ulnar nerve (Dawson, 1947). His technique of averaging made it possible to measure such low amplitude responses against the background of the much larger EEG amplitudes. This procedure involves selecting EEG samples that are time-locked to the stimulus, i.e. the evoked potentials, and averaging or superimposing these on each other, whereby the random EEG signals (noise) cancel each other out.

Indeed such pioneering research formed the basis for the huge array of clinical experiments performed in the late twentieth century, such as those investigating the effects of different drugs or of different stimuli on the electrophysiology of the brain. Its many clinical applications

include the detection of optic tract lesions in multiple sclerosis patients and the use of evoked potential abnormalities to localise lesions in patients with focal pathology of the nervous system. Today, ERPs are widely employed in the investigation of a variety of sensory and cognitive processes such as visual function, attention and memory. The most up-to-date techniques include the coregistration of ERPs with functional imaging (fMRI) and magnetoencephalography (MEG).

1.3 Physiological Basis of ERPs

The normal EEG is generated by excitatory and inhibitory synaptic potentials of large populations of pyramidal neurons in the cerebral cortex. The amplitude of this signal depends on the synchronized activation of these groups of neurons, which are perpendicularly directed to the cortical surface, with extended dendritic arborizations in superficial layers parallel to the cortical surface (Caspers, 1980; Speckmann, 1982; Pedley, 1990;).

In order to gain a clearer insight into the neurophysiological processes underlying the EEG, it is necessary to provide a brief description of electrochemical signal transmission in the brain. Excitatory or inhibitory signals are brought about by the release of neurotransmitters from the axon of the pre-synaptic neuron to the cell body or dendritic tree of the post-synaptic neuron, thereby altering the electrical potential across the cell membrane. This membrane is usually in a state of electrochemical equilibrium (resting potential = – 70mV) due to the constant influx and outflow of electrically charged ions. Any change in the resting potential will make the cell either more or less likely to generate an action potential (fire). Depolarization occurs when an excitatory signal causes ion channels to open, producing an influx of positive ions and a less negative membrane potential, from –70mV to 0 mV or higher. Such an electrical change is known as an excitatory post-synaptic potential (EPSP). If depolarization reaches a certain threshold at approximately + 30mV, an action potential is generated and the neurotransmitter is

released onto another cell. The voltage change associated with chemical signalling at an inhibitory synapse is known as an inhibitory post-synaptic potential (IPSP). IPSPs make the neuron less likely to fire by producing a more negative membrane potential, making the threshold for action potential propagation more difficult to reach. This is known as hyperpolarization. The EEG represents the summated effects of these depolarizations and hyperpolarizations.

The physiological underpinnings of the EEG have also been described in terms of sinks and sources (neural current sources). Excitatory synaptic input (EPSP) produces a local current sink, which draws positive ions into the cell, thus raising the membrane potential towards 0 mV. Local synaptic sinks are balanced by distant passive sources. When the sink draws this current (ions) into the cell, they pass through the neuron and are emitted at another location, known as a positive source. For example, if there was a sink at a branch of the cell's dendritic tree, the distant source may occur at the cell body. The existence of a negative sink in one part of the neuron and the positive source in another means that the cell may be seen as a dipole. However an IPSP causes current to flow across the membrane into the extracellular fluid, thereby creating a more negative membrane potential. This is balanced by sinks distributed along distant portions of the membrane. Similarly this may be considered as a dipole. For a review of these mechanisms, see Nunez, 1987.

If a scalp potential is due to synaptic activity distributed over an area of less than 1 cm^2, the large number of microsources is known as a single dipole source. Usually scalp potentials are due to larger areas of activity. A homogenous dipole layer consists of large numbers of parallel dipoles with synchronized activity. However, dipole layers rarely occur with completely homogenous polarities of sinks and sources. A more common phenomenon is for the layer to consist of a mixture of polarities of dipoles, whereby the overall potential will reflect the majority of dipole polarities.

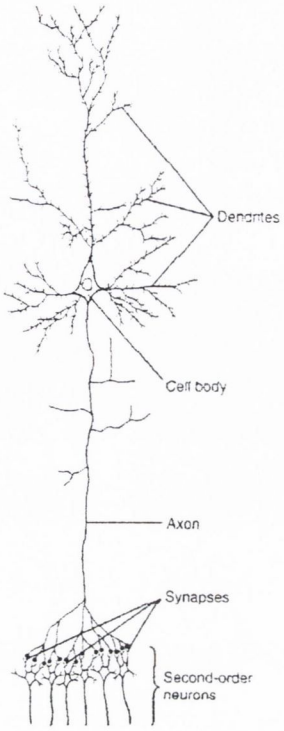

Figure 1.1 Structure of neuron, showing its important functional parts. Adapted from Guyton, AC: Basic Neuroscience: Anatomy and Physiology. Philadelphia: WB Saunders Co., 1987)

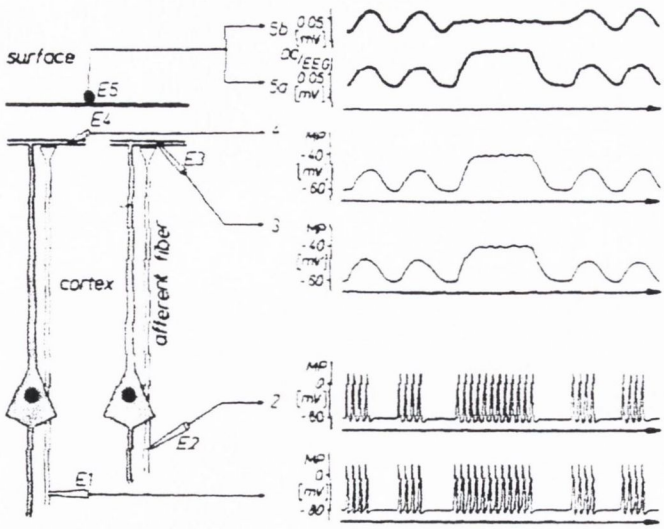

Figure 1.2. A model showing the principles of EEG wave generation. The model consists of two large cortical pyramidal cells of vertical orientation, with terminals of afferent fibres projecting on apical superficial dendritic arborizations of these cells. Bursts of action potentials in the afferent fibres (E1-E2) visible in the lower two traces, generate through excitatory synapses depolarizations in membrane potentials (MP) (E3-E4) in pyramidal dendrites. The extracellular field potentials recorded at the cortical surface (E5) have an opposite polarity. Adapted from Speckmann & Elger, 1982.

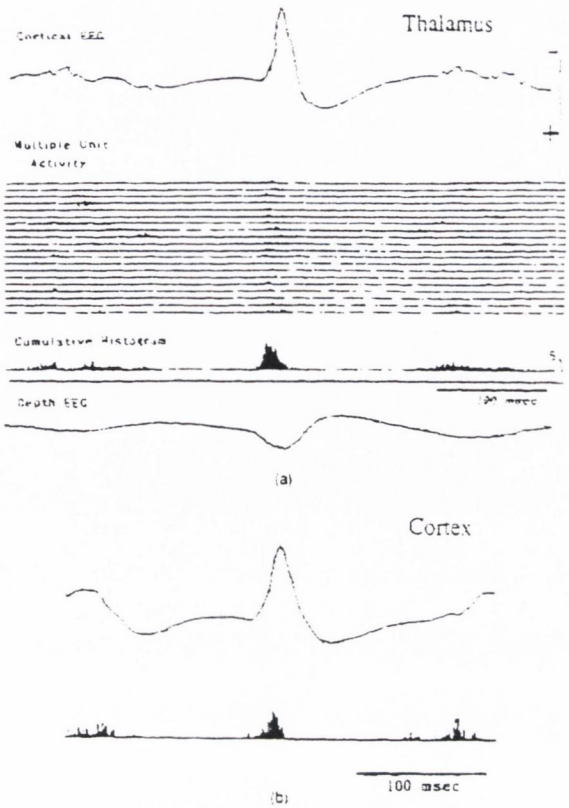

Figure 1.3 Correlation of cortically recorded spike-wave discharges with 'multiple unit activity' of (a) thalamic neurons and with (b) cortical neurons. All registrations are from rats and the spike of the spike-wave discharge is taken as a trigger. The 'cumulative histogram' of the neuronal activity reveals that cellular firing is related to the large negative spike and that the positive waves preceding and following the spike are related to neuronal inhibitions with cell silence. The figure further shows that thalamic neuronal firing precedes cortical firing. Note that the polarity of the depth EEG, registered of deep cortical layers and shown at the bottom of (a), has an opposite polarity compared to the superficial recorded EEG. Adapted from Coenen, 1995.

The spatial orientation of the neuronal population is an important determinant of EEG activity, as only those populations with an "open-field" orientation are capable of summation. Such a description applies to sets of neurons that are aligned in parallel layers in the same axis, for example in the thalamus and the cerebral cortex. "Closed field" potentials however are thought to be generated by concentrically aligned neurons which tend to cancel each other out, and therefore cannot be recorded from distant scalp electrodes. Examples of closed field organisation include the midbrain nuclei.

Many studies have shown that the polarity of ERPs is related to either neuronal excitation or inhibition. Vaughan (1969) observed that the first negatively directed wave in the visual ERP of a monkey was associated with an increase in excitation, and the second positive wave with inhibitory activities. Comparison of evoked potentials and neuronal spiking activity shows that neuronal discharge gives rise to negative ERP components, while cellular inhibition underlies positive components. Thus EPSP/depolorizations correspond to negative ERP deflections, while IPSPs/hyperpolarizations underlie positive deflections. Specifically, scalp recorded negative potentials may be due to depolarization of pyramidal cell dendrites creating an extracellular surface current sink, with the reverse situation occurring in the case of scalp recorded positives. Although this polarity reversal between intracranial and scalp recorded activity is true in most cases, the opposite relationship, where scalp positives are due to neuronal excitation and negatives to inhibition, has also been found (Kostopoulos, 1984).

1.4 Event-related potentials

Event-related potentials (ERPs) represent scalp-recorded changes in the brain's electrical activity time-locked to some definable event such as the presentation of a word. ERP components are commonly defined

along an "exogenous/endogenous" dimension. This dimension correlates roughly with time, whereby in each sensory modality, exogenous components tend to occur at earlier latencies than do endogenous components. They are generated in an obligatory fashion following stimulus presentation and occur irrespective of the subjects' psychological state. An example of this is given by the auditory brainstem potential. Endogenous ERPs are thought to reflect the activity of neuronal networks involved in the cognitive processing of sensory information and can occur several hundred milliseconds after the stimulus. Examples of endogenous ERPs include the P300 and the N400 waveforms as well as the ERP repetition effect, which shall be discussed at length later in this chapter.

There are several reasons why ERPs are useful for studying cognitive function in general and memory in particular. Because the temporal resolution of ERPs is in the order of milliseconds, they are well suited to addressing questions about the time course of the neural correlates of stimulus-locked cognitive processes. Thus, upper-bound estimates of the time required by the nervous system to discriminate between different classes of stimuli (e.g. new and old words in a recognition task) can be made directly. Such temporal resolution is presently unattainable with other functional neuroimaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). A major drawback of this method, however, is that there are no solutions for the localization of the sources of ERP activity. In this respect, ERPs compare poorly with PET and fMRI, which allow task-related changes in cerebral activity to be localised with a spatial resolution of less than a centimetre. Although this does not compromise the investigation of whether stimuli from different experimental conditions engage distinct neural populations, it limits the strength of the neuroanatomical conclusions that can be drawn. A second advantage of the ERP technique is that ERP waveforms can be formed "off-line", after the experimental trials have been sorted into different conditions on the basis of the analysis of the subject's behaviour. Finally, ERPs can be

employed to investigate whether different experimental conditions engage functionally dissociable cognitive processes. This is based on the assumption that if two experimental conditions are associated with qualitatively different patterns of scalp electrical activity, those conditions engaged non-overlapping neural, and hence functional, processes. However, purely quantitative differences in the ERPs associated with two conditions suggest evidence for different levels of engagement of the same neural/functional processes.

1.5 P300

The scalp-recorded human P300 was first described by Sutton *et al.* in 1965 and has been intensely researched over the past two decades (for a review, see Polich & Kok, 1995). The P300 is a positive potential, maximal over the midline vertex site, occurring approximately 300 ms after the stimulus presentation. The P300 is usually elicited using a so-called "odd-ball" stimulus paradigm, whereby target and non-target stimuli are presented in a quasi-random sequence, usually with the target stimuli occurring 15-20% of the time. P300 elicitation is contingent upon target recognition. The P300 has been extensively researched because of its significance as a means to assess cognitive function in a variety of circumstances (Polich, 1993a; Pritchard, 1986; Polich, 1986b, Segalowitz & Barnes, 1993).

The P300 may be a neural correlate of several cognitive functions including sequential information processing, short-term memory and decision-making (Squires, 1976; Squires, 1977). It is possible that the P300 represents several processes occurring in sequence, each contributing to the efficient assimilation of new stimulus information. The P300 potential is generated whenever attentional resources are required to process a new stimulus that is different from previous stimuli (Polich, 1989a). Donchin *et al.* (1986) proposed that the P300 represents the updating of working memory which involves the transfer of stimulus

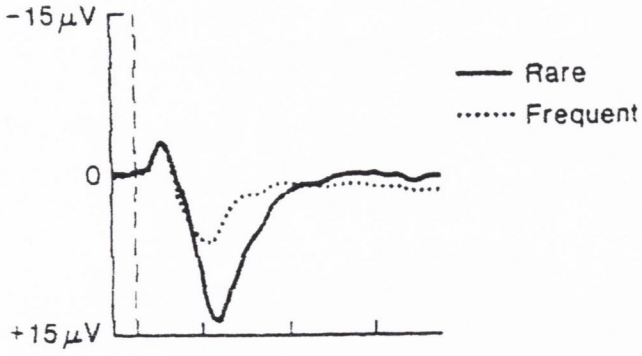

Figure 1.4. Grand average of the auditory evoked potential of humans in an 'oddball'-paradigm. Following an initial negative wave, a prominent P300 becomes visible, especially when a rare stimulus is presented. Stimulus onset is displayed at the broken vertical line and positivity is directed downwards. The time scale indicated on the x-axis is 400 msec. Adapted from Coenen, 1995.

information from short-term to long-term memory scores, stimulus assimilation and decision to respond (context updating theory).

At a neurophysiological level, the P300 may be an expression of the hyperpolarizations of thalamocortical neurons (see Section 1.3). As the P300 occurs under conditions needing selective attention to distinguish a target stimulus from a standard one, inhibitory activities may have a role in the process of comparing or evaluating information. It has been proposed that correct information may be more easily accessible by the closure of alternative pathways (Coenen *et al.*, 1995).

1.5.1 Neuroanatomical source

The scalp-recorded P300 appears to be the product of multiple cortical generators (Smith, 1990; Rugg, 1994) with some small contribution from subcortical generators (McCarthy *et al.* 1989). There is conflicting evidence that the hippocampus/medial temporal lobe and the thalamus/basal ganglia are important in P300 generation. The evidence for a hippocampal/medial temporal lobe source comes from human depth electrode (Halgren *et al.*, 1980) and magnetoencephalography (Okada *et al.*, 1983) studies. However comparisons of scalp and intracerebral waveforms (Altafullah, 1986), recordings from patients with unilateral temporal lobe pathology (Stapleton, 1987; Rugg *et al.*, 1991), and the effects of medial temporal lobe lesions on a monkey analogue of P300 (Paller *et al.*, 1988), suggest that the hippocampus is not necessary for the generation of the scalp P300. Another possible P300 generator site is the inferior parietal cortex (Smith *et al.*, 1990; Knight *et al.*, 1989). More recent evidence, based on depth electrode and magneto-EEG recording techniques, suggests that subcortical structures in the thalamus (Rodgers *et al.*, 1991) and the basal ganglia (Kropotov & Ponomarev, 1991) may play a role in P300 generation. Other topographical evoked potential mapping and electromagnetic recordings of current sources have suggested the temporal parietal cortex as the primary generator source of the P300 (Pritchard, 1981). Furthermore,

animal studies have demonstrated that the basal forebrain's cholinergic system may be involved in P300 generation (Harrison, 1988).

1.5.2 P300 Latency

P300 latency is thought to reflect the speed of stimulus classification when an infrequent stimulus results in a shift in attention (Kutas & Donchin, 1977). It is affected by stimulus quality (McCarthy, 1981) and memory set size (Brookhuis, 1981). P300 latency is often longer than reaction time, suggesting that P300 process is not a causal element in overt decision but reflects subsequent memory storage processes that enable subject to use current information to prepare for future events.

1.5.3 Neurotransmitter modulation of the P300

Several neurotransmitter systems appear to modulate the P300 (for review see Frodl-Bausch, 1999). Administration of scopolamine, the muscarinic cholinergic antagonist, induces short-term memory impairment accompanied by P300 latency prolongation in young, healthy subjects (Callaway, 1984). Potter *et al.* (2000) reported that scopolamine abolished the auditory P300, indicating the role of cholinergic neurotransmitter systems in P300 generation. Such an effect is partly reversed with physostigmine, an anticholinesterase (Meador *et al.*, 1987). Withdrawal of dopaminergic agonist therapy in Parkinson's patients causes a delay in P300 latency, with a reversal to normal return to therapy (Stanzione *et al.*, 1991). The noradrenergic and serotonergic systems also influence the P300. Pineda *et al.* (1989) demonstrated that destruction of the locus coeruleus in monkeys, thereby removing the ascending noradrenergic supply to the neocortex, affects the P300. Studies have reported that serotonin selective drugs reduce P300 amplitude (d'Ardhuy, 1999), implicating the serotonergic system in P300 generation/modulation. Clearly therefore, the cholinergic, dopaminergic, noradrenergic and serotonergic neurotransmitter systems all have a modulatory effect on the P300.

1.6 The ERP Repetition Effect

Several recent studies have shown that ERPs may reflect processes occurring during the storage of items and their subsequent retrieval. Much of this research has found that words presented to a subject for a second time evoke a more positive-going ERP than words presented for the first time in a trial. This is what is known as the ERP repetition effect, which reflects the modulation of two underlying components, namely, the N400 and the P300 (for a review, see Rugg, 1995).

The N400 is thought to represent a period of associative activation, leading to the formation or the access to the representations of items in memory (Halgren, 1984; Halgren, 1990; Halgren & Smith, 1987). The amplitude of this component is influenced by the overall amount of activation that is available for a representation as a result of a prior exposure (Karayandis *et al.*, 1991). As outlined in section 1.4, the P300 reflects activity related to attention allocation and activation of memory.

Two theories have been proposed in the attempt to identify the ERP repetition effect with specific processes such as semantic activation or access to episodic traces. The semantic theory suggests that the repetition effect results from the temporary modification of abstract pre-existing memory representations in lexical memory (Morton 1969; Morton, 1979; Monsell, 1985). They propose that the N400 reflects processes dependant on the activation levels of word detectors. When the activation level of the detector is boosted by the prior presentation of the same or related word, the activation required to exceed the detectors threshold is lowered, thereby reducing the N400 amplitude. This resembles the context integration hypothesis, which describes the N400 as the result of extensive processing required to integrate a stimulus with the context in which it occurred. Attenuation of the N400 with repetition reflects the need for less associative activity for items repeated in same context, leading to an attenuated N400 and an enhanced ERP repetition

effect (Halgren & Smith, 1987; 1989; Rugg, 1990; Rugg & Doyle, 1994; Holcomb, 1993; Van Petten, 1991).

The episodic theory proposes that the repetition effect is due to the formation and subsequent retrieval of a specific memory about an item's prior presentation (Jacoby, 1983; Feustel, 1983; Salasoo, 1985). Such accounts emphasise the fact that non-words, which possess no representation in memory prior to their first presentation, show repetition effects of a similar magnitude to those found with words (Rugg & Nagy, 1987). Now it is believed that the repetition effect is subserved by both a short-term semantic activation system and a long-term episodic memory system with interface structures that coordinate the functioning of both (Guillem *et al.*, 1999)

A body of recent work has focused upon the ERP repetition effect in terms of recollection, where recollection is defined as the ability to identify the context in which a recognised test item was experienced. Two topographically distinct ERP repetition effects have emerged from such studies. The left parietal effect (Paller, 1995; Rugg, 1995; Rugg, 1998; Smith, 1993; Wilding, 1995, 1996) consists of a positive-going wave which is maximal at temporo-parietal electrode sites and larger over the left than the right hemisphere; onset is ~400ms post-stimulus and duration ~400-600ms. This effect has been interpreted as a reflection of the contribution of the medial temporal lobe system to the retrieval of recently encoded episodes, possibly representing hippocampally- modulated cortical activity thought to underlie such retrieval processes (Alvarez & Squire, 1994; McClelland *et al.*, 1994).

The right frontal effect (Wilding & Rugg, 1996; Donaldson & Rugg, 1998; Rugg & Schoerscheidt, 1998; Mark, 1998; Duzel, 1997) also has an onset at ~400ms post-stimulus, but is more sustained over time and is maximal over frontal regions of the scalp where it shows a right-greater-than-left asymmetry. This effect is larger when elicited by items that are correctly assigned to their encoding context, suggesting that it too

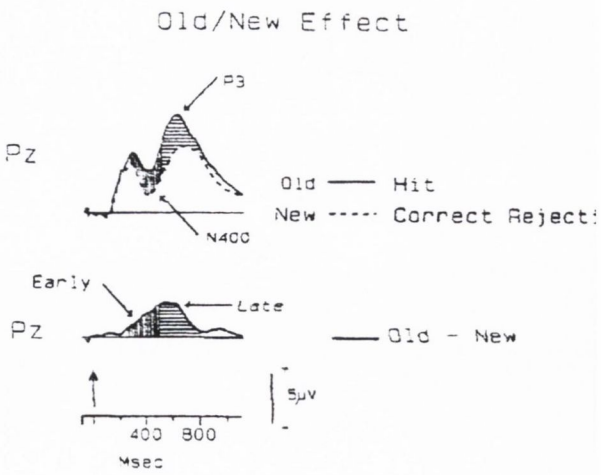

Figure 1.5 Top row. Grand mean ERPs elicited by previously studied (old) and unstudied (new) words recorded at the midline parietal (Pz) scalp site during the test phase of a study/test paradigm.

Bottom row. The result of subtracting the ERPs elicited by new items from the ERPs elicited by old items, i.e. the old/new difference waveform. In the top row, vertical hash marks indicate the N400 region, and horizontal hash marks, the P3 region of the old/new effect. In the bottom row, these are referred to as the early and late regions of the old/new effect. Arrow marks stimulus onset, with time lies every 200 ms.

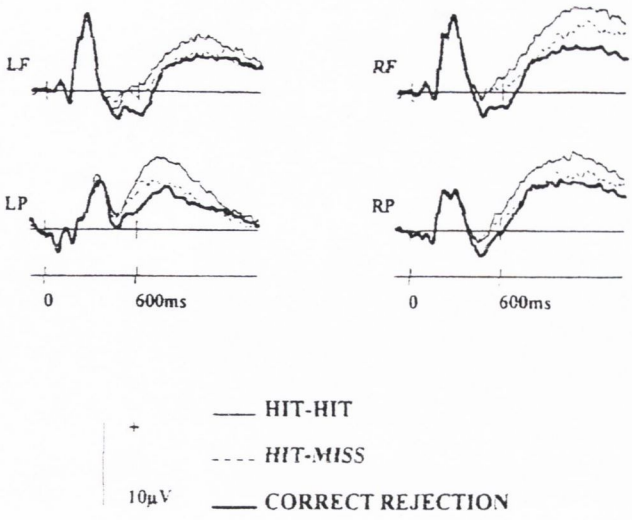

Figure 1.6 ERPs from left and right frontal (LF, RF) and parietal (LP, RP) electrodes, illustrating the left parietal and right frontal repetition effects. Hit-Hit: recognized old items for which source was correctly assigned; Hit-Miss: recognized old items attracting incorrect source judgement; Correct Rejection: correctly classified new items. Adapted from Wilding & Rugg, 1996.

reflects processes associated with recollection. It has been suggested that it reflects processes that contribute to the integration and maintenance of retrieved information, possibly supported by the prefrontal cortex (Squire *et al.*, 1993; Knowlton & Squire, 1995). Wilding and Rugg suggested that these parietal and frontal effects reflected neuroanatomically and cognitively distinct contributions to recognition memory, associated with, respectively, episodic retrieval devoid of contextual information, and the successful retrieval of the source.

1.6.1 Neuroanatomical source

As noted earlier (Section 1.3), it is not possible to address the issue of the locations of intracerebral generators by much more than informed speculation. Some studies suggest that anatomical generator for the ERP repetition effect is probably located in the temporal lobes. Grunwald & Elger (1995) generated the repetition effect via a visual oddball paradigm using depth electrodes inserted into the anterior medial temporal lobe. Rugg *et al.* in 1991 found that patients with left or right temporal lobectomy do not show a more positive- going ERP in response to word recognition. In a study carried out by Grunwald *et al.* (1998), subjects with hippocampal sclerosis had an abnormal ERP response to new (though not repeated) words and subjects with extra-hippocampal lesions had abnormal responses to both new and repeated words. Thus a repetition effect was not found for any of the subjects. This implies that the repetition effect depends on both novelty detection (with hippocampal and extra-hippocampal temporal loci) and repetition detection (with an extra-hippocampal temporal locus).

The left parietal effect may reflect the contribution of the medial temporal lobes to episodic retrieval. However it has been suggested (Rugg, 1995) that neural activity in the medial temporal regions does not volume conduct to the scalp. Wilding & Rugg (1996) suggested that the effect may reflect changes in cortical activity caused by cortico-hippocampal interactions (McClelland *et al.*, 1995). The scalp

distribution of this effect suggests that this activity originates in the left hemisphere, as might be expected considering the importance of this hemisphere in verbal memory (Smith, 1989).

Behavioural and PET studies suggest that the right frontal effect arises in the prefrontal cortex. Stuss *et al.* (1994) observed that memory for source is disproportionally impaired after damage to the prefrontal cortex. PET studies have consistently reported that episodic memory retrieval is associated with activation of the right dorsolateral prefrontal cortex (Fletcher *et al.*, 1997).

1.6.2 Direct and Indirect Memory Tasks

In many studies ERP repetition effects have been elicited by direct, continuous recognition memory tasks whereby subjects discriminate between new and repeated words (Rugg and Nagy, 1989) and also by indirect tasks, which requires a response to occasional target words (Rugg, 1987; Nagy and Rugg, 1989). In direct tasks, subjects are required to retrieve information about a past event. In the indirect tests, no reference is made to the past and the repetition of the critical words is incidental to the task. The repetition effect in both tasks therefore serves as an index of memory.

In a study carried out by Rugg *et al.* (1997), the functional similarity of ERP repetition effects obtained in direct and indirect tests and the sensitivity of these effects to age and interitem lag were investigated. The young group's effects were larger in the direct than the indirect task, while the reverse was the case for the old subjects. The robustness of the old subjects' repetition effects in the indirect task, compared to the fragility of the effects in the direct test suggests that word repetition in the two tasks engage dissociable processes. They concluded that the ERP effects from the direct task contain a larger contribution from the LPC than do the effects in the indirect task, which may reflect N400 modulation. It has been proposed that LPC generators are more age-

sensitive than N400 generators, presumably because of the involvement of episodic memory in the direct recognition test. The age-related impairment of the processes supporting episodic memory is indeed well documented. N400 modulation, prominent in the indirect task because of its sensitivity to such semantic judgement tests, apparently remains intact with age. Furthermore, it has been proposed that effects elicited by indirect tasks are associated with implicit memory, while those evoked by direct tasks are a reflection of explicit memory (Swick, 1997; Friedman 1995).

This chapter underscores the insights offered into cognition through the use of ERPs. The employment of direct and indirect memory tasks, which elicit the ERP repetition effect, shall serve to extend existing knowledge on hormonal and emotional effects on cognitive processing and on memory.

Chapter 2

Sex Hormones and Cognition

2.1 Introduction

A burgeoning literature documents the importance of the reproductive endocrine system in cognitive processing, at a biochemical, behavioural and electrophysiological level. There is much neurobiochemical evidence indicating multiple effects of oestrogen and progesterone on the brain, particularly on neurotransmitter systems. Such neurophysiological findings run in parallel with the recent emergence of Hormone Replacement Therapy (HRT) and cognitive function as a research domain. Natural fluctuations in ovarian steroid hormones across the menstrual cycle allow for non-invasive studies of the effects of sex hormones on cognition in young women. While a range of studies exist on the effect of the menstrual cycle on psychometric measures, the area of menstrual cycle effects on event-related potentials has received little scientific attention. Event-related potentials (ERPs) are a unique investigative tool in neuropsychology in that they serve as a window for viewing the neurophysiological processes between the presentation of a stimulus and a response. The employment of ERPs as a research technique in menstrual cycle studies may serve to address the considerable gaps in our knowledge of sex hormones and cognition that remain at the beginning of the 21st century. Investigation of the ERP repetition effect (an electrophysiological index of memory) across the menstrual cycle also offers a different perspective on memory changes coincident with hormonal fluctuations across the cycle.

Thus the overall aim of this research was to investigate the effect of the menstrual cycle on a broad range of cognitive measures, from behavioural and electrophysiological measures of memory and mood to attention and visual memory. This part of the thesis concerns two studies with the common theme of menstrual cycle effects on cognition. The first examined the effect of the menstrual cycle on ERPs, namely the P300 and the ERP repetition effect, as well as verbal memory, as measured by paragraph recall and paired associates,

and mood, as assessed by the Profile of Mood States (POMS) Inventory. Thus this study focused upon the sensitivity of verbal memory at a behavioural and electrophysiological level to hormonal fluctuations across the menstrual cycle. The second study extends such research by investigating the effect of the menstrual cycle on attention and visual memory, as measured by the intra-dimensional/extra-dimensional set shift task, the Paired Associate Learning (PAL) and Delayed Matching to Sample (DMTS) tasks respectively.

2.2 Hormonal changes across the menstrual cycle

For women with 28- to 30-day cycle lengths, the menstrual cycle may be divided into two general phases, start-cycle and mid-cycle. The start-cycle phase extends from Day 1 to 5 and is characterized by low serum concentrations of oestradiol and progesterone. Concentrations of oestrogen rise during the follicular (preovulatory) phase and peaks several days prior to ovulation. As second oestrogen peak occurs post-ovulation during the luteal phase. In contrast, progesterone is very low throughout the follicular phase, begins rising just prior to ovulation, then rises dramatically to peak during the luteal phase. The mid-cycle phase encompassed Days 14-16 in this research, which is characterized by high concentrations of both oestrogen and progesterone. Thus mid-cycle may be considered as encompassing the late follicular and early luteal phases described in many menstrual cycle studies. Expected hormone concentrations were confirmed by radioimmunoassay in this research to validate the menstrual phase, because accuracy in determining menstrual stage is likely to be a major factor in contributing to incongruent results across previous studies (see Section 2.7).

2.3 Neurobiology of oestrogen

Several neurobiological studies have reported a variety of effects of oestrogen on brain function (McEwen, 2002). One mechanism for the proposed facilitatory effect of oestrogen on cognition may be related to the high density of oestrogen receptors in the hippocampus and the cerebral cortex, areas known to subserve memory and attentional processes (Ciocca *et al.*, 1995). The

hippocampus is believed to play a vital role in the encoding and consolidation of verbal and non-verbal information into short-term memory (Frisk & Milner, 1990; Squire, 1992). It has been speculated that oestrogen activity in this region might underlie effects of HRT on aspects of cognition in postmenopausal women (Sherwin, 1999). The role of the prefrontal cortex in oestrogenic effects on cognition shall be discussed later in this chapter.

2.3.1 Neuroanatomical effects

Oestrogen has important effects on neuroanatomy, namely in the promotion of neuronal outgrowth (synaptogenesis). The greater the number of spines protruding from neuronal dendrites, the greater the ability of the neuron to communicate with other neurons. Early studies found that oestrogen administration to foetal hypothalamic cultures was associated with an increase in dendritic spine density by 30% (Toran-Allerand, 1980; Toran-Allerand *et al.*, 1983). These findings were replicated in adult hypothalamic (Frankfurt *et al.*, 1990) and hippocampal studies (Gould *et al.*, 1990, 1991; Woolley *et al.*, 1990, 1992, 1993, 1994, 1997; McEwen *et al.*, 1994; Gazzaley *et al.*, 1996). Woolley *et al.* (1990) found that spine density alters cyclically across the estrus cycle – a 32% decrease in synapses in the CA1 region of the hippocampus observed in the 24 hour period from proestrus (when oestrogen levels are highest) to estrus (characterized by low oestrogen levels). Gould *et al.* (1991) reported that bilateral oophorectomy in female rats caused a decrease in dendritic spine density. This however was prevented by oestrogen administration following surgery. As changes in dendritic spine density are likely to reflect changes in synaptic density, oestrogen seems to enhance function of the hippocampus, a brain region critical for memory processes (Milner, 1958).

2.3.2 Neurophysiological effects

Oestrogen influences four major neurotransmitter systems in the brain: the basal forebrain cholinergic system, the midbrain serotonergic system, the brainstem noradrenergic system and the midbrain and hypothalamic dopaminergic systems (McEwen *et al.*, 1995, 1997). Neurophysiological

processes such as cholinergic activation and long-term potentiation are also oestrogen-sensitive. Oestrogen induces choline acetyltransferase (ChAT), a rate-limiting enzyme essential to acetlycholine formation (Loy *et al.*, 1988; Luine *et al.*, 1975, 1980; Luine & McEwen, 1983; Luine *et al.*, 1985; Gibbs, 1994). Acetlycholine is a neurotransmitter that plays an integral role in memory and attention. Choline acetyltransferase and acetlycholine levels changes across the estrus cycle (Luine *et al.*, 1975). Oestrogen deficiency is associated with the loss of ChAT activity in the basal forebrain (Gibbs *et al.*, 1998; McMillan *et al.*, 1996), an effect which is reversed by oestrogen replacement. Oestrogen administration is also associated with the growth of cholinergic neurons (Honjo *et al.*, 1992; Mudd *et al.*, 1998). Oestrogen receptors have been found to co-localize with nerve growth factor receptors in cholinergic neurons of the basal forebrain of the rat (Toran-Allerand *et al.*, 1992), suggesting that oestrogen regulates neurotrophic factors in the brain. Oestrogen also facilitates long-term potentiation in the hippocampus (Good *et al.*, 1999), a phenomenon crucial in learning and memory.

Some female epileptic patients show variation in the frequency of seizures over the menstrual cycle. These patients have a greater number of generalised seizures during the follicular (high oestrogen) than during the luteal (high oestrogen and progesterone) phase (Backstrom *et al.*, 1986). On this basis it was suggested that oestrogen may increase brain excitability.

Such specific influences of oestrogen on neuroanatomy (synaptogenesis) and neurophysiology (cholinergic activation, long term potentiation, brain excitability) could explain its proposed ability to maintain aspects of cognitive function.

2.4 Neurobiology of progesterone

Progesterone receptors have also been found in the hippocampal limbic system, the hypothalamus and the cerebral cortex (Sherwin, 1999). Woolley & McEwen (1993) observed that pretreatment with a progesterone receptor antagonist inhibited the proestrous to estrous decrease in dendritic spine

density. These results suggested that progesterone caused the decrease in dendritic spine density that occurred between the proestrous and estrous phases of the cycle. Thus progesterone may have a detrimental effect on the structural integrity of certain brain regions.

Progesterone has a variety of effects on catecholaminergic pathways and on the basal forebrain cholinergic system (Sherwin, 1999). Progesterone may increase monoamine oxidase activity, thereby activating serotonin metabolism and negatively influencing mood (Holzbauer *et al.*, 1973). This sex hormone seems to mitigate oestrogen's effects – while oestrogen increases brain excitability, progesterone reduces it. Progesterone has been shown to reduce the frequency of epileptic discharges (Backstrom *et al.*, 1985). A progesterone-dependent decrease in oestradiol receptors may explain progesterone's antagonism of oestrogenic effects. Progesterone reduces endometrial oestradiol receptors without altering their affinity or physical properties (Bayard *et al.*, 1978). Thus one may speculate that when progesterone levels are high e.g. in the luteal phase of the menstrual cycle, there may be a reduction of oestrogen receptors within the CNS.

Overall, considerable evidence suggests a direct effect of oestrogen and progesterone on human brain structure and function.

2.5 Progesterone and cognition

No clear association has been established between progesterone levels and cognitive function. Seyle (1942) was the first to document the sedative and hypnotic properties of progestogen (a synthetic form of progesterone). Merryman *et al.* (1954) reported that high doses of progesterone induced deep sleep. Another study found that progesterone can induce anesthesia in rats and blocks neuronal pathways within the reticular activating system and pathways connecting the hypothalamus with the limbic system (Holzbauer *et al.*, 1976). Arafat *et al.* (1988) published a case report showing dose-dependant tranquillising effects of progesterone on cognition. Animal studies have shown that progesterone metabolites are barbiturate-like modulators of the GABA

receptor (Mendelson *et al.*, 1987). A clinical trial on 56 post-menopausal women (de Lignieres *et al.*, 1982) found that high elevations of plasma progesterone were associated with unpleasant hypnotic effects. Conflicting reports have arisen from more recent studies. Women who performed poorly on a clock drawing task had higher levels of serum progesterone (Paganini-Hill *et al.*, 1996). Similarly, Rice *et al.* (2000) showed that women with progestogen added to HRT had worse performance on mental tracking than those using unopposed oestrogens. However, two studies found no effect of adding a progestogen to a HRT treatment regimen on cognition (Kampen & Sherwin, 1994; Hogervorst, 1999). Although the results of basic neuroscience and human studies suggest that progesterone and its synthetic forms might induce unfavourable effects on cognition, no evidence is currently available from clinical studies to substantiate such an effect.

Cumulatively, such neurobiological studies on the effects of oestrogen and progesterone on cognition provide a strong biological plausibility for the studies reviewed in the proceeding sections of this chapter and for the studies undertaken as part of this thesis.

2.6 HRT and Cognition

Much evidence from both experimental and observational studies points to a possible relationship between HRT (which contains synthetic forms of oestrogen) and aspects of cognitive function in women.

2.6.1 Experimental studies

50 years ago, Caldwell & Watson carried out one of the earliest controlled studies on the effect of HRT on cognition. 28 women were given oestradiol or placebo once a week. After 6 months, subjective memory self-rating scores increased significantly, whilst a significant fall in scores in placebo-treated subjects was observed (Caldwell & Watson, 1952). As hormone replacement therapy became more popular in the 1960s and 1970s, more reports of hormonal effects on cognition began to emerge. Michael & Kantor (1970)

administered conjugated oestrogen or placebo to 18 postmenopausal subjects in a double-blind study. They reported a significant improvement in oestrogen-treated subjects on the Hospital Adjustment Scale, a measure of social functioning. Similarly, Kantor (1973) gave conjugated equine oestrogen or placebo to 50 subjects and found that Hospital Adjustment Scale scores improved with conjugated oestrogen and deteriorated with placebo.

Hackman & Galbraith (1976) found that Guild Memory Scale scores (a measure of immediate and recent memory) showed an improvement after 6 months in 9 women given oestrone daily compared to placebo. Subsequently however, no statistically significant difference was found (Sherwin, 1988). In 1977, Campbell & Whitehead carried out a double-blind crossover on 125 post-menopausal women with severe/moderate vasomotor symptoms. Oestrogen was superior to placebo in improving memory (subjective self-rating) and alleviating insomnia, headache and anxiety. An uncontrolled study carried out by Schneider (1982) also reported an improvement in self-reported memory with oestrogen treatment.

Sherwin (1988) carried out a study on 50 premenopausal women before and after surgical menopause. Following surgery, oestrogen-androgen, oestrogen alone, androgen alone or placebo treatments were administered for 3 months, then crossover for another 3 months. Testing was carried out before and after surgery. Those who received oestrogen maintained preoperative scores on paragraph recall, whilst those given placebo had lower scores compared to preoperative baseline. Using a similar design, the same group (1990) found that paired associates scores were maintained in women on oestrogen and that there was a decrease in scores relative to preoperative baseline for the placebo group (n=12). Paragraph recall scores improved in the oestrogen group, while placebo group scores stayed the same.

Philips & Sherwin (1992) performed tests on 19 women before and after surgical menopause, then treated them with oestrogen and placebo. Scores decreased significantly on immediate and delayed recall of paired associate test in placebo group coincident with drastic reduction in oestrogen levels. Mood scores remained stable, suggesting that oestrogen exerted its effects directly on

cognitive functioning, not secondarily via an effect on mood. Sherwin & Tulandi (1996) found that those given a gonadotrophin agonist (to suppress ovarian hormones) had lower verbal memory scores compared to pre-treatment baseline. This deficit was reversed in those given the agonist with oestrogen. The scores remained low however in those given the agonist with placebo. Wolf (1999) gave transdermal oestradiol for two weeks to 38 healthy elderly women in a double-blind, placebo-controlled study. Oestradiol-treated women who reached higher oestradiol levels performed better after treatment in delayed recall of paired associate test than those who attained lower levels. In same year, Hogervorst (1999) found a positive effect of oestradiol and progesterone on word recall (n=22). Such well-controlled studies provide compelling evidence that exogenous oestrogen enhances or maintains verbal memory.

A number of negative findings concerning HRT and cognition have also been published. Rauramo (1975) reported no differences between surgically menopausal women given estradiol valerate or placebo (n=88) on an Integration Memory Test, Manifest Anxiety scale, simple and choice reaction time task and letter cancellation. Ditkoff (1991) found no changes in 36 surgically menopausal women given oestrogen or placebo on Digit Span (WAIS), Digit Symbol, and depression tests. Goebel (1995) administered oestrogen and progesterone to 89 postmenopausal women and observed no effects on the Trail Making Task (speed). In 1998, Polo-Kantola reported that oestrogen replacement therapy was not superior to placebo on tests of Digit Span, Benton Visual Retention Test, speed/alertness and vigilance (n=70). Duka *et al.* (2000) looked at the effects of three-week transdermal oestrogen replacement on memory, frontal lobe functions and visuospatial abilities (n=19 treated, n=19 placebo). Memory function and visuospatial abilities improved significantly with oestrogen replacement. In another placebo-controlled, double-blind trial (Binder, 2001), oestrogen and progesterone or placebo were given to 52 elderly women. No significant differences were found for verbal fluency, Wechsler Paired Associate Learning, Trailmaking A and B, and cancellation random letter tests.

Several possible explanations for such discrepant findings are possible. Some studies used subjective self-report measures, which may be considered unreliable (Campbell, 1977; Schneider, 1982). Many investigations administered tasks that are sensitive to only one or two cognitive domains and then generalised their findings to all domains (e.g. Ditkoff, 1991). Few studies reported the participants' use of medication, which may have affected test performance. A variety of different oestrogen preparations, doses and routes of administration were used. No information was given on dose-response relationships or on the differential rates of diffusion of oestradiol into the brain. It is unknown whether oral hormone drugs heavily metabolized by the liver reach the brain in similar concentrations as parenterally administered preparations which bypass the so-called "first-pass hepatic effect". With the exception of Phillips & Sherwin (1992), these studies did not measure mood – any hormonal effects on cognition may be secondary to its effects on mood. Such randomized trials are subject to bias when subjects fail to adhere to the treatment group to which they were assigned. Selection bias may result if analysis is based only on women adhering to their treatment group. Due to ethical and economic considerations, such studies are small, short-term trials in very motivated subjects who may have been biased by expectancy effects.

2.6.2 Observational studies

Observational research in this field is based on prospective and cross-sectional data and has investigated the association between HRT (oestrogen) status and cognition. The majority of these studies have compared current ORT users to current non-users.

Prospective studies

Mixed reports have emerged from observational studies. In a large (n=800) cross-sectional, prospective, cohort-based study, Barrett-Connor & Kritz-Silverstein (1993) observed no differences between past, current or never-users on tests of verbal (Buschke Selective Reminding Test) or visual memory (Visual Reproduction) or attention (Trailmaking Test-B). It should be noted

however that their analysis failed to include women who had become demented (3.6% of the sample. Another cohort study (n=6110) found no appreciable differences on Delayed Word Recall, Digit Symbol and Word Fluency tests between those who did and did not use ORT (Szklo *et al.*, 1998). Another cohort study was carried out in 1999 by Barrett-Connor on 393 community-dwelling women not using replacement oestrogen. High endogenous oestrogen levels were not associated with better performance on a variety of neuropsychological tests, including the Bushcke Selective Reminding test, category fluency, visual recall, the MMSE and Trails B.

Jacobs *et al.* (1998) followed 727 community-dwelling elderly women prospectively for 30 months. Oestrogen users performed significantly better on verbal memory (Bushcke Selective Reminding tests) and verbal abstract reasoning tests at baseline and subsequently. This association remained after adjusting for age, education, race and Apolipoprotein E genotype. 9651 elderly women were followed for 4 to 6 years found that past (but not current) use was associated with smaller age-related declines on retesting (Matthews *et al.*, 1999). They reported that ORT users performed better on the MMSE, attention/speed (Trail making B and the Digit Symbol) tests, even after adjusting for age and education. Steffens *et al.* (1999) reported better cognitive performance as measured by the MMSE in HRT current and past users relative to non-users. Hogervorst (1999) observed 342 women and noted improved simple speed test performance but not on verbal memory or the Stroop test (speed of information processing) in HRT users. Yaffe (2000) followed 2716 ORT users and non-users and found a positive effect of HRT use on the MSE test. That same year Rice (2000) observed improved performance on the Cognitive Abilities Screening Instrument in oestrogen users than never users. Grodstein (2000) reported better animal fluency in postmenopausal women taking HRT relative to non-users (n=2138).

Cross-sectional studies

A case-control study carried out on 71 women found that ORT users scored significantly higher on immediate and delayed paragraph recall compared to non-users (Kampen & Sherwin, 1994). Robinson (1994) observed an advantage

in ORT users (n=144) on test of verbal fluency (proper name recall). Kimura (1995) also found that ORT users (n=54) performed better on tests of verbal fluency, perceptual speed, visuospatial and verbal memory. Superior performance was observed in transsexual men taking ORT compared to those who were not (Miles *et al.*, 1998). Carlson & Sherwin (1998) carried out a study on healthy elderly men and women matched for age and education and reported that men and ORT users performed better than female ORT non-users on forward and total Digit Span, coincident with their higher oestrogen levels. Resnick *et al.* (1998) observed superior performance in 32 ORT users on the California Verbal Learning Test and the Benton Visual Reproduction Test. Nappi (1999) observed worse verbal memory in oophorectomized women than in those who had experienced a natural menopause and that time since surgery correlated with verbal memory scores (r = -0.6). Duff *et al.* (2000) observed that oestrogen users (n=38) exhibited significantly better performance on a verbal and spatial task, but did not differ from nonusers (n=35) on control tasks involving simple passive recall. Verghese *et al.* (2000) observed positive effects of HRT use on the Block Design, Clock Drawing and Blessed Information Memory and Concentration test (n=35). Maki *et al.* (2001) carried out a study on age- and cognitive status-matched HRT-users (n=103) and non-HRT users (n=81). HRT had a beneficial effect on verbal memory, including encoding and retrieval. Similarly a recent study by Wolf *et al.* (2002) observed that high endogenous oestrogen levels in 38 healthy elderly women were correlated with improved verbal memory (paired associates) (r=0.38).

Many limitations are inherent in these studies. Several studies failed to measure circulating hormone levels (Barrett-Connor *et al.*, 1993; Robinson *et al.*, 1994; Kimura *et al.*, 1995; Jacobs *et al.*, 1998). The majority of these studies failed to ensure that ORT users were tested while receiving oestrogen alone. Progestins included in the HRT regime are neuroactive and may cause dendritic spine involution. Observational data may be subject to more biases than randomized trials. One of the limitations is that the female participants studied may not be representative of the population. Another bias may occur if those choosing to use ORT are systematically different from those not selecting to use this therapy. It has been well established that women who take HRT tend to be

more highly educated and from higher socio-economic groups, thus introducing a systematic bias in these studies. As education and socio-economic status are themselves protective against cognitive decline in ageing, this is a serious confound in studies attempting to attribute causality to oestrogenic prevention of cognitive decline with ageing. Some studies have attempted to remove this bias by matching for or adjusting for socio-economic variables (Kampen *et al.*, 1994; Robinson *et al.*, 1994). Although this helps to mitigate these confounds, it is unlikely that this strategy negates them entirely. With the exceptions of the two cohort studies, sample sizes are relatively small, ranging from 54 (Kimura, 1995) to 144 (Robinson *et al.*, 1994) women.

Overall findings from both experimental and observational studies that have examined the putative oestrogen-cognition relationship provides evidence for the hypothesis that oestrogen helps to maintain aspects of short- and long-term memory in women.

2.7 Menstrual cycle and cognition

Due to the reliable cyclicity of ovarian hormone secretion during various phases of menstrual cycle, much research has investigated whether oestrogen and progesterone levels were associated with scores on tests of cognitive function during different menstrual cycle phases. Although generalised measures of cognitive performance do not reliably vary over the menstrual cycle (Sanders & Reinisch, 1985), systematic variation has been obtained on some tasks tapping specific cognitive abilities. Hampson & Kimura (1988) administered a battery of cognitive tests during the follicular and midluteal phases of the menstrual cycle. This battery included "female" tests of verbal fluency, articulation, manual coordination, and perceptual speed, as well as "male" tests of deductive reasoning and spatial skills. During the high oestrogen and progesterone phase (midluteal phase), verbal articulation improved and deductive reasoning and spatial ability decreased. In a second study, Hampson (1990) controlled for the potential effects of progesterone on performance by testing women during both the preovulatory oestradiol surge and the follicular phase. Results paralleled those in the previous study, and a

hormonal assay revealed a curvilinear relationship between oestradiol and spatial ability, with optimal performance associated with intermediate levels.

These findings (better verbal and worse visuospatial performance in women at mid-cycle) are supported by many other (Wickham, 1958; Postma *et al.*, 1999; Anderson, 1972; Komnenich, 1978; Broverman, 1981; Gordon & Lee, 1986; Beatty & Troster, 1987; Kramer *et al.*, 1988; Moody, 1997; Maki *et al.*, 2002) but not all studies (Gordon & Lee, 1993). Together these results suggest that during the luteal phase, when oestrogen and progesterone levels are high, performance on certain tests favouring women were better, while performance on tests favouring men were poorer, than during menses when these hormones are low.

Hartley *et al.* (1987) conducted a study on menstrual cycle effects on immediate and delayed verbal memory, immediate memory for acoustically and semantically confusing word lists, and verbal reasoning. Speed of verbal reasoning was slower during ovulation, while recall showed no differences. Hormonal measurement was not carried out however, leaving interpretation of results unclear. Philips & Sherwin (1992a) reported that women performed better on long-term visual memory during the luteal phase and scores were significantly correlated with plasma progesterone. These results were only observed for a subgroup of the participants. No between-phase differences on verbal memory tests were observed.

Maki (2002) observed improved performance on test of conceptual implicit memory at the midluteal phase relative to follicular phase. As expected, decreased mental rotations and improved motor skills and fluency were found in the midluteal phase. Oestradiol levels were correlated with verbal fluency and negatively with mental rotations and perceptual priming. It was concluded that oestrogen "may facilitate the automatic activation of verbal representations in memory".

Many of these studies are fraught with methodological problems however – small sample sizes were employed and, with the exception of the Phillips &

Sherwin, Hampson and Maki studies, the menstrual cycle phase was not confirmed by hormonal assay. Cumulatively these psychometric findings suggest that alterations in gonadal steroid levels across the menstrual cycle exert effects on specific cognitive domains. Although there are fluctuations in several hormones (oestrogen, progesterone, follicle-stimulating hormone and luteinizing hormone) across the menstrual cycle, oestrogen has been suggested to be a more likely candidate as the instigator of this salutary effect at the mid-cycle phase because of the wealth of data linking it to neural processes (see Section 2.3).

2.8 Sex hormones and mood

2.8.1 Oestrogen and mood

Neurobiological evidence suggests that oestrogen has a beneficial effect on mood. These biochemical effects include the enhancement of serotonin transmission. Oestrogen is thought to enhance serotonergic transmission by decreasing monoamine oxidase (MAO) activity, increasing free tryptophan (a precursor of serotonin) availability in the brain, and enhancing serotonin transport.

(i) Monoamine oxidase activity

The serotonin deficit hypothesis is one of the most important theories of depression and is the basis for the use of the type of antidepressant drugs known as selective serotonin reuptake inhibitors (Maes & Meltzer, 1995). The link between serotonin and sex steroid hormones oestrogen and progesterone was first established by Luine *et al.* (1975). In this study, ovariectomized rats were treated with various doses of oestradiol benzoate for 3-7 days. A reduction in the amount of serotonin-catalysing MAO in the corticomedial amygdala and the basomedial hypothalamus was observed in the oestrogen-treated rats. These oestrogen-dependant changes in MAO were blocked when the oestrogen antagonist MER-25 was administered. Such findings established that oestrogen reduces MAO in parts of the brain important in mood regulation.

(ii) Tryptophan effects

Thomson *et al.* (1977) found a significant positive correlation between total oestrogen concentration and that of free plasma tryptophan in perimenopausal women. Tryptophan is a precursor of serotonin and the metabolism of serotonin is partly dependent on free plasma tryptophan. While most tryptophan in plasma is bound to albumin, oestrogens in plasma bind to globulin present in low concentrations in plasma and with lower affinity to albumin. It was suggested that the link between oestrogen and free plasma tryptophan is due to the actions of oestrogen on the tryptophan-binding site of albumin. These findings suggest another mechanism by which oestrogen affects serotonin metabolism.

(iii) Serotonin transport

Platelets have an active transport mechanism for serotonin. Platelet serotonin content has been shown to be significantly lower in peri- and postmenopausal women with depression. Furthermore, platelet serotonin content has been positively correlated with oestrone and oestradiol concentrations in nondepressed women (Guicheney *et al.*, 1988).

Another mechanism by which oestrogen may enhance mood is by increasing the number of imipramine-binding sites available for the active transport of serotonin. Imipramine-binding sites in the brain are thought to modulate the presynaptic uptake of serotonin and tritiated imipramine binding to platelets is regarded as a biological correlate of depression. In a double-blind, crossover study carried out by Sherwin (1990), high levels of oestrogen were associated with positive mood and a higher number of tritiated imipramine binding sites on platelets in oestrogen-treated surgically menopausal women. Such effects were reversed when placebo was administered.

(iv) Noradrenergic effects

It has been proposed that oestrogen may also lead to increased noradrenaline activity through decreased MAO levels. Kugler *et al.* (1980) found that administration of clonidine (an alpha-adrenergic agonist known to cause reduction in plasma and CNS noradrenaline levels) caused a decrease in mental activity as measured by EEG, reduced information processing, increased reaction time and a negative effect on well-being and mood. The finding that oestrogen can increase noradrenaline activity may add to the evidence supporting the link between oestrogen and mood.

2.8.2 Progesterone and mood

One piece of compelling evidence supporting an effect of progesterone on mood is its influence on MAO. As described previously, MAO is the enzyme responsible for the breakdown of serotonin, noradrenaline and dopamine. In contrast to oestrogen, progesterone has been shown to have a stimulatory effect on MAO, thus increasing the breakdown of serotonin, noradrenaline and dopamine and reducing their duration of action (Holzbauer *et al.*, 1973). Such evidence supports the theory that progesterone has a negative impact on mood.

2.9 HRT and Mood

It has been hypothesised that if oestrogen has a beneficial effect on mood, then HRT users should show less mood disturbance than nonusers. Indeed this has been the focus of many clinical and observational studies, as introduced below.

2.9.1 Clinical studies

Clinical trials have yielded inconsistent results. Bowman & Bender (1931) were the first to look at the effect of ovarian hormone on mood in menopausal women and published 7 case reports of "involutional melancholia" (former term for the menopause) treated with amniotin, a water-soluble extract from cattle foetal fluids. Another series of case studies (Ripley, 1940) found that

mild depressive reactions were treated more effectively with oestrogenic hormone than were "well defined depressive illnesses".

Schneider *et al.* (1977) looked at oestrogen as a possible therapeutic agent for depression. Clinically depressed and non-depressed women were given oestrogen treatment for 1 month. No improvement in depression scores of the clinically depressed group was found. However the non-depressed group reported significantly increased feelings of well-being and had improved scores on a depression rating scale.

Klaiber *et al.* (1979) carried out a similar study but used larger doses of oestrogen. Women with severe clinical depression were divided into treatment and placebo groups. The treatment group was given large pharmacological doses of oestrogen. Depression ratings were significantly lower in 90% of the oestrogen-treated group by the end of the 3 months.

In a randomized, double-blind study, healthy, non-depressed postmenopausal women received either 0.625mg or 1.25mg oestrogen or placebo for 3 months. (Ditkoff *et al.*, 1991). Depression scores improved significantly in both oestrogen treatment groups but not in the placebo group at the end of the 3 months. Furthermore, Schmidt *et al.* (2000) reported that 0.05mg/day is associated with significant improvement in mood in depressed peri-menopausal women with and without hot flushes

Some negative findings are also present in the literature. Montgomery *et al.* (1987) reported that after 2 months, perimenopausal women receiving oestradiol implants scored significantly better than the placebo group on self-rating scales of distress, anxiety and depression. After 4 months, the placebo group had also improved so that there was no significant difference between the placebo and the oestradiol / oestradiol and testosterone groups. In a cross-sectional study carried out by Palinkas *et al.* (1992), women aged 50-59 did not show an improvement in depression scores. However, with women over the age of 60, depressive symptom scores were significantly lower in those treated with HRT. A negative correlation was observed between hot flushes and

insomnia and mood in this cohort. This suggested that by relieving physical symptoms, HRT removed sources of stress, thus leading to improved mood. Shleifer *et al.* (2002) found no effect of acute oestradiol on mood in 12 post-menopausal women. This finding suggests that more chronic exposure to oestrogen is required to yield mood-enhancing effects.

2.9.2 Observational studies

Surprisingly, several observational studies have found greater mood disturbances among current or previous HRT users than non-users (Matthews, 1990; Kuh, 1997; O'Connor, 1995; Porter, 1996; Collins, 1995; Palinkas, 1992; Goldani von Muhlen, 1995; Lee, 1996). These findings may be attributable to various limitations in subject selection and definition of menopausal status.

Much of the research that gives rise to the perceived relationship between HRT and mood is derived from clinic or patient samples of women who have sought treatment for menopausal symptoms, thus presenting a biased view of the menopause. Such studies therefore are likely to overestimate the prevalence of mood disorders among menopausal women. The inconsistency with which researchers have defined menopause status (i.e. peri- or post-menopausal) also presents a major challenge in comparing studies. Many studies have looked at surgically menopausal women, who experience more sudden hormonal changes and tend to be of poorer health and more distressed than those who experience natural menopause (Brett, 1997; Kuh, 1997).

Taken together, strong evidence from clinical studies in particular points to a significantly beneficial influence of HRT (oestrogen) status on mood.

2.10 Menstrual cycle and mood

Several studies have shown significant relationships between menstrual cycle phase and mood (Sanders *et al.*, 1983; Collins *et al.*, 1985; Cockerill *et al.*, 1992; Choi, 1995; Williams, & Krahenbuhl, 1997). Other experiments

(Abplanalp *et al.*, 1979; Slade, 1984; Bowen & Grunberg, 1990; Laessle *et al.*, 1990; Kanarek *et al.*, 1995, Einon, 1997; Compton & Levine, 1997) have reported negative findings. However, due to huge variation in methodologies employed and phases selected for analysis, it remains difficult to evaluate the effect of the cycle on mood in general terms. Only four of these studies verified the menstrual cycle phases by hormonal assay (Abplanalp *et al.*, 1979; Laessle *et al.*, 1990; Collins *et al.*, 1985). Several studies used unstandardized tests e.g. mood diaries and questionnaires and reported negative findings (Sanders *et al.*, 1983; Einon, 1997; Compton *et al.*, 1997). A variety of different cycle time points were selected e.g. days 19-24 (luteal phase) in the Philips & Sherwin study and days 10-20 (intermenstrual phase) in the Abplanalp report, making inferences about mood changes concomitant with specific cycle phases difficult.

2.11 Oestrogen and electrophysiological measures of cognitive processing

Electrophysiological studies further substantiate the psychometric and clinical findings discussed above relating oestrogen to brain function changes in women. EEGs have been employed to determine the effect of exogenous oestrogen at a neurophysiological level on both premenopausal and postmenopausal women.

2.11.1 Oestrogen and EEG in pre-menopausal women

Some studies have investigated the effects of exogenous oestrogen on EEGs in young women but they have been hampered by the use of different preparations and have been conflicting. In 1945 Cress & Greenblatt observed no difference in the EEGs of three women taking progesterone and a synthetic oestrogen analogue. West & West (1967) also found no difference in EEGs of women with headaches on or off an oral contraceptive. In 1971 Vogel *et al.* discovered that oestrogen reduced "photic driving" on EEGs while combined oestrogen and progestogen increased it.

2.11.2 Oestrogen and EEG in postmenopausal women

Many studies have found significant EEG changes in oestrogen – treated postmenopausal women. Okhura *et al.* (1994) administered oral conjugated equine oestrogen (CEE) to 15 postmenopausal women with AD for six weeks. Delta activity was reduced bi-frontally and theta activity was reduced in the left frontal region after six weeks treatment. Such changes were correlated with increased perfusion to these areas as measured by SPECT scanning. Saletu *et al.* (1995) compared EEG changes in 53 postmenopausal women with depression given topical oestradiol or placebo. An increase in alpha and theta activity was observed in the left temporal region of the ORT treated subjects after 3 months of treatment.

It must be noted that as neither of these studies measured the effect of oestrogen on normal controls, the effects observed may represent an interaction with the pathological state. It is also noteworthy that Ohkura found a reduction in theta activity in ORT treated subjects, while Saletu showed an increase and that different brain regions were affected. The use of different ORT preparations for varying lengths of time and the different disease states of the subjects may account for these inconsistencies.

2.11.3 Menstrual cycle and EEGs

Much research (Dusser de Barenne *et al.* 1942; Pitot *et al.*, 1954; Lambe *et al.*, 1953; Roubieck *et al.*, 1968) has shown that the EEG alters across the menstrual cycle. In general it has been observed that faster wave activity (beta or alpha) occurs when oestrogen levels are high at mid-cycle and slower wave activity (theta or delta) occurs when they are low during menstruation.

2.11.4 Menstrual cycle and Evoked Potentials

Three types of evoked potential have been investigated in relation to their changes across the menstrual cycle, namely the Basal Auditory Evoked Response (BAER), the Visual Evoked Potential (VEP) and the P300 potentials. Some authors have demonstrated that BAER latency varied across the

menstrual cycle (Zani *et al.*, 1989; Elkind-Hirsch *et al.*, 1992). Both observed an increase in wave V latency at mid-cycle. The latter group subsequently showed that the delay in wave V latency was associated with elevated oestradiol and testosterone (Elkind-Hirsch *et al.*, 1994). However Fagan & Church (1986) and Howard *et al.* (1992) found no alteration in BAER latency during the menstrual cycle.

Kaneda *et al.* in 1997 carried out the first study of the effect of the menstrual cycle on flash visual evoked potentials (FVEP). 44 women with regular cycles were used, with 21 recorded at the follicular phase and 23 during the luteal phase. They examined 23 inter-peak amplitudes and found that one VEP inter-peak amplitude component (P5-N7) was significantly larger at luteal phase. The significance of this finding is questionable however as one significant finding in 23 would be similar to that expected through chance.

Using a standard oddball auditory paradigm, Fleck *et al.* (1988) studied P300 potentials to auditory tones in 20 females at start-cycle and mid-cycle. Half the subjects were taking oral contraceptives. No effect between or within groups was observed across the cycle. Ehlers *et al.* (1996) looked at P300 to auditory tones in 15 healthy young women. No significant differences were found in P300 latency or amplitude across the cycle.

However three studies using visually presented stimuli with an emotional content have found effects. Using a novel visual paradigm, Johnston & Wang (1991) and Wang & Johnston (1993) observed that emotionally pleasing stimuli (male models and babies) elicited larger P300 amplitudes during the luteal phase. Krug *et al.* (2000) looked at changes in ERPs in response to stimuli with and without reproductive significance across the menstrual cycle. During the ovulatory phase, amplitude of the LPC (but not P300) to sexual stimuli was larger than that elicited by other stimulus categories (babies, ordinary people, and body care).

In summary, there is good evidence that the background EEG varies in response to the menstrual cycle. Studies of stimulus-related evoked potentials

are either conflicting (i.e. BAER) or sparse (i.e. VEP). Studies of event related potentials are so far confined to the auditory P300 elicited in oddball paradigms and the P300 in response to emotional visual stimuli. In order to more fully examine the effects of sex hormones on cognitive processes (such as memory), studies of ERPs in response to more complex testing procedures are necessary. Specifically, a testing procedure that allows memory to be represented from an electrophysiological viewpoint is required.

2.12 The CANTAB battery

The CANTAB battery was recently developed to improve the comparative assessment of cognition from animals to man. The theoretical rationale for the tests is based on two themes: firstly, animal tests which established the neural substrates of certain domains of cognitive function were adapted for human subjects. This cross species comparison allows an objective evaluation of pharmacological therapy for patients with cognitive disorders. Secondly, these tests provide a componential analysis of cognitive function, allowing the characterization of elementary processes contributing to cognition. The use of CANTAB as a methodological approach offers many advantages. Each test begins at a simple level, so that virtually all subjects achieve a score above floor levels. Moreover, if successful, a subject proceeds to difficult versions of the same test, which avoids ceiling effects. The CANTAB battery also has the advantage that all tests are non-verbal and are administered using a computer and touch-sensitive monitor that allows immediate feedback.

Very extensive data are available on relationships between scores on component tests of the battery and clinical evidence for damage to specific brain areas, principally frontal and temporal lobe regions (Owen *et al.*, 1995). These tests are sensitive to deficits in patients with Alzheimer's Disease (AD) and Parkinson's Disease (PD) (Sahakian *et al.*, 1988; 1990; Morris *et al.*, 1988; Downes *et al.*, 1989). Such studies have shown different profiles of deficits in different forms of these neurodegenerative disorders and are important in establishing neural substrates of the disorders. For example, it has been proposed that impairments in attentional shifting in AD may reflect temporal

lobe deficits, whilst impairments in attentional shifting in PD may depend on frontal lobe forms of dysfunction. This battery has also been employed in the study of cognitive function in several other populations, such as alcoholics, anxiety disorder patients, depressed patients and schizophrenics.

Clearly therefore, the CANTAB battery is a sensitive tool in the evaluation of cognitive function and dysfunction. As shall be discussed below, few studies have employed this technique to investigate the effects of HRT on cognition. No study to date has looked at the effects of the menstrual cycle on attention and visual memory by this method. The relationship between oestrogen and the prefrontal cortex, upon which the attentional task is dependent, shall be introduced, followed by a review of studies pertaining to oestrogen and attention.

2.12.1 Oestrogen and the prefrontal cortex

The hippocampus has long been presumed the primary site of oestrogen action on cognition. However, several recent lines of research raise the possibility of modulatory effects of oestrogen in the prefrontal cortex, which plays a vital role in executive functioning processes, including working memory, directed attention, response inhibition, dual task co-ordination, cognitive set switching and behavioural monitoring (Miller & Cummings, 1999). Bixo *et al.* (1995) reported that the prefrontal cortex is the principal target for oestrogen in the adult brain, with oestradiol concentrations two times higher in the prefrontal cortex than in the temporal cortex and seven times higher than in the hippocampus. Oestrogen influences activity of several neurotransmitters in the prefrontal cortex. Singh (1994) observed a 56% reduction in ChAT in the frontal cortex of female rats 28 weeks after ovariectomy, an effect reversed/prevented by oestradiol replacement. Oestrogen replacement in ovariectomized rats caused a 41% increase in serotonin binding sites in the frontal cortex (Summer & Fink, 1995). Overall there is compelling biological evidence that the prefrontal cortex is an important mediator of oestrogen's role in cognition.

Neuroimaging studies in humans have found systematic differences in prefrontal cortex activity related to differences in oestrogen status. In a functional Magnetic Resonance Imaging (fMRI) study, Shaywitz *et al.* (1999) found that menopausal women treated with CEE for 21 days had increased activation in the superior frontal gyrus during a verbal memory task. Berman *et al.* (1997) reported a loss of a previously observed regional cerebral blood flow increase in the prefrontal cortex when oestrogen levels were suppressed by a GnRH agonist. Normal activation patterns resumed when oestrogen/progesterone was added to the agonist regime. An observational study (Duff *et al.*, 2000) supports these findings, whereby oestrogen users (n=38) performed significantly better than non-users (n=35) on a verbal and spatial task, each with a prominent prefrontally-mediated component. They concluded that tasks that recruit prefrontal cortex – dependent information processing is sensitive to oestrogen status.

Cumulatively, such evidence supports oestrogenic effects on prefrontal cortex-dependant tasks. These findings are further supported by studies on the effect of HRT on measures of attention, a process dependant upon the prefrontal cortex.

2.12.2 Oestrogen status and attention

Several positive findings have emerged from studies of HRT and attention. In an experimental study, Fedor-Freybergh (1977) reported that attention scores were superior in women taking estradiol. Schmidt (1996) carried out neuropsychological tests on 210 post-menopausal women (70 ORT users) and found that oestrogen users did better on tests of attention and visual motor skills. These findings remained after adjusting for age and education. Significant effects of oestrogen treatment on attention (Stroop) in postmenopausal women with AD were reported by Asthana *et al.* (1999, 2001).

Four recent observational studies have also investigated the effect of HRT use on attentional measures. Portin *et al.* (1999) found that women (n=63) with low oestrogen levels made more errors in a sustained attention test. Similarly Smith

et al.(2001) observed that attention (digital vigilance) test scores were significantly higher in ORT users (n=16) relative to non-users (n=13). However a study on age- and cognitive status-matched HRT-users (n=103) and non-HRT users (n=81) found no appreciable differences in measures of attention (Maki *et al.*, 2001). Another observational study compared the performance of 9 HRT-users to 10 non-users on a battery of frontally-mediated tasks (Keenan, 2001). They reported that the HRT-users outperformed women without HRT on tests requiring directed attention, inhibition of inappropriate responses and cognitive set switching.

Together these findings suggest that attention, a process reliant on the prefrontal cortex, is sensitive to oestrogen status. The Intra-Dimensional/Extra-dimensional (ID/ED) shift task was chosen to examine the effects of hormonal fluctuations across the menstrual cycle on attentional processing.

2.12.3 Oestrogen status and visual memory

As the relationship between oestrogen and the hippocampus, upon which the visual memory tasks are dependent, were established in Section 2.3, the literature review shall continue with an introduction to studies on oestrogenic effects on visual memory.

While the effect of HRT on verbal memory has been well documented, the sensitivity of visual memory to hormone therapy has not been well established. Five experimental studies have documented HRT effects, two of which report positive findings. Vanhulle & Demol (1976) found no changes in postmenopausal women following oestrogen administration on the Benton Visual Retention test. No effect of oestradiol valerate was found on immediate and delayed recall of visual material (Phillips & Sherwin, 1992). Duka *et al.* (1999) carried out an experimental trial on the effects of three-week transdermal oestrogen replacement on memory, frontal lobe functions and visuospatial abilities. Significant treatment effects were reported for visual learning and memory (paired associate learning). Linzmayer *et al.* (2001) reported a positive effect of HRT on visual memory in a double-blind, placebo-

controlled study. Similarly Asthana *et al.* (2001) found significant effects of oestrogen treatment on visual memory (Figure Copy/Memory).

Four observational studies have also reported positive findings. Resnick *et al.* (1997) found a beneficial effect of HRT on the Benton Visual Retention Task. This test measures short-term visual memory and visual perception, aspects of performance that may also be present in the paired associate learning task. Similarly Smith *et al.* (2001) showed that ORT users (n=16) had higher scores in Wechsler Memory Scale Visual Reproduction (delayed recall) than non-users (n=13). Farrag *et al.* (2002) observed a significant decline in visual memory (WMS) in 35 oestrogen deficient women (surgically menopausal) relative to 18 controls. Another observational study (Kampen & Sherwin, 1996) reported that men with high oestrogen levels performed better on two tests of visual memory than those with normal but lower levels.

However such evidence of a relationship between oestrogen and visual memory is far from conclusive. Two observational studies (Barrett-Conner *et al.*, 1999; Drake *et al.*, 2000) have found that oestradiol and oestriol levels related negatively to visual memory, line orientation and visual span. Furthermore, two other studies reported no effects of oestradiol on visual memory (Carlson *et al.*, 1998; Polo-Kantola *et al.*, 1998). Such inconsistent findings may be attributable to methodological differences and limitations inherent in observational studies (see Section 2.6.2).

Overall, these findings suggest that visual memory exhibits oestrogen sensitivity. Paired Associate Learning, a test of visuo-spatial paired association learning and the Delayed Matching to Sample, a measure of acquisition and encoding of visual information, were employed to tap into any possible effects of the menstrual cycle on visual memory function.

Chapter 3

Sex Hormones and Cognition Methodology

3.1 The effect of the menstrual cycle on electrophysiological measures of memory and mood

3.1.1 Participants

A total of 17 women with spontaneous menstrual cycles participated in the study. They replied to advertisements posted around the hospital and university (postgraduate science/medical students). 23 women were originally recruited for the study, but 6 were excluded due to excessive eyeblink artifact in the ERP recordings. Thus the final sample comprised 17 women. All subjects gave informed consent and the local ethics committee approved the study. All subjects reported normal or corrected-to-normal vision. Characteristics of the participants are summarized in Table 3.1.

Table 3.1. *Characteristics of participants*

Age	
Mean	22.7
Range	19-35
Cycle length (days)	
Mean	28.8
Range	27-30
Education (years)	
Mean	14.3
Range	12-17

3.1.2 Inclusion/Exclusion criteria

All subjects were women with spontaneous regular menstrual cycles between 25 (minimum) and 35 (maximum) days in length. Those taking any prescription medication or the oral contraceptive pill were excluded from the study, as were those with Late Luteal Phase Dysphoric disorder (as assessed by self-report of key symptoms according to the DSM-IV – see Appendix A), chronic diseases or a personal psychiatric history.

3.1.3 Procedure

Subjects who met the inclusion criteria attended for electrophysiological recording on two occasions, corresponding to the menstrual (day 2-5) and mid-cycle phases (14 days before the beginning of the next cycle) of the menstrual cycle. Day 1 was not used to avoid possible confounding effects of physical discomfort on the first day of bleeding. Test sessions were counterbalanced, whereby half the subject group were tested first in the menstrual phase and the other half tested initially in the ovulatory phase. Task order was also counterbalanced – half the subject group did the direct task first, and the other half did the indirect task first. Each session lasted approximately 100 minutes. This consisted of the ERP testing, followed by tests of mood (POMS), paragraph recall and paired associates learning (psychometric tests of verbal memory). As regards the ERP testing, both the direct and the indirect test lasted approximately 10 minutes each, with a 5 minute rest break in between. At the end of the session, blood samples were collected by a registered nurse/doctor to determine serum concentrations of oestrogen and progesterone.

3.1.4 Hormone Assay

Serum concentrations of oestradiol (E_2) and progesterone (P_4) were measured by commercially available radioimmunoassays (Autodelfia™, Wallac Oy, Turku, Finland). The sensitivities were 1.4 pg/ml for oestradiol determination and 0.05 ng/ml for progesterone determination.

Intraassay coefficients of variation were less than 4.2% between 240 and 2601 pg/ml for oestradiol and less than 3% between 0.7 and 9.6 ng/ml for progesterone. All samples from an individual woman were analyzed in duplicate in the same assay.

3.1.5 Plasma sex hormone concentrations

As shown in Table 3.2, oestradiol and progesterone levels were significantly elevated at mid-cycle compared to start-cycle.

Table 3.2. *Sex hormone concentrations across the menstrual cycle*

Oestrogen	**Mean**	**Median**	**S.D.**	**P value**
Start	192.2	167	96.6	
Mid	406.7	392.5	214.8	0.0016
Progesterone				
Start	2.5	1.6	2.5	
Mid	12	4.3	16.7	<0.0001

3.1.6 ERP list stimuli and list structure

The stimulus lists were selected from a pool of 496 English nouns, including 40 animal names. The animal names and nouns ranged in length from 3 - 7 letters (mean = 5 letters for both). According to the Francis and Kucera (1967) corpus, the animal names had a mean frequency of occurrence of 5.4 per million, and the nouns had a mean frequency of occurrence of 16.3 per million. In the indirect task, 20 of the words in a list were animal names (targets), whereas in the direct test these words were replaced by 20 non-animal words randomly selected from the initial 496 word pool. For the two tests, some of the words taken from the remaining word pool were repeated after a mean of 6 (range 1-12) intervening words. For each task, two sequences were

constructed, each of a different pseudorandom order. Two lists were produced, one for each sequence. Rotation of lists and tasks across subjects at each timepoint ensured that each word sequence and repeating item occurred equally frequently in each test and that each subject encountered a different combination of items and sequences for each task. Words were displayed on a computer monitor (white characters on a black background) in central vision. The stimuli subtended a vertical angle of approximately 0.3° and a horizontal angle of 1.5°. Stimulus duration was 500 milliseconds and the interstimulus interval 3.0 seconds. Stimuli were visually presented using STIM™ version 3.0.

3.1.7 Task Procedure

Following application of the recording electrodes, subjects were seated and given a response pad to hold. They were informed that a series of words would be presented one at a time. For the indirect task they were instructed to respond by clicking on button 2 on the response pad whenever they saw the name of an animal (n=20), otherwise to click on button 1 for all other words (n=100). For the direct task, they were instructed to press button 1 when a word appeared for the first time (n=100) and button 2 when a repeated word (n=20) was presented. Both response speed and accuracy were emphasized. They were further instructed to maintain fixation on the centre of the screen and to blink only between trials i.e. when no words are being presented on the screen. After delivery of instructions, participants were given 10 practice trials with items different to those used in the experimental list proper. Responses faster than 200ms or slower than 2.5 s were treated as errors. Hand used for each response was alternated across participants.

3.1.8 ERP recording

Scalp EEG was recorded using a 32-channel electrode cap (QuikCap™). For n=8 participants, midline frontal, fronto-central, central, centro-

parietal, parietal and occipital electrodes (Fz, FCz, Cz, CPz, Pz, Oz, respectively), left and right parasaggital electrodes (F3, C3, P3, O1 and F4, C4, P4, O2), and left and right temporal sites (F7, FT7, T7, TP7, P7 and F8, FT8, T8, TP8, P8) were employed. For n=9 participants, Fz, Cz, Pz, C3 and C4 were used. To detect eyeblink artifacts, electro-oculogram (EOG) was recorded bipolarly from electrodes placed on the outer canthus of the left eye and above the supraorbital ridge of the right eye. Electrode impedance was measured at the beginning and end of the recording and never exceeded 5 kΩ. All channels were referenced to linked mastoids. All eyeblink and movement artifacts were manually removed from the continuous files using Neuroscan's Scan software (Scan 4.1). In addition, sweeps were rejected if the potential amplitude in the EOG or EEG exceeded 60μV. A 250ms prestimulus interval was used to baseline correct the recorded ERPs. The EEG signal was filtered (zero phase digital filtering) with a bandpass of 0.05-30 Hz and a digital-sampling rate of 256 Hz. Trials where the subject made an incorrect response were excluded from further analysis. The EEG 250ms before to 1250ms after each word was then averaged to produce an evoked potential. It was averaged for correct "new" words and for correct "old" words. A minimum of 16 trials per stimulus category per subject was included in the statistical analysis. The mean amplitude in the 250-1000ms latency windows in the evoked potential produced by both new and repeated words was analyzed. The accuracy of the response (percentage correct) and reaction times (milliseconds) were also recorded. For more detail on these procedures see Section 3.2.

3.1.9 Paragraph Recall Test

The paragraph recall test (Wechsler, 1987) is a validated and sensitive measure of verbal declarative memory performance (see Appendix B). Subjects listened to a short narrative with 25 bits of information, followed by immediate verbatim recall. The maximum score is 25. Two paragraphs were given at each test session (i.e. start-cycle and mid-cycle) and scores for correct recall were tabulated using established

scoring methods. Administration of two alternate sets of paragraphs were counterbalanced across subjects in order to prevent any response bias (e.g. to particular paragraph content) from affecting the results.

3.1.10 Paired Associate Test

This test, a subset of the Wechsler Memory Scale Form 1 (1987), is a standardized measure of verbal memory performance (see Appendix D). This consists of 10 word pairs, six forming "easy" associations (e.g. baby-cries) and the other four "hard" word pairs that are not readily associated (e.g. cabbage-pen). The list was read three times, with a memory trial following each reading. The total score is one-half the sum of all correct associations for the easy pairs plus the sum of all correct associations to the hard pairs. The highest possible score is 21. The words are randomized in each of the three learning trials to prevent positional learning. Two equivalent sets of word pairs were used in this study. One set of word pairs was given at each test session (start-cycle and mid-cycle) and scores for correct recall were tabulated using established scoring methods. Administration of the two alternate sets of word pairs were counterbalanced across subjects in order to prevent any response bias from affecting the results.

3.1.11 Profile of Mood States (POMS)

The Bipolar form of the Profile of Mood States (POMS-BI) is designed to measure six bipolar subjective mood states (McNair *et al.*, 1976). A scale composed of 12 adjectives defines each mood state. One pole represents the positive aspects of the dimension while the other pole refers to the negative aspects. The form itself lists 72 adjectives in a cyclical order. Such adjectives or items are scored 0, 1, 2 or 3. Six hand-scoring stencils are applied to calculate the final score. The 6 positive subscales can have scores ranging from 0 to 18 while the 6 negative subscales have scores between 0 and - 18. The final scores are computed by subtracting the sum of the negative scores from the sum of the

positive scores and adding a constant of 18. Thus each scale has a 0-36 possible range (see Appendix C).

3.1.12 Statistical Analysis

ERP parameters were statistically analyzed in an analysis of variance (ANOVA) with factors representing Cycle (start or mid), the type of Task (direct or indirect), Word ("old" or "new") and Electrode (Fz, Cz, Pz, left or right temporal). A repeated measures design was used and the Greenhouse-Geisser (Winer, 1971) three-step approach to significance testing was employed when relevant. Post hoc t-tests were calculated to follow up significant main effects of Cycle, Word, Task and Electrode site as well as respective interactions. To limit familywise Type 1 errors when degrees of freedom were 3 or greater, Hochberg's stepwise Bonferroni procedure was adopted for the post hoc contrasts (Keselman, 1998). The Wilcoxon Signed Rank test was employed for the hormone level analysis, whereas the paired t-test was used for the psychometric test data (ERP behavioural data, paired associate test, paragraph recall test and the POMS mood inventory). The Spearman Rank method was employed for correlation analysis.

3.2 ERP Methods: Application procedure and recording issues

3.2.1 Electrode cap application procedure

Participants were seated and their clothes covered with a protective gown. The electrode cap was placed securely on the head, so that the midline electrodes (AFz, Fz, FCz, Cz, CPz, Pz, Oz) were aligned along the saggital axis of the head. It was also ensured that the frontal ground electrode (Afz) was approximately 4 inches from the nasion. The two horizontal electro-oculograms (HEOG) were pulled out to the outer canthus or corner of each eye. Each earlobe and above and below the left eye was cleaned using Omni-prep solution on some cotton wool and allowed to dry. Ten-20 electro-conductive paste was then smeared onto

each ear lobe and above and below the left eye. Some paste was also placed on the two earlobe ground electrodes and pressed onto the earlobes, using adhesive electrode pads to hold them in place. The cap's ear flaps were pulled down and the chin-strap was attached to further secure the cap. Some paste was placed onto the two VEOG electrodes and two adhesive electrode pads were used to hold them in position.

3.2.2 Gel Application

A 10 ml syringe was filled with QuikGel™ and a blunt needle was placed on it. The needle was inserted into an electrode cup and gently swirled to remove any hair that may be in the way, to ensure a clear path from electrode to scalp. While lifting the needle out, about 1 ml of gel was inserted into the electrode cup, until some of the gel appeared at the top of the electrode. The cup was pressed down against the head to remove any air bubbles. Excess gel was wiped away with a paper towel. This procedure was continued for all 32 electrodes. The gel was then left to dry for approximately 10 minutes.

3.2.3 Impedance reduction

Electrode impedance is a measure of how well the electrodes are conducting electrical activity from the scalp. The Scan™ 4.1 software presents a colour-coded measure of impedance quality of each electrode. The scale ranges from pink, indicating poor impedance, through green to black, signifying good impedance (< 5kOhms). The cap was connected into the electrode board. The calibration and impedance were then checked. If the impedance codes were all pink, all connections from the cap to the amplifier were checked. If there was no change, the needle was re-inserted into AFz and swirled to remove air bubbles or hair. If they remained pink, it was ensured that the earlobe electrodes were still attached. If the impedance was green/blue, the needle was inserted into each cup, swirled and more gel was added if required. When all the electrodes were black, testing could then begin. Participants were

informed of the problems caused by blinks, head/neck movements, muscle bursts, facial movements and twitches and asked to keep them to a minimum. They were also asked to restrict eyeblinks to between trials i.e. after the response to one trial and before the beginning of the next. The testing session then began.

3.2.4 Cap washing

After testing was completed, the electrode cap was unplugged from the electrode board. The chinstrap, earlobe electrodes and the VEOG electrodes were removed. The conductive paste was removed from these electrodes using Q-tips. The electrode cap was carefully lifted off and the participant's face and ears were cleaned using a paper towel and prep pads. The participants were allowed to wash their hair in a sink provided with a shower attachment.

The cap was placed in a sink and turned inside out. The inside of the cap was washed out for 2-3 minutes, ensuring that all traces of gel were removed. The outside of the cap was then washed, paying attention to areas near the hole at the top of each cup where gel may be difficult to wash out. The cap was removed from the sink and left to dry. The syringe was washed out and the needles discarded. The cap was sterilised using 70% alcohol solution.

3.2.5 The reference electrode

The reference electrode is an important aspect of electrophysiological recording. Ideally this reference electrode should be located where no electrical activity due to sources or sinks is detectable (see Section 1.3). This idealized case defines a True Reference. This provides a comparison recording site by which scalp potentials may be extracted and measured. However there are several issues to be considered in relation to the reference electrode.

In micro-electrode recordings, the reference electrode is placed at a distance equal to many times the spatial extent of the source area. Although no local sources may exist nearby, it may still not be a True Reference. A large number of distant sources may contribute to source activity at the reference or a highly conducting current path (e.g. cerebro-spinal fluid) may exist between sources and the reference, which would enhance potentials at the reference electrode. These problems are particularly relevant when considering the scalp-recorded EEG. Firstly, the recording electrode is usually located at least one centimetre from the source, thus blurring the distinction between recording and reference electrodes. The second problem is due to the poorly conducting skull. The average electrical conductivity of the skull has been estimated to be only about $1/80^{th}$ that of brain tissue (Nunez, 1987). Furthermore, various skull holes near the ears, eye sockets and jaw create distortion of the potentials. Thus a mix of local and global source activity may contribute to the scalp-recorded potentials.

In these studies, a linked-ear/mastoid form of reference was employed. This method however presents two difficulties. If the contact resistances are too small, then current may flow between the ears, thereby altering the pattern of current flow and the potentials recorded. Secondly, even if these resistances are great, unless they are equal, the ear whose wire is of the lesser resistance becomes the lone reference.

3.2.6. Amplification and A/D Conversion

The recording system consists of the amplifiers that bring the microvolt signals into some range where they can be converted from analog to digital form. The amplifier gain (1000 in our research) is the ratio of the output signal to the input signal. The resolution of the A/D converter is the number of levels that are discriminated over a particular range usually expressed as a power of 2 (bits). The gain of the recording system can be specified in terms of resolution, i.e. as the number of microvolts per least significant bit (smallest level discriminated by the

A/D converter) or as the number of bits per microvolt. In our case the resolution was 0.084 μV per least significant bit. Analog-to-digital conversion should be carried out at a rate that is sufficiently rapid to allow the adequate registration of those frequencies in the signal that determines the measurements. The minimum rate is twice the highest frequency in the signal to be measured.

3.2.7. Ocular Artifact Rejection/Reduction

Of all the potential sources of artifact in EEG recordings, the most prominent are those contributed by eye movements. Electrodes placed in the frontal and temporal regions of the scalp are susceptible to many types of ocular artifact. Such contamination must be removed or reduced to obtain reliable, artefact-free data. Two procedures may be employed to ensure that the influence of artefact was minimized or eliminated: manual eye-blink deletion and ocular artefact compensation.

One method for dealing with artifact-contaminated trials is to remove them from the averaging process. Any trials showing electrical activity greater than a criterion level (> 60μV in this research) in any recording channel should be rejected from averaging. Such rejection protocols decrease the number of trials available for averaging. If the number of rejected trials is very high (more than a third), the data may become difficult to interpret. Given a set amount of time or number of stimuli presented, the ERPs will show increased background noise because fewer trials will be accepted for averaging. Given a set number of accepted trials, cognitive trials may habituate because of the longer time required to reach this number. Furthermore, the trials may not be representative of the cognitive processes occurring: trials with EOG artifact may differ systematically from those without.

Although rejection procedures may be used to eliminate artifacts in most normal subjects, such protocols will not be satisfactory if the artifacts are very frequent. In these conditions, compensation procedures may be

employed to "correct" the EEG for eye movements. This approach assumes that the EEG recorded at the scalp comprises the true EEG signal plus some fraction of the EOG. This fraction (or propagation factor) represents how much of the EOG signal spreads to the recording electrode. Two assumptions are made: firstly, that ocular contamination is a linear function of the EOG amplitude and secondly, the EOG signal contains no contribution from the EEG. The ocular reduction program searches all the sweeps in the continuous file and detects the largest blink. It then calculates the average impact of this blink on all the electrodes (propagation factor), applying the appropriate weights to anterior compared to posterior leads. This average artefact measure is then subtracted from all sweeps containing blinks on a sweep-by-sweep, point-by-point basis, thus reducing the impact of the ocular artefact. However, such compensation procedures are not perfect. There may be changes in propagation factors over time due to changes in posture/direction of gaze, or to changes in the electrode-skin interface especially around the eyes. The use of one EOG channel for each type of eye movement (vertical eye movements and blinks) is an approximation. EOG electrodes also record EEG from the frontal regions of the brain as well as eye movement potentials. This causes two difficulties. First, it can distort the regression equation used to calculate the EOG propagation factors. Second, multiplying the EOG recording by the propagation factors and then subtracting this from the EEG recording will remove a portion of the frontal EEG signal as well as the EOG.

3.2.8 Continuous to Epoch files

The continuous file is the unprocessed data file containing the scalp-recorded EEG from the 32 channel array. This file also contains triggers sent from the stimulus-presentation computer at the time of stimulus presentation. These triggers allow the extracted ERPs to be time-locked to the presentation of the stimulus. The first step in analysis is "epoching", whereby the continuous file is divided into time epochs or sweeps, with each sweep corresponding to a trial or stimulus

presentation. This process extracts the ERP signal from the EEG. The stimulus trigger represents the zero millisecond (ms) time point on the x-axis. The epoch duration is chosen to include a designated period prior to stimulus presentation (i.e. the pre-stimulus interval) and a certain duration post-stimulus (from 500 to 1300 ms, depending on the interstimulus interval of the task involved). In all electrophysiological studies described in this thesis, an intertrial interval of –250 to 1250 ms was employed.

3.2.9 Baseline Correction

This procedure is applied to the epoch file to subtract average voltage offset from each data point. The average of the –250 to 0 ms prestimulus range of ERP data was calculated. This was then used as a correction factor and was subtracted from the original data set.

3.2.10 Filtering

Filtering, whereby a limit is set to the frequency in which the ERP signal of interest is known to occur, is used to remove noise (unwanted electrophysiological signals) from the epoched data. Most ERP laboratories impose signal sampling low and high frequency constraints of 0.01-0.5 Hz and 20-30 Hz respectively. Some investigators use the terms "low pass" to refer to high frequency filters, and "high pass" filters to refer to low frequency filters, i.e. the "low pass" filter passes frequencies higher than the specified level, and the "high pass" filter allows sampling of frequencies lower than the specified upper limit. In this research, the low pass filter was set to 30 Hz while the high pass frequency was set to 0.05 Hz. Zero Phase Shift filtering was employed. This makes two "passes" through the filter, once in each direction. While slower than analog filtering, this procedure has no distorting effect on ERP component latencies.

3.2.11 Averaging/sorting

Averaging refers to the summation of a series of EEG epochs that are time-locked to the stimulus or event of interest. This procedure results in the cancelling out of the random EEG fluctuations not time-locked to the stimulus (EEG noise), leaving the evoked potential voltage x time function in evidence. For effective use of the averaging procedure, the ERP signal should be constant over trials, the EEG noise should be random between trials, and the ERP signals should be independent of background noise. If these conditions apply, the "signal-to-noise" ratio is calculated to be increased by a factor of the square root of the number of trials in the average. In this research, a minimum of 16 trials per stimulus condition was chosen.

3.2.12 Measurement of ERP waveforms

P3 amplitude was defined as the maximum positive peak between 250 and 500 ms post-stimulus. P3 latency was measured from the stimulus onset to the peak within this interval. LPC amplitude was defined as the maximum positive peak between 500 and 700 ms post-stimulus. LPC latency was measured from the stimulus onset to the peak within this interval. Identification of ERP waves was determined independently by two observers who had to agree before measurement of latency and amplitude could take place.

3.3 CANTAB measures across the menstrual cycle

3.3.1 Participants

A total of twelve women with spontaneous menstrual cycles participated in the study. They replied to advertisements posted around the hospital and university (postgraduate science/medical students). Characteristics of the participants are summarized in Table 3.3. All subjects gave informed consent and the local ethics committee approved the study. All

subjects reported normal or corrected vision and were right-handed.

Table 3.3. *Characteristics of participants*

Age	
Mean	23
Range	19-35
Cycle length (days)	
Mean	28.9
Range	27-30
Education (years)	
Mean	15
Range	14-16

3.3.2 Inclusion/Exclusion criteria

All subjects were women with spontaneous regular menstrual cycles between 25 (minimum) and 35 (maximum) days in length. Those taking any prescription medication or the oral contraceptive pill were excluded from the study, as were those with Late Luteal Phase Dysphoric disorder (as assessed by self-report of key symptoms according to the DSM-IV), chronic diseases or a personal psychiatric history.

3.3.3 Procedure

Subjects who met the inclusion criteria attended the Mercer's Institute for Research on Ageing for testing on two occasions, corresponding to the menstrual (day 2-5) and mid-cycle phases (14 days before the beginning of the next cycle) of the menstrual cycle. Day 1 was not used to avoid possible confounding effects of physical discomfort on the first day of bleeding. Test sessions were counterbalanced, whereby half the subjects were tested first in the menstrual phase and the other half tested

initially in the ovulatory phase. The three tests took approximately 40 minutes in total to administer.

3.3.4 Intra/Extra Dimensional (ID/ED) Shift test

This task is an attentional set-shifting test whereby the subject must switch between shapes and dimensions. Two dimensions were used in this test – purple-filled shapes and white lines. Simple stimuli were composed of one of these dimensions, while compound stimuli were composed of both, namely white lines overlying purple-filled shapes. Subjects had to satisfy a set criterion of learning at each stage (six consecutive correct responses). If the subject failed to reach this criterion at any stage the test terminated after a predetermined number of trials (50). Presentation of shapes or lines was randomized. The subject learned which of the stimuli were correct by pointing to it. When the criterion was reached, contingencies were reversed so that the previously incorrect stimulus became correct. The stimuli progressively changed from single to compound.

Once the subject had learned the compound discrimination, new compound stimuli were displayed, again varying along the same dimensions (shape and line). In the case of IDS, subjects were required to continue to attend to the formerly relevant dimensions and learn which of the two new exemplars was correct. In the case of EDS, subjects had to shift attention to the previously irrelevant dimension and learn which of the two exemplars were correct. After successfully performing either an ID or an ED shift the contingencies were reversed (IDR/EDR). The dependant measures used from this task were "trials to criterion" and "latencies" for IDS, IDR, EDS, EDR.

3.3.5 Paired Associate Learning (PAL) test

This task requires the subject to remember patterns associated with different locations on the screen. Subjects were first presented with six

boxes, which "open up" in turn, revealing an abstract pattern. Subjects were instructed to try to remember the location of each pattern. When all the boxes have opened up, the hidden patterns appear one at a time in the centre of the screen and subjects must indicate where each pattern was hidden. If an incorrect response was made, the boxes were reopened to remind subjects of the correct location. This procedure was repeated until subjects correctly identified the locations of all the patterns or until a maximum of ten reminder trials had been provided. Feedback was not provided until subjects had correctly identified the location of all patterns. Subjects who were successful at the six box stage were then presented with eight boxes and an identical procedure was followed.

Performance was assessed by two measures (1) "Trials" – the total number of presentations required (maximum score=10 presentations per trial) to correctly identify the pattern-location associations. Subjects unable to complete were assigned the maximum score of 10 for each unfinished trial; (2) "Errors" – the total number of errors made (incorrect pattern locations) summed across both stages. Subjects not completing a stage were assigned the worst score obtained by a subject attempting a set. The number of patterns placed correctly on the first presentation of each trial gives an index of "list memory" and the number of repeat reminder presentations required provides a measure of "list learning".

3.3.6 Delayed Matching to Sample (DMTS) test

In this test, a complex visual pattern is presented and then, after a short delay, four choice patterns appear. Each pattern comprises four sub-elements, each of a different colour. One of the choice patterns is identical to the sample, one is a novel distractor pattern, one has the shape of the sample and the colours of the distractor and the fourth has the shape of the distractor and the colours of the sample. All four choice patterns have one quadrant in common with the sample to discourage strategies based on encoding single quadrants. In some trials the sample and the choice patterns are shown simultaneously, while in others a

delay of 0, 4 or 12 seconds is introduced between presentation of the sample and the choice patterns. There are 40 counterbalanced test trials, including 10 simultaneous and 10 at each of the 3 delay intervals.
The measures used were the "total correct" and "latency".

3.3.7 Statistics

The CANTAB data was statistically analysed using the Wilcoxon Signed Rank test. The means, medians and standard deviations were calculated. Examining the residuals for normality and constancy of spread against predicted values subsequently tested the validity of the data. It was confirmed that outliers indeed represented measured values rather than errors– they were then included in the subsequent analysis

Chapter 4

Sex Hormones and Cognition: Results

4.1 The effect of the menstrual cycle on electrophysiological and behavioural measures of memory and mood

4.1.1 Behavioural performance

Direct task

For the direct task, there was no significant difference between the percentage correct for new (p=0.5) or old words (p=0.1) across the menstrual cycle. No significant difference was found across the menstrual cycle between the reaction time (RT) for new (p=0.94) and repeated (p=0.87) items. Accuracy and reaction time measures for this task are summarized in Table 4.1.1.

Table 4.1.1. *Performance data from the Direct task across the menstrual cycle*

	Start	**Mid**
New items		
% Correct	94.5	94.2
S.D.	5.5	6.1
Reaction time (ms)	909	920
S.D.	209	174
Repeated items		
% Correct	82.7	80.5
S.D.	13.2	12.6
Reaction time (ms)	913	932
S.D.	209	174

Indirect task

No significant difference was observed between the percentage correct for new words across the cycle (p = 0.13). The mean percentage correct for the recognition of old words in the indirect test changed significantly

across the menstrual cycle, with mean scores of 89 ± 3 % at start-cycle and 96.2 ± 1.2 % at the mid-cycle stage (p=0.03). Differences between reaction time for new and old items across the cycle were not significant (p =0.3 and p=0.35 respectively). Accuracy and reaction time measures for this task are shown in Table 4.1.2.

Table 4.1.2. *Performance data from the Indirect task across the menstrual cycle*

	Start	**Mid**
New items		
% Correct	92.2	95.6
S.D.	8.4	5.6
Reaction time (ms)	818	788
S.D.	152	161
Repeated items		
% Correct	89	96
S.D.	3	1.2
Reaction time (ms)	815	785
S.D.	154	161

4.1.2 ERPs

Evoked potentials produced in response to whether the word was seen previously ("old") or not ("new") in the memory test were analyzed. The effects of repetition were quantified by measurement of the 250-1000ms latency region. Such effects were also studied in relation to the two different test sessions i.e. start and mid-cycle and across the two different task types. Although 32 channels were used for a subset of the participants (n=8), the analysis is restricted to data from the electrode sites common to all (Fz, Cz, Pz, C3 and C4). For topographical illustration all channels employed are displayed in Figures 1 to 6. The mean amplitudes of the ERP repetition effect at start-cycle and mid-cycle in the direct and indirect tasks are shown in Tables 4.1.3 and 4.1.4 and are illustrated in Figures 4.1 – 4.4. Subtraction grand average

waveforms from the direct and the indirect tasks at start-cycle and mid-cycle are shown in Figures 4.5 and 4.6.

The data was evaluated using repeated measures ANOVAS with factors of word type (new/old), task type (direct/indirect), electrode site (Fz, Cz etc.) and cycle point (Start/Mid). Mean amplitude analysis of the 250-1000 ms latency region revealed a very reliable word repetition effect [$F(1,16) = 24.3$, $p < 0.0001$]. This was due to the fact that the mean amplitude of the ERP to repeated words was more positive by 1.7 μV on average. An overall effect of cycle was not observed [$F(1, 16) = 0.44$, $p = 0.5$] and the effect of cycle on task was also insignificant [$F(1, 16) = 0.008$, $p = 0.7$]. No significant main effect of cycle was found on the word category effect [$F(1, 16) = 0.15$, $p = 0.9$], suggesting that the repetition effect was stable across the menstrual cycle. Furthermore, a 3-way cycle x word x task interaction was not significant: [$F(1, 16) = 0.14$, $p = 0.7$].

The ANOVA performed across both tasks confirmed that overall mean amplitudes were maximal at Pz, electrode: [$F(4, 13) = 9.3$), epsilon=0.4, $p=0.001$]. The repetition effect was more pronounced at posterior rather than anterior recording sites, word x electrode: [$F(4, 13) = 7.4$, epsilon=0.6, $p = 0.01$]. Also, overall mean amplitudes were greater during the direct than the indirect test at Pz: task x electrode: [$F(4, 13) = 4.3$, epsilon=0.7, $p = 0.01$]. An overall effect of task was not observed [$F(1, 16) = 0.02$, $p = 0.9$] and the word x task interaction was not significant [$F(1,16) = 0.08$, $p = 0.92$].

Table 4.1.3. *Mean Amplitude (μV) of the ERP Repetition Effect in the Direct Task for the 250-1000 ms latency region at start-cycle and mid-cycle*

	Fz	**Cz**	**Pz**	**C3**	**C4**
Start					
Mean	1.05	3.5	3.9	2.1	2.1
S.D.	3.3	2.7	3.4	3.3	2.2
Mid					
Mean	0.8	1.9	3.7	1.8	2.5
S.D.	4.3	3.8	3.7	2.3	3.2

Table 4.1.4. *Mean Amplitude (μV) of the ERP Repetition Effect in the Indirect Task for the 250-1000 ms latency region at start-cycle and mid-cycle*

	Fz	**Cz**	**Pz**	**C3**	**C4**
Start					
Mean	1.4	2.6	3.4	2	2.3
S.D.	3.0	2.7	2.9	2.2	2.4
Mid					
Mean	1.7	2.8	2.6	1.4	1.6
S.D.	2.7	2.4	2.8	2.4	2.4

P300 Analysis (250-500 ms)

The latency intervals for the P300 and LPC components were chosen based on previous studies on menstrual cycle effects on late positivity (e.g. Krug *et al.*, 2000) and on visual inspection of the ERP responses obtained in the present experiments. The mean amplitudes and latencies of the P300 at start-cycle and mid-cycle for the direct and indirect tasks are reported in Tables 4.1.5 and 4.1.6 and displayed in Figures 4.7 and 4.8. Analysis of variance with repeated-measures factors representing Cycle (start or mid-cycle), the type of Task (direct or indirect) and Word category (old or new) was carried out.

P300 amplitude was greater at start-cycle than mid-cycle by 2.85 ± 0.2 μV [$F(1, 16) = 13.7$, $p = 0.002$]. This cycle effect was not dependent on the type of task [$F(1, 16) = 0.7$, $p = 0.41$] or word (i.e. cycle x task x word interaction was not significant [$F(1, 16) = 0.314$, $p=0.58$] and the cycle x word interaction was not significant [$F(1, 16) = 0.073$, $p = 0.8$]). A significant word effect was observed [$F(1, 16) = 16.7$, $p=0.001$], showing that P300 amplitude was greater for old words compared to new words. The overall effect of task was insignificant [$F(1,16) = 0.45$, $p = 0.51$]. The word x task interaction was also insignificant [$F(1, 16) = 1.4$, $p = 0.25$]. P300 latency did not vary significantly across the cycle [$F(1, 696) = 3$, $p = 0.07$].

LPC (P600) Analysis (500-700 ms)

LPC amplitude was defined as the maximum positive peak between 500 and 700 ms post-stimulus. The mean amplitudes and latencies of the LPC at start-cycle and mid-cycle for the direct and indirect tasks are reported in Tables 4.1.5 and 4.1.6 and displayed in Figures 4.7 and 4.8.

Like the P300, an overall effect of cycle was found [$F(1, 16) = 47.5$, $p = 0.0001$]. This means that LPC amplitude was greater at start-cycle than mid-cycle by 0.7 ± 0.26 μV. Again this cycle effect was not dependant on the type of task [$F(1, 16) = 3.6$, $p = 0.07$] or word (i.e. the cycle x

task x word interaction was not significant [F(1, 16) = 0.58, p=0.45] and the cycle x word interaction was not significant [F(1, 16) = 0.39, p = 0.53]). A word effect was not observed [F(1, 16) = 1.35, p=0.26]. An effect of task [F(1, 16) = 0.8, p = 0.38] was not found. The word x task interaction was insignificant [F(1, 16) = 1.1, p=0.31]. There was no effect of cycle on LPC latency [F(1, 696) = 0.7, p = 0.4]. An effect of test on LPC latency was observed [F(1, 16) = 5.1, P=0.03], whereby the direct task gave rise to longer latencies than the indirect task.

Table 4.1.5. *Mean amplitude and latency of the P300 and LPC in the Direct Task at start-cycle and mid-cycle at Pz*

Cycle	**P300 Amplitude**	**P300 Latency**	**LPC Amplitude**	**LPC Latency**
Start				
Mean	11.9	342.9	9.8	634.3
S.D.	5.6	74	6.8	56
Mid				
Mean	8.4	327.2	9.5	644.9
S.D.	5.5	55.4	6.7	55.4

Table 4.1.6. *Mean amplitude and latency of the P300 and the LPC in the Indirect Task at start-cycle and mid-cycle at Pz*

Cycle	**P300 Amplitude**	**P300 Latency**	**LPC Amplitude**	**LPC Latency**
Start				
Mean	10.1	337.9	9.7	611.5
S.D.	5.2	50.1	4.7	62.9
Mid				
Mean	8.6	333.1	8.02	612.7
S.D.	5.5	54.8	5.2	79.5

4.1.3 Verbal memory tasks (Paragraph Recall and Paired Associate Learning)

As shown in Table 4.1.7, no significant differences were observed between scores at start and mid-cycle on either of these tests.

Table 4.1.7 *Verbal memory scores at start-cycle and mid-cycle*

Paragraph Recall	Start	Mid
Mean	35.2	36.4
S.D.	5.6	5.5
p value	0.1	
Paired Associates		
Mean	20	20.1
S.D.	1.1	1.1
p value	0.9	

4.1.4 POMS

Table 4.1.8 shows that significant differences were observed for all 6 mood scales between start and mid cycle, with an increase in scores at mid cycle compared to start cycle.

Table 4.1.8. *POMS mood test scores at start-cycle and mid-cycle*

Scales	Composed	Agreeable	Elated	Confident	Energetic	Clearhead
Start						
Mean	20.8	27.1	21.4	18.6	16.3	22.5
S.D	7.2	3.8	6.4	5.9	7.2	5.9
Mid						
Mean	26.6	30.3	27.8	23.3	24.0	27.4
S.D.	7.2	4.2	6.1	6.4	7.5	6.4
p value	0.002	0.02	0.003	0.003	0.002	0.003

4.1.5 Correlational Analysis

Spearman Rank correlations were conducted. No significant correlations were observed between sex hormone levels and behavioural test performance or the ERP data. No significant correlations were found between mood scores and behavioural performance or the ERP data (see Tables 4.1.9 and 4.1.10).

Table 4.1.9. *Correlation analysis for ERP, behavioural and mood measures and sex hormone levels at start-cycle.*

	Oestradiol (Start)	**Progesterone (Start)**
P3 Amplitude	0.4	0.1
P3 Latency	-0.6	-0.3
P6 Amplitude	0	0.2
P6 Latency	0	0.3
% Correct – Direct	0.1	-0.2
% Correct – Indirect	0	-0.3
Reaction time	-0.5	0
Composed	-0.2	-0.3
Agreeable	0.1	0.1
Elated	0.1	-0.5
Confident	-0.2	-0.6
Energetic	0.1	-0.3
Clearheaded	-0.2	-0.3

Table 4.1.10. *Correlation analysis for ERP, behavioural and mood measures and sex hormone levels at mid-cycle.*

	Oestradiol (Mid)	**Progesterone (Mid)**
P3 Amplitude	0	0.1
P3 Latency	-0.2	-0.6
P6 Amplitude	0.2	0.2
P6 Latency	0.3	0
% Correct – Direct	-0.4	0.1
% Correct – Indirect	-0.3	0.2
Reaction time	0	0.2
Composed	-0.2	0
Agreeable	0.2	0
Elated	0	0.2
Confident	-0.1	0.2
Energetic	-0.2	0.2
Clearheaded	-0.1	0.2

4.2 CANTAB Results

4.2.1. Intra-dimensional/extra-dimensional set shift task

The average response latency did not vary across the cycle ($p = 0.8$). Performance as indicated by the average number of trials to criterion did not change between the cycle time-points ($p = 0.38$). See Table 4.2.1.

4.2.2. Paired Associate Learning

As shown in Table 4.2.2, the total number of errors in all sets in this task did not vary with the cycle ($p=0.25$), although a trend was observed towards a higher error rate at mid-cycle (10.4) relative to start-cycle (8.8). The number of trials to success was also insignificantly ($p=0.09$) higher at mid-cycle (12.5) compared to start-cycle (13.75).

4.2.3. Delayed Matching to Sample (DMTS)

Table 4.2.3 shows that the number of total correct scores in this task changed insignificantly across the menstrual cycle ($p=0.08$), with slightly higher scores at mid-cycle (37) compared to start-cycle (34.6). The latency for correct responses did not alter across the cycle ($p = 0.38$).

Table 4.2.1. *Set Shift Task measures across the menstrual cycle*

	Start	**Mid**
Set Latency		
Mean	1321.3	1300.4
Median	1282.6	1204.6
S.D.	241.9	418.5
Set trials to criterion		
Mean	7.6	7.8
Median	7.4	7.3
S.D.	1	1.3

Table 4.2.2. *Paired Associate Learning (PAL) measures across the menstrual cycle*

	Start	**Mid**
Errors		
Mean	8.8	10.4
Median	6.5	8.5
S.D.	6.4	9.7
Trials to success		
Mean	12.5	13.7
Median	11.5	12.5
S.D.	2.5	3.7

Table 4.2.3 *Delayed Matching to Sample (DMTS) measures across the menstrual cycle*

	Start	**Mid**
Correct		
Mean	34.6	37
Median	36	37
S.D.	5.3	1.6
Latency		
Mean	3362.2	3328.5
Median	3242.5	3317.5
S.D.	657.4	610

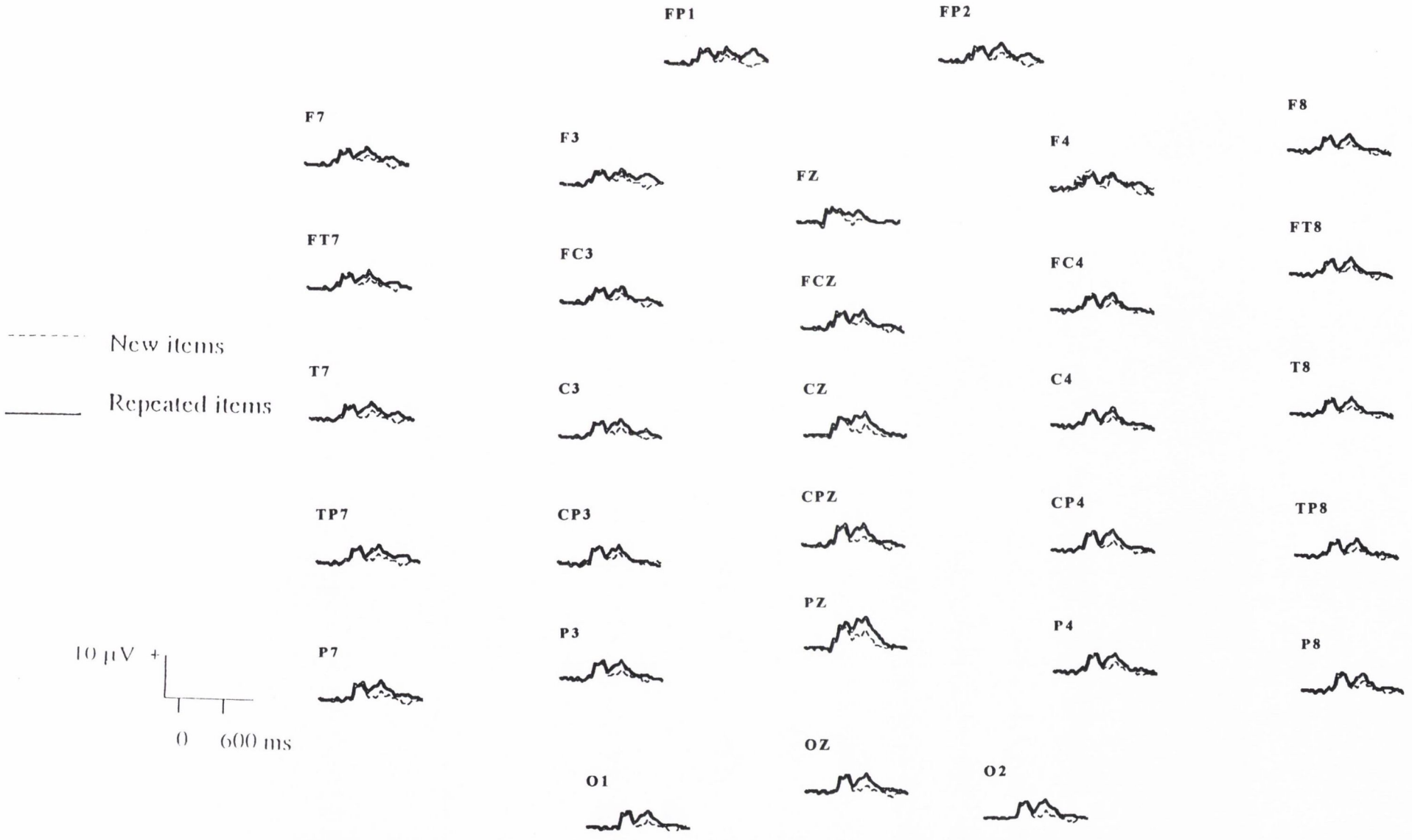

Figure 4.1. Grand average waveforms from the direct task at start-cycle for the first presentations (new items) and for repeated items.

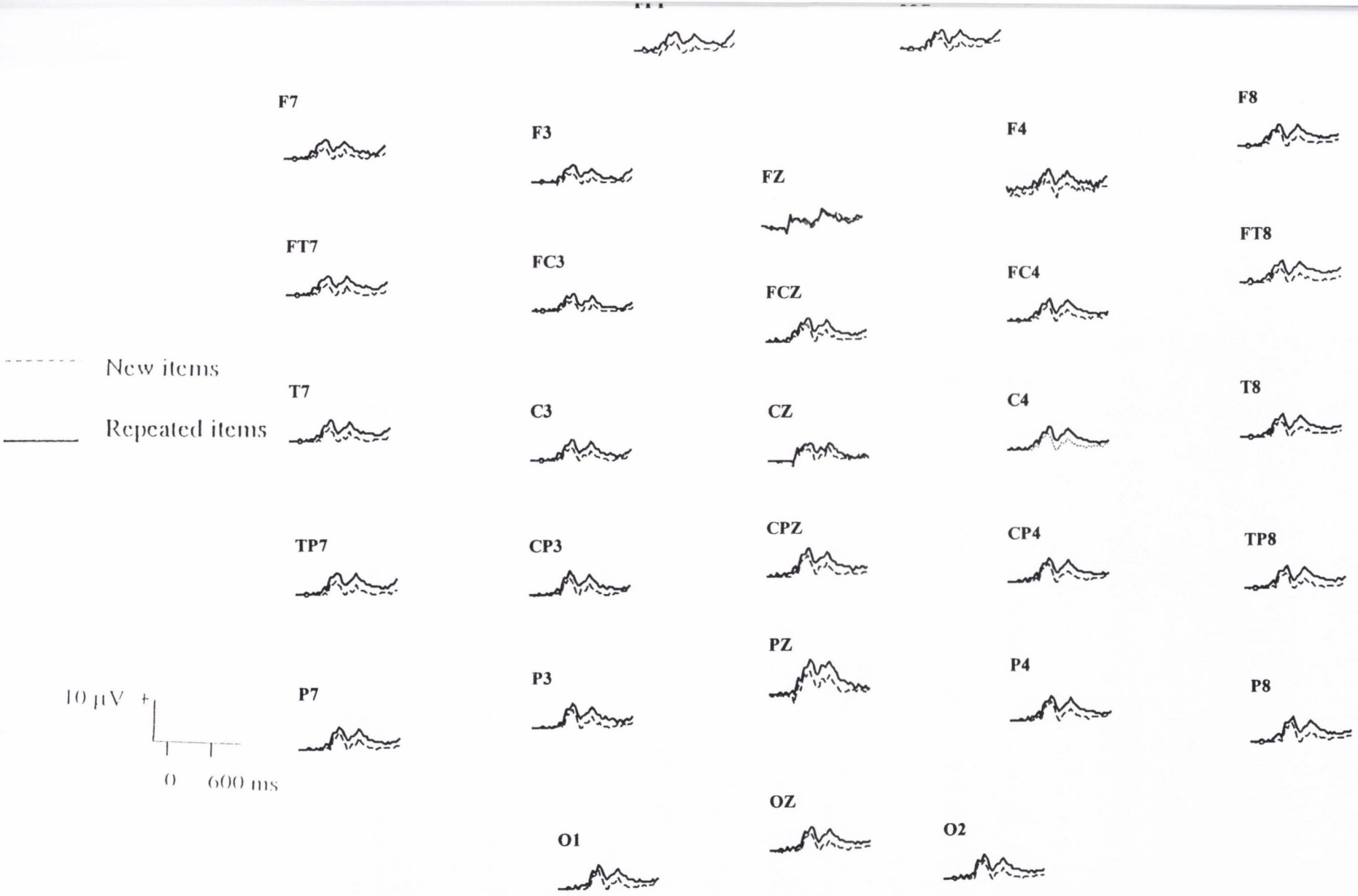

Figure 4.2. Grand average waveforms from the indirect task at start-cycle for the first presentations (new items) and for repeated items.

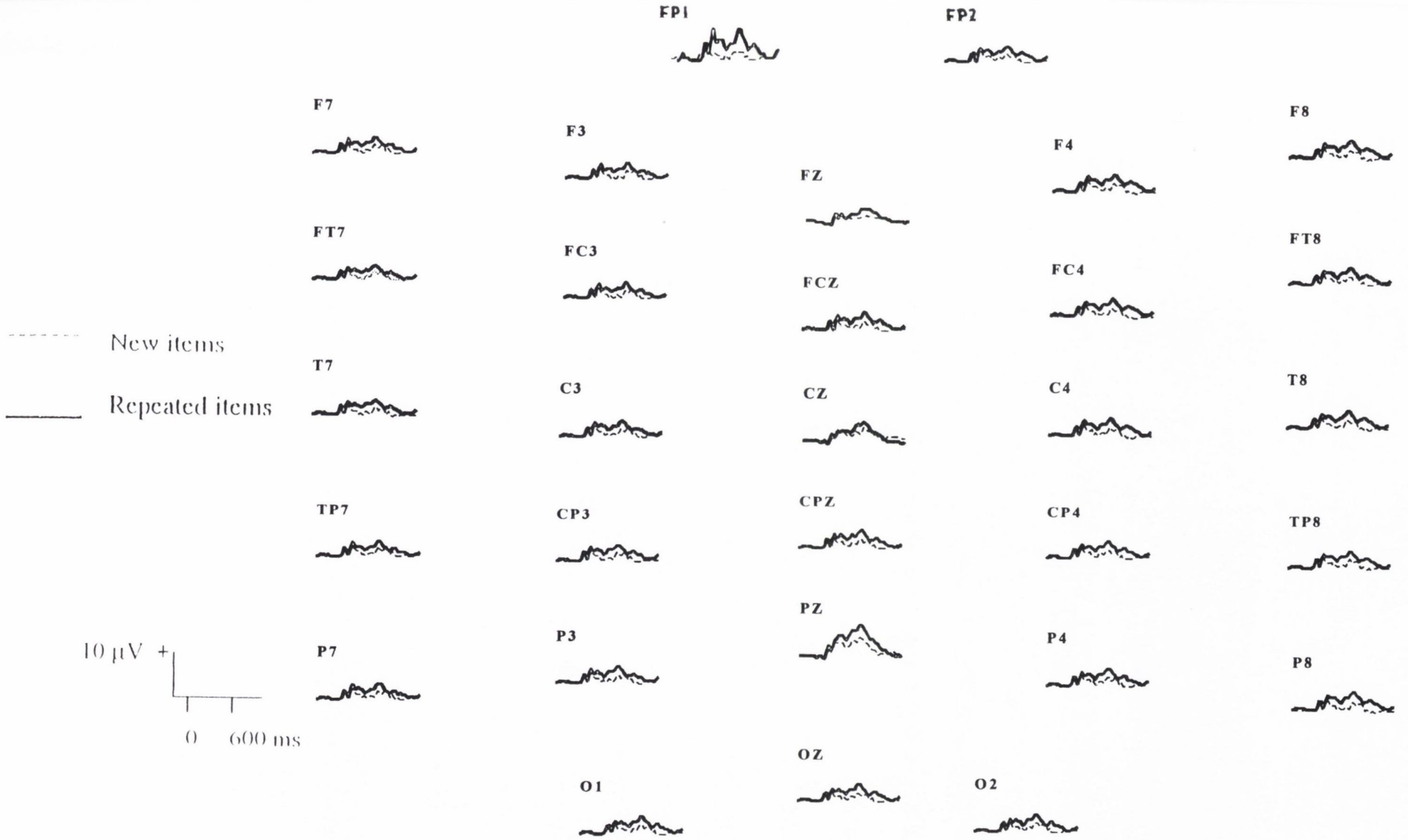

Figure 4.3 Grand average waveforms from the direct task at mid-cycle for the first presentations (new items) and for repeated items.

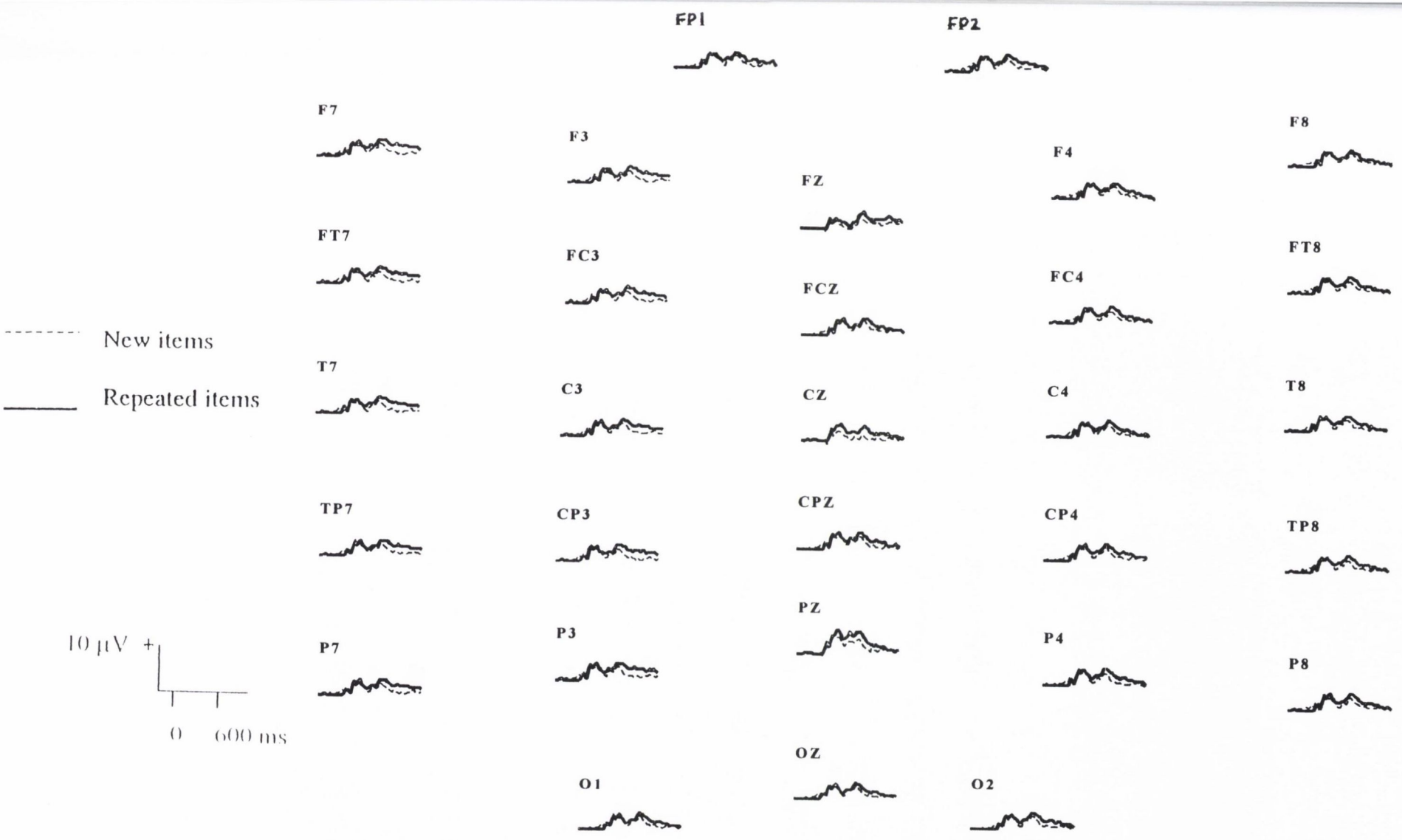

Figure 4.4. Grand average waveforms from the indirect task at mid-cycle for the first presentations (new items) and for repeated items.

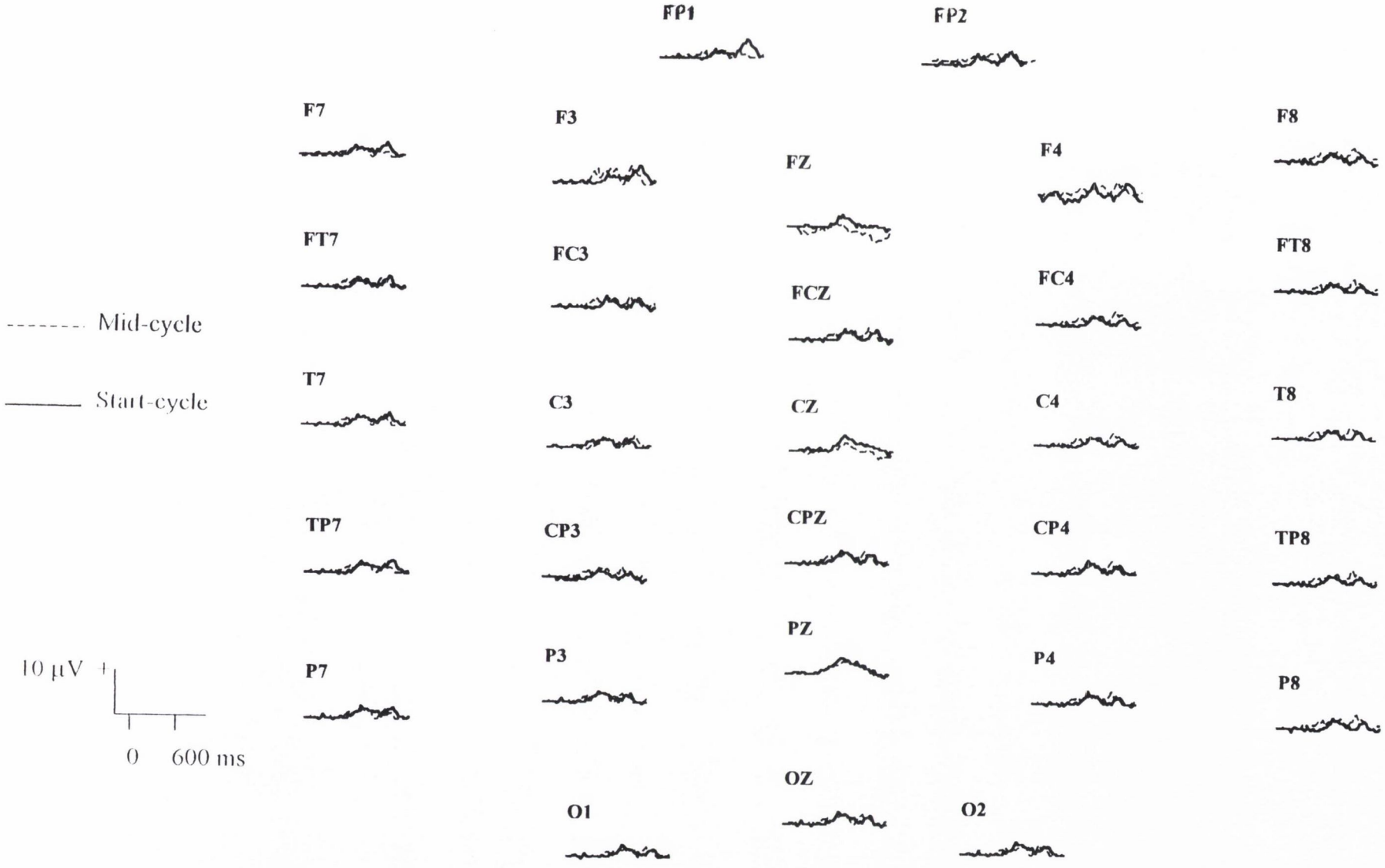

Figure 4.5. Grand average subtraction waveforms from the direct task for start-cycle and mid-cycle.

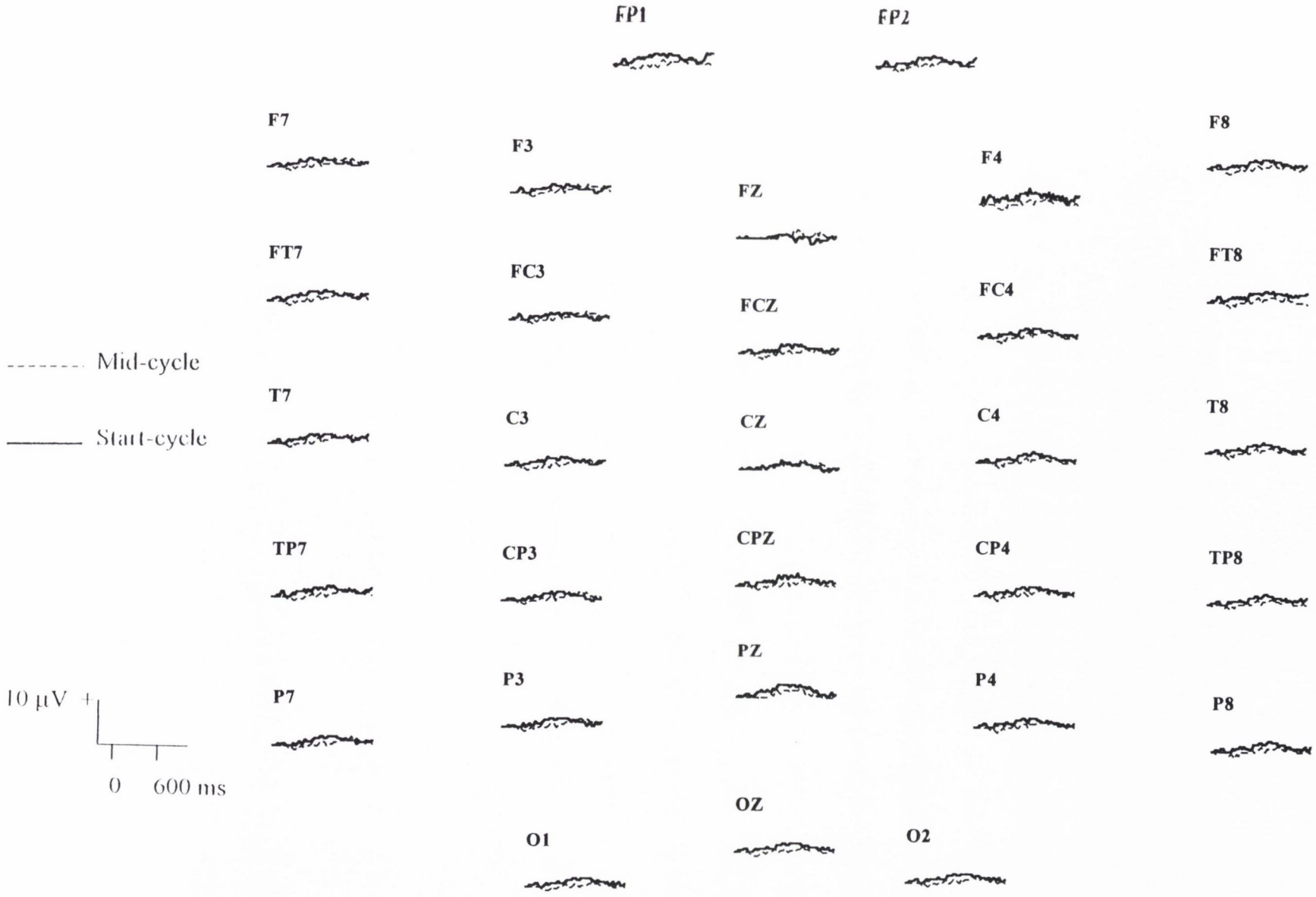

Figure 4.6. Grand average subtraction waveforms from the indirect task for start-cycle and mid-cycle

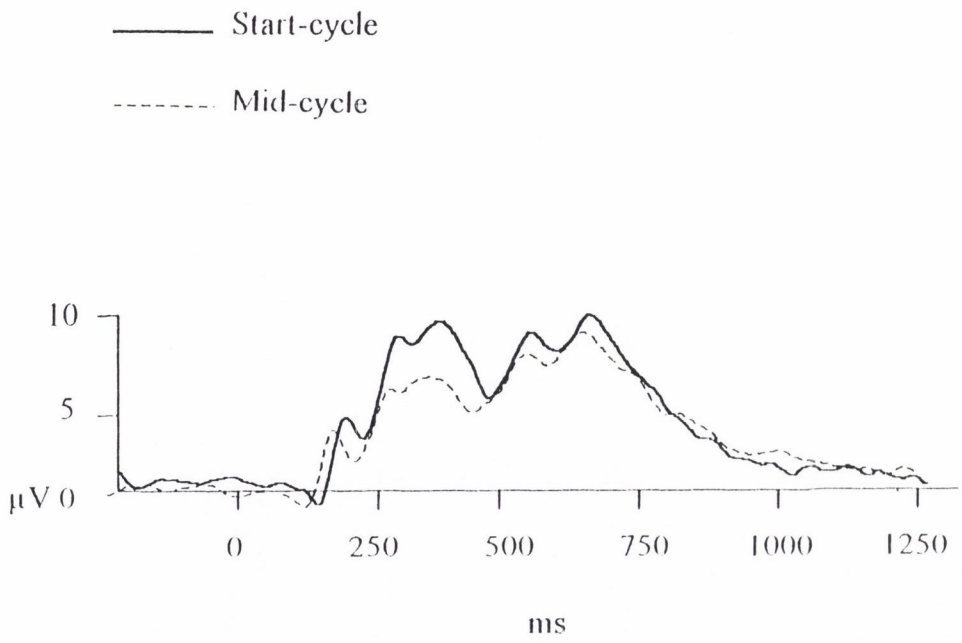

Figure 4.7. P300/LPC amplitude at the Pz electrode at start-cycle and mid-cycle for the direct task.

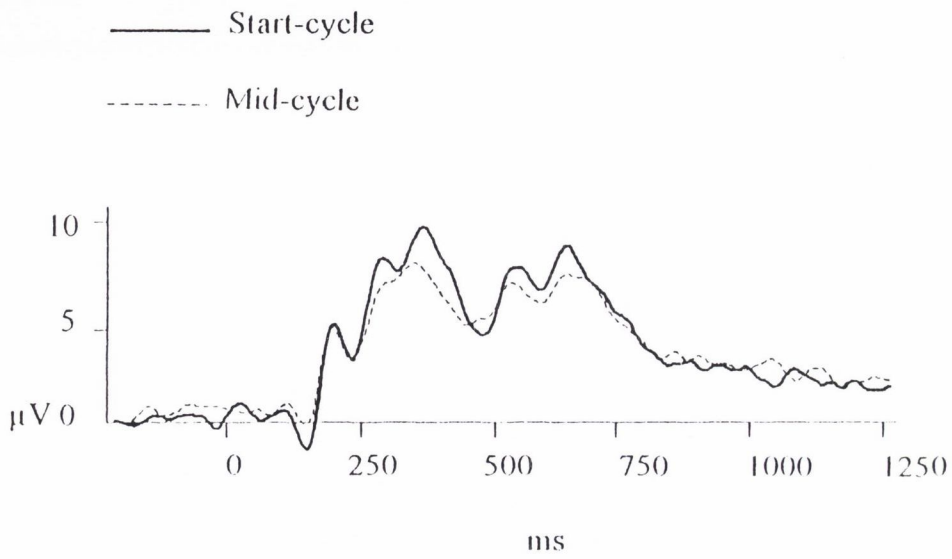

Figure 4.8. P300/LPC amplitude at the Pz electrode at start-cycle and mid-cycle for the indirect task.

Chapter 5

Sex Hormones and Cognition: Discussion

5.1 The effect of the menstrual cycle on electrophysiological and behavioural measures of memory and mood.

5.1.1 Overall findings

This study examined, by means of ERPs, the effects of the menstrual cycle on the processing of word recognition stimuli. Plasma oestrogen and progesterone were significantly higher at mid-cycle compared to start-cycle, thus confirming the menstrual cycle phase. The ERP repetition effect between 250-1000ms, evoked by both direct and indirect memory tasks, was stable across the menstrual cycle. However ERP measures of stimulus processing i.e. the P300 and the LPC were sensitive to hormonal variations across the cycle, with higher amplitudes at start-cycle compared to mid-cycle. While recognition accuracy, reaction times, paragraph recall and paired associate test scores did not vary with the cycle, mood as assessed by the POMS inventory was significantly enhanced at mid-cycle relative to start-cycle.

5.1.2 Electrophysiological measures of verbal memory across the menstrual cycle

Event-related potentials (ERPs) were employed to investigate differences in brain activity elicited by repeated and unrepeated stimuli, with the goal of examining memory processes across the menstrual cycle. ERPs to words correctly identified as "old" were more positive than those to words correctly identified as "new" from 250 to 1000 ms post word onset. This is known as the ERP repetition effect observed in ERP studies of recognition memory (Friedman, 1990; Rugg & Nagy, 1989; Rugg *et al.*, 1991; Allan *et al.*, 1998; Johnson, 1995; Rugg, 1995). Both direct and indirect memory tasks were employed to elicit the ERP repetition effect

in this study. It has been proposed that ERP effects elicited by indirect tasks are associated with implicit memory, while those evoked by direct tasks are a reflection of explicit memory (Swick, 1997; Friedman 1995).

Most studies of hormonal effects on memory have focused on recall and recognition tasks to measure explicit memory function. Several studies have demonstrated positive effects of HRT on explicit measures of verbal memory (Sherwin, 1988; Sherwin & Phillips, 1990; Phillips & Sherwin, 1992; Wolf, 1999; Hogervorst, 1999). However, no difference in electrophysiological measures of explicit memory as assessed by the direct memory task was observed across the menstrual cycle. Two previous studies also failed to find an effect of the menstrual cycle on explicit memory tests (Hartley, 1987; Phillips & Sherwin, 1992a). These discrepancies may be attributable to the fact that oestrogen levels induced by exogenous HRT treatment in previous studies were supraphysiological. Thus, the failure to find an effect of the menstrual cycle on such verbal memory measures in the present study may be due to the fact that plasma sex hormone levels are at significantly lower levels across the menstrual cycle. Furthermore, increases in progesterone levels at mid-cycle may counter the effect of oestrogen on memory (see Chapter 2).

Only one study has directly examined the influence of the menstrual cycle on implicit memory (Maki *et al.*, 2002). They found that high levels of ovarian hormones facilitated conceptual implicit memory. However no effect of the menstrual cycle on implicit memory in electrophysiological terms as measured by the indirect task was found in the current study. It is well documented that explicit memory can influence or contaminate implicit memory processes elicited by this task (Rugg, 1995). Nonetheless, no instructions were given in the indirect task to try to remember items for later recognition, which should have decreased the use of explicit strategies in the participants.

Cumulatively this suggests that electrophysiological measures of both

explicit and implicit memory are insensitive to hormonal changes across the menstrual cycle. Oestrogen's proposed facilitatory effect on cognition appears to be dependent on the cognitive domain under scrutiny and does not translate to verbal memory at an electrophysiological level.

A novel finding of this study was the start-cycle increase in P300 and LPC amplitude. This finding lies in opposition to results from recent reports concerning menstrual cycle effects on ERPs. Johnston & Wang (1991) and Wang & Johnston (1993) observed that reproductive stimuli (male models and babies) evoked larger P300 amplitudes during the luteal phase than any other phase. Krug (2000) found that, during the ovulatory phase, LPC amplitude to sexual stimuli was larger than that elicited by other stimulus categories (babies, ordinary people, and body care). Such an apparent anomaly may be explained by the fact that different types of paradigms were employed - emotional processing in response to pictorial stimuli in the cases of Wang & Krug; and neutral processing of verbal stimuli in the case of this study. It has been widely documented that emotional processing is lateralized to the right hemisphere (Borod *et al.*, 2002) and verbal processing is predominately in the left hemisphere (Beaumont, 1971). It may be that the menstrual cycle has differential hemispheric-dependent effects on different types of processing. This is supported by a previous study on changes in functional cerebral asymmetry across the menstrual cycle (Chiarello *et al.*, 1989). They reported that lexical decision response asymmetry varied across the cycle and that this was due to variation in left hemisphere, but not right hemisphere performance. Thus this report and the current findings support the view that the left hemisphere, which is dedicated to verbal processes, may be particularly sensitive to levels of sex hormones in adult women (Hampson & Kimura, 1988).

One way of interpreting these findings is to look at the P300/LPC as an index of inhibitory control of cognitive activity (Coenen *et al.*, 1995). As oestrogen is known to increase cortical excitability (Sherwin, 1999), high levels of this hormone at mid-cycle may cause a removal of inhibitory

control i.e. a reduced P300/LPC amplitude, thereby inducing greater cognitive activity at mid-cycle relative to start-cycle. This increased cognitive processing at mid-cycle, when oestrogen levels are high, parallels previous literature documenting significant facilitatory effects of this sex hormone on cognition (see Chapter 2).

Although both oestrogen and progesterone levels are elevated at mid-cycle, these findings are more likely to be attributable to oestrogen. A wealth of data links oestrogen to cortical excitability and promotion of neural processes (McEwen *et al.*, 2000). Furthermore, beneficial effects of HRT on cognitive task performance have been extensively reported (for review, see Hogervorst *et al*, 1999). Progesterone, on the other hand, appears to have the opposite effect on cognitive processing. Progesterone is known to decrease brain excitability (Holzbauer, 1976) and its sedative-hypnotic properties have been widely reported (Tapanacinen *et al.*, 1989). Indeed animal data show that progesterone metabolites are barbiturate-like modulators of the GABA receptor (Mendelson, 1987). Freeman *et al.* (1992) reported that progesterone levels were associated with an inhibitory effect on information processing.

Therefore, although sex hormone changes across the menstrual cycle had no effect on electrophysiological measures of verbal memory, it exerted a reliable influence on electrophysiological correlates of verbal processing. This suggests that cognitive activity in response to verbal stimuli (i.e. verbal processing) as measured by ERPs, rather than on verbal memory (as indexed by the ERP repetition effect) *per se*, is sensitive to hormonal changes during the menstrual cycle.

An effect of test on LPC latency was observed whereby the direct task gave rise to longer latencies than the indirect task. It may be that explicit memory processing in the direct test would require a greater length of time, giving rise to longer latencies for this task.

5.1.3 Behavioural measures of verbal memory across the menstrual cycle

No significant relationship between reaction times and stage of the menstrual cycle was observed. Indeed many studies have examined the effect of the menstrual cycle on reaction times with negative findings (Pierson & Lockhart, 1963; Kopell *et al.*, 1969; Zimmerman & Parlee, 1973; Hunter *et al.*, 1979; Hutt *et al.*, 1980). These results support the majority of findings that reaction times are insensitive to the menstrual cycle.

Paragraph recall, a measure of propositional memory (Loring & Papanicolaou, 1987), did not change as a function of menstrual cycle phase. Two studies agree with the current finding. An effect of the menstrual cycle on paragraph recall scores was not demonstrable in Phillips & Sherwin's 1992 study. Hartley *et al.* (1987) also failed to find significant differences across menstrual, ovulatory and luteal phases on the immediate or delayed recall of a prose passage. However previous findings on surgically menopausal women (Sherwin, 1988; Sherwin, 1990; Phillips & Sherwin, 1992) suggested that oestrogen may have enhancing effects on immediate paragraph recall. Thus, improved scores in the surgically menopausal women during oestrogen treatment may be due to a pharmacological effect of the steroid, since plasma oestrogen levels were supraphysiological. As suggested earlier, it is likely that such findings in older women do not generalize to young cycling women, because the decline in oestrogen levels after surgical menopause is more pronounced and abrupt, and thus more likely to cause memory changes compared to the less-pronounced variations in endogenous oestrogen fluctuations across the cycle.

As regards the paired associate task, a measure of rote verbal learning/retention, a significant phase change was hypothesized on the basis of previous findings from older women (Caldwell & Watson, 1952; Phillips & Sherwin, 1992). There is evidence that oestrogen may enhance

adrenergic function (Klaiber *et al.*, 1982), a neurotransmitter system which, if pharmacologically disrupted, is associated with impairment on the paired associate task (Frith, 1985). The current finding of no effect of the menstrual cycle on performance of this test lies in opposition to Phillips & Sherwin (1992), who reported that plasma oestrogen levels were associated with paired associate scores. However this result emerged from a small subgroup only. Once again, these findings suggest that effect of oestrogen on paired associates may be apparent only when high doses of the hormone are administered as is the case in HRT regimens, and is not sensitive to changes in the natural hormonal milieu across the menstrual cycle.

It should be noted that such negative results may also be attributable to variations in the types of cognitive strategies used to successfully recall information. For example, in the case of paragraph recall, one subject may passively repeat the last few sentences heard, while another may have used more efficient encoding strategies. Thus such individual variations may mask possible changes in performance concomitant with cyclic hormonal fluctuations.

5.1.4 Mood measures across the menstrual cycle

Most research in this field has focused on mood in women selected for the presence of pathological symptoms. This is known as the "premenstrual syndrome" or PMS (Rubinow & Schmidt, 1995). However the existence of this syndrome is irrelevant to the question of a general influence of the menstrual cycle on mood. As one of the exclusion criteria for participation in this study was severe PMS, otherwise known as Late Luteal Phase Dysphoric Disorder (LLPDD), this study was concerned with mood in non-pathological individuals only. A highly significant difference in mood scores was observed between start and mid cycle across all 6 subscales, with higher scores found at mid cycle. This agrees with several studies (Sanders *et al.*, 1983; Cockerill *et al.*, 1992; Choi *et al.*, 1995; Williams *et al.*, 1997). Yet it must be noted that this is

not a universal phenomenon (Slade, 1984; Bowen *et al.*, 1990; Kanarek *et al.*, 1995, Einon, 1997; Compton *et al.*, 1997; Black, 1990). Such conflicting results may be due to methodological shortcomings. Only four of these studies verified the menstrual cycle phases by hormonal assay (Abplanalp *et al.*, 1979; Laessle *et al.*, 1990; Collins *et al.*, 1985). Several studies used unstandardized tests e.g. mood diaries and questionnaires and reported negative findings (Sanders *et al.*, 1983; Einon, 1997; Compton *et al.*, 1997). Furthermore, a variety of different cycle time points were selected in these studies e.g. days 19-24 (luteal phase) in the Philips & Sherwin study and days 10-20 (intermenstrual phase) in the Abplanalp report, making inferences about mood changes concomitant with specific cycle phases difficult.

The enhancement of mood at mid-cycle relative to start-cycle may be due to the increase in plasma oestrogen levels at this time-point. This finding is supported by a variety of neurobiological evidence indicating a beneficial effect of oestrogen and mood (Luine *et al.*, 1975; Thomson *et al.*, 1977; Guicheney, 1988; Sherwin, 1990; Kugler, 1980). This effect is proposed to arise by the oestrogen-induced enhancement of serotonin transmission. Oestrogen has been shown to cause a decrease in the activity of monoamine oxidase (MAO), the enzyme that catabolizes serotonin (Luine & McEwen, 1977). This suggests that oestrogen may have a slightly positive effect on mood.

The mid-cycle increase in mood found in this study parallels findings from other clinical and observational studies documenting a significant facilitatory effect of HRT on mood (Werner, 1934; Ripley, 1940; Furujelm & Fedor-Freybergh, 1975; Schneider, 1977; Klaiber, 1979; Ditkoff, 1991; Schmidt, 2000). For example, Sherwin (1985) conducted a double-blind, crossover study on sex hormones and mood in surgically menopausal women. Women who received oestrogen, androgen or the combined preparation had significantly lower depression scores than the placebo group. These findings were confirmed by Sherwin (1988), reporting that surgically menopausal women treated with oestrogen or an

oestrogen/androgen combination had more positive moods than the placebo group. Progesterone however has been shown to have a stimulatory effect on MAO, thus increasing the breakdown of serotonin, noradrenaline and dopamine and reducing their duration of action (Holzbauer, 1973). Therefore, in this study, oestrogen may be a likely candidate as the instigator of this increase in mood at mid-cycle.

Although these mood findings are most likely to be attributable to hormonal changes as a function of menstrual cycle phase, the influence of cultural expectancy on mood as measured by self-report cannot be discounted. These explanations make recourse to the belief that the start-cycle is associated with negative mood and impaired performance and, as such, predisposes subjects to produce results consistent with those beliefs (Olasov & Jackson, 1987). However a proliferation of data supports a biological plausible explanation for the facilitatory effects of oestrogen on mood.

The possibility was considered that the start-cycle increase in P300/LPC amplitude may have occurred secondary to the observed changes in mood across the menstrual cycle. Several studies have described a relationship between cognitive function and mood (for a review see Blaney, 1986). However no such correlation was observed. This suggests that menstrual cycle effects on ERP amplitude and mood were independent of each other.

One of the strengths of this study is that the menstrual cycle phase was retrospectively validated using hormone measurements. Serum oestradiol concentrations were almost three times higher at mid-cycle than during menstruation, confirming that initial cycle assessment, based on menstrual histories provided by subjects, was valid for differentiating time points with significantly different oestradiol concentrations.

In conclusion, the electrophysiological data suggest that while ERP correlates of memory are stable across the menstrual cycle, correlates of

stimulus processing are responsive to hormonal fluctuations throughout the menstrual cycle. The psychometric data results indicate that mood may be sensitive to the menstrual cycle phase. The task-specificity of these results suggests that hormones may be highly selective in their influence on cognitive processes.

5.2 CANTAB measures across the menstrual cycle

5.2.1 Overall findings

This study has demonstrated that attention, as measured by the Intra-Dimensional/Extra-Dimensional (ID/ED) Set Shift Task, and visual memory, as measured by the Paired Associate Learning (PAL) task and the Delayed Matching to Sample (DMTS) task, were insensitive to hormonal variations across the menstrual cycle. Although the results of the oestrogen and progesterone plasma assays demonstrated the predicted rise in these sex hormones at the mid-cycle phase and fall at start-cycle, these hormone changes were not coincident with changes in attentional or visual memory function.

5.2.2 Attentional measures across the menstrual cycle

The ID/ED set shift task is a well-validated test of attention which involves the use of working memory to form a cognitive set and apply a conceptual strategy, but also necessitating maintenance and then shifting of the set when appropriate (Sahakian, 1990). Neither the numbers of errors made nor the response latency changed across the menstrual cycle. Similarly, an early study by Gamberale *et al.* (1975) found that performance on the Stroop task, another test of attention, was unaffected by the menstrual cycle A study on the effect of oestrogen treatment on this test also reported negative findings (Duka *et al.*, 2000). These studies concur with the present finding that performance on this task was unaffected by the cyclicity of hormonal secretion during the menstrual cycle.

However this current finding contradicts several HRT studies on other attentional measures (e.g. the Stroop Colour Word Interference test; Digit Vigilance). Several clinical (Fedor-Freybergh, 1977; Schmidt *et al.*, 1996; Asthana *et al.*, 1999) and observational (Portin *et al.*, 1999; Smith

et al., 2001; Keenan, 2001) studies have reported that attention is sensitive to HRT status. As discussed in Section 5.1.3, results of HRT studies cannot be generalized to menstrual cycle studies due to the dramatically different levels of endogenous sex hormones.

The present result partly agrees with findings reported by Berman *et al.* (1997). They employed Positron Emission Tomography (PET) to measure regional cerebral blood flow (rCBF) in 11 young women during ovarian suppression induced by a gonadotrophin agonist (Lupron), Lupron plus oestradiol and Lupron plus progesterone treatment. They observed a marked reduction of the typical Wisconsin Card Sorting Test activation pattern, with no rCBF increase in the prefrontal cortex. This was reversed by addition of oestrogen or progesterone to the Lupron regimen with normalization of the rCBF pattern and a return of prefrontal activation. Notably however no differences in the behavioural results were observed.

The current finding is also at variance with a previous study investigating menstrual cycle effects on attention. Hall & Leathard (1999) observed that the performance of 35 women on a continuous attention test was highest in the luteal phase (when oestrogen levels are elevated) and decreased at menstruation (when oestrogen levels are at their nadir). The most likely reason for this discrepancy may be the employment of attentional tasks that are dependent on stimulus processing in different brain regions. It is well established that the ID/ED task provides a measurement of inhibition in the prefrontal lobes (Owen *et al.*, 1990, 1991). The continuous attention test described in the Hall & Leathard study is a more global measure of attention, which is not dependent on inhibitory, prefrontal-related functions.

Thus it appears that inhibitory cognitive function as measured by the ID/ED set shift task does not vary as a function of menstrual cycle phase. Furthermore, this finding does not support studies detailed in Chapter 2 highlighting the role of oestrogen in performance on prefrontal cortex-

dependent tasks (Keenan *et al.*, 2001).

5.2.3 Visual memory measures across the menstrual cycle

To date, this is the first study to investigate the relationship between the menstrual cycle and visual memory using the Paired Associate Learning (PAL) and the Delayed Matching to Sample (DMTS) tasks. The PAL test is a form of delayed response procedure, which tests the ability to form visuo-spatial associations. The DMTS is a test of complex visual pattern and spatial recognition memory. No study has investigated the effect of HRT on these tasks. In this study, measures of visual memory did not alter as a function of menstrual cycle stage.

The effects of oestrogen on visual memory, as assessed by many other types of task (Figure Copy/Memory, Benton Visual Memory test, Visual Reproduction test) have proven difficult to demonstrate (for review, see Sherwin, 1998). Although many clinical (Duka *et al.* 2000; Linzmayer, 2001; Asthana, 2001) and observational (Resnick *et al.*, 1997; Smith, 2001; Farrag, 2002; Kampen & Sherwin, 1996) studies have shown a significant beneficial effect of oestrogen on a measurement of visual learning and memory, several others have reported negative results (Vanhulle & Demol, 1976; Phillips & Sherwin, 1992; Carlson, 1998; Polo-Kantola, 1998). Indeed two studies have demonstrated negative correlations between HRT use and visual memory performance (Barrett-Connor *et al.*, 1999; Drake, 2000). Similarly, Duff *et al.* (2000) reported no effect of HRT on a test of visual memory for simple geometric designs (Recurring Figures). These inconsistencies in the empirical findings may be partly a result of methodological shortcomings (see Chapter 4), although the specific aspects of visual memory function being assessed may also contribute to variability in outcomes.

The present finding disagrees with Phillips & Sherwin's (1992) study, which reported that women performed better on tests of long-term visual memory in the luteal phase relative to the menstrual phase and was

correlated with progesterone levels. This finding is questionable however as only one-half of the subjects showed a decline in visual memory scores to values below those of the overall sample during the menstrual phase.

Any influence of the increase in circulating oestrogen levels at mid-cycle phase may have been opposed by that of the concurrent rise in progesterone levels, a sex steroid which appears to have anti-oestrogenic properties (Klaiber *et al.*, 1971; Beattie *et al.*, 1972). For example, while oestrogen has a stimulatory effect on catecholamine synthesis in the rat hypothalamus, progesterone has an inhibitory effect (Beattie *et al.*, 1972). Furthermore, whilst oestrogen treatment has been found to significantly reduce monoamine oxidase activity (an enzyme which degrades catecholamine) in amenorrheic and post-menopausal women, the administration of a progestin along with oestrogen was associated with a marked increase in MAO activity (Klaiber *et al.*, 1971). Thus it may be possible that the mid-cycle phase rise in progesterone may have dampened any association between oestrogen levels and task performance that might have otherwise emerged across the menstrual cycle. Indeed this argument may also be applied when considering the failure to find an effect of the menstrual cycle on the attentional ID/ED set shift task. Furthermore, the relatively small sample size in the current study may have made it more difficult to obtain significant findings.

The possible presence of ceiling effects in these tasks should also be taken into account when considering these negative findings. However all participants made a substantial number of errors and reported difficulty in performing the tasks. Therefore the lack of effect on the attention and visual memory tests is unlikely to be due to ceiling effects.

In conclusion, although the tests comprising the CANTAB battery have demonstrated sensitivity to a range of cognitive dysfunctions and pharmacological treatments (Owen, 1991), the present findings suggest that they are not responsive to hormonal fluctuations across the menstrual cycle.

Chapter 6

Emotion and cognition: introduction

6.1. Introduction to emotion and cognition

Emotion is one of the most potent driving forces of human behaviour and is crucial to the survival of all higher organisms. It provides guidance in selecting relevant stimuli from the environment and is indispensable for adaptive functioning (Borod, 2000). However, our understanding of emotion has lagged considerably behind knowledge of other cognitive domains, both theoretically and empirically. The primary reason for this is that emotion is more abstract and more difficult to quantify than any other aspect of behaviour. Although much research has been conducted on the neural mechanisms underlying emotional processing in recent years, many questions remain concerning the effect of emotion on recognition memory at a neuropsychological and electrophysiological level and the role of subject characteristics such as age and gender.

The overall aim of this research was to examine the effect of emotional material on cognitive processing. This research encompassed a number of studies to satisfy this aim, including constructing a standardized set of emotional words for an Irish population and examining the impacts of age and gender on emotionally influenced memory.

In order to establish a word corpus of known emotional relevance to the population being studied, it was necessary to document the emotional content of the words being used. Therefore a set of emotional words standardized in terms of valence and arousal for an Irish population was created. Word valence represents a spectrum along which all words can be

located ranging from positive, pleasant words at one end to negative, unpleasant words at the other, with neutral words lying in between. Word arousal denotes a spectrum of emotional intensity, ranging from feelings of calmness to excitedness in response to a word. The words identified as being emotionally relevant were employed in the production of word lists which, in turn were deployed to examine the effect of gender and age on emotional processing and emotional memory. A further aim of this word rating study was to look at the effect of gender on the emotional responses to each word. It was anticipated that this study would complement other gender studies undertaken in the course of this project as detailed below.

Having created the standardized emotional word corpus, word lists were constructed composed of three word categories, namely positive, negative and neutral words. A word categorization study was conducted in order to ensure that the sets of positive, negative and neutral words had equivalent levels of semantic similarity. These word lists were used to assess the impact of emotion on memory i.e. to investigate if memory processes differ in response to positive, negative or neutral words. Previous studies have drawn attention to the emotional memory effect which describes the superior retentive capacity for emotional, relative to neutral, stimuli. This was investigated using behavioural measures such as percentage correct and free recall. In tandem with the emotional memory effect documented in behavioural studies, there is also evidence that brain activity, as measured by electrophysiological methods, is sensitive to the emotional content of stimuli. This research extended these findings by looking at the ERP repetition effect in response to words of different emotional categories.

As well as investigating the effect of emotion on memory, variations within emotional memory were also examined. The

first of these concerned the effect of gender on emotional response at a behavioural (percentage correct and free recall) and electrophysiological (ERP repetition effect) level. As such this project examined the impact of gender on emotional memory. Furthermore, electrophysiological analysis was extended to examine gender differences in emotional processing. The second aspect examined was the impact of age on the emotional memory effect in behavioural terms (percentage correct and free recall). Therefore age effects on recognition memory and free recall for positive, negative and neutral words was focused upon.

6.2 Word Rating Study

The aim of this study was to obtain a set of normative ratings for emotional words in an Irish population. Such ratings were then used to select words to be employed in direct and indirect memory tasks to analyse the effect of emotional words on memory. The Affective Norms for English Words (ANEW) was developed to provide a set of normative emotional ratings for a large number of words in the English language (Bradley & Lang, 1999). This is a set of verbal materials that have been rated in terms of pleasure and arousal. The existence of this affective collection is useful in comparing results across different investigations of emotion, as well as in allowing replication within and across research laboratories assessing basic or applied problems in the study of emotion.

A dimensional view was employed regarding the emotional judgements used to standardize materials. This approach assumes that emotion can be defined as a coincidence of values on a number of different strategic dimensions. This view is founded on Osgood's work (Osgood, Suci & Tanenbaum, 1957). Factor analyses conducted on a wide variety of verbal judgements indicated that the variance in emotional assessments

was accounted for by three major dimensions: the two primary dimensions concern emotional valence (ranging from pleasant to unpleasant) and arousal (ranging from calm to excited). Such dimensional views of emotion map easily onto the behavioural dimensions of direction (approach or avoidance) and vigour (mobilization) advocated by a biphasic organization of emotional responses (Hebb, 1949; Konorski, 1967; Lang *et al.*, 1990). This model allows the graphical illustration of the similarities/differences between emotions in terms of space. Dimensional views of emotion have been advocated by a large number of theorists, including Mehrabian & Russell (1974) and Tellegen (1985).

These approaches have been criticised as being overly parsimonious in that, rather than assuming independent, specific emotional states (e.g. fear, anger, and joy), two primary dimensions define the spectrum of emotional behaviour. Nonetheless, this is a useful and widely employed framework by which emotional response can be investigated. Valence and arousal ratings for each word have been obtained in previous rating studies, allowing precise placement of these stimuli in a two-dimensional affective space. This study employed this organisation of emotion to determine the emotional response of a group of Irish students to words of differing emotional content. As well as creating a standardized set of emotional verbal stimuli for an Irish population, the effect of gender on ratings of emotional valence or intensity (arousal) was investigated. This served to complement the other behavioural and electrophysiological study on the effect of gender on emotional memory.

6.3 Neuroanatomy and neurophysiology of emotional memory

The neural organisation of emotion spans multiple brain regions, from brainstem adaptive reflexes, to visceral and somatic integration of the hypothalamus, to control of memory in cortico-limbic networks. Recent imaging studies have examined metabolic and blood flow measures of the human brain while viewing emotional stimuli. Viewing affectively arousing material has been reported to be associated with activation in the bilateral amygdaloid complex (Schneider *et al.*, 1997), medial prefrontal coretx, thalamus, hypothalamus and midbrain (Lane *et al.*, 1997), anterior cingulate cortex (Lane *et al.*, 1997, 1998), anterior temporal cortex, amygdala and hippocampal formation (Reiman *et al.*, 1997), orbitofrontal cortex (Royet *et al.*, 2000), left prefrontal cortex and fusiform gyrus (Dolan *et al.*, 1996). In short, previous research strongly supports the involvement of widespread neuroanatomical networks in emotional processing.

More specifically, the amygdala has been the focus of extensive research in emotional studies. Much evidence suggests that the amygdala plays a role in selectively processing emotionally, particularly emotionally threatening, information (Adolphs, 1999; Adolphs *et al.*, 1999). Furthermore, an imaging study of healthy subjects reported right amygdala activation in response to viewing, rehearsing and recalling negatively valenced words (Kiehl *et al.*, 1998). Other studies also implicate the amygdala in emotional responsiveness to various aversive stimuli (Zald *et al.*, 1997; Breiter *et al.*, 1996; Irwin *et al.*, 1996; Ketter *et al.*, 1996).

The proposed role of the amygdala in emotional memory has been rooted in several lines of research, namely lesion and neuroimaging data. Several studies have shown that emotionally-influenced memory is deficient in patients with

bilateral amygdala lesions, whilst memory for neutral material is normal (Cahill *et al.*, 1995; Adolphs *et al.*, 1997). Two recent Positron Emission Tomography (PET) studies lend further credence to the hypothesis that the amygdala is selectively involved in memory for emotionally arousing stimuli (Cahill *et al.*, 1996; Hamann *et al.*, 1999). Subjects underwent PET scanning while viewing a series of emotionally negative or neutral films. There was a high correlation between free recall scores for emotional films and amygdaloid activity. Consistent with findings from patients with amygdala lesions, this study suggests that the amygdala mediates the influence of emotional arousal on memory.

McGaugh (2000) has proposed a memory modulatory framework of amygdala function. This theory suggests that when the amygdala is activated in response to emotionally arousing stimuli, it modulates memory storage and consolidation via anatomical connections to the hippocampus (LeDoux, 1995) and via interactions with stress hormones.

Evidence from many sources supports the view that the amygdala modulates memory processes in the hippocampus. The amygdala projects to the hippocampal and entorhinal cortex (Amaral, 1992). Amygdaloid influences also modulate long-term potentiation in the hippocampus (Ikegaya, 1996). Furthermore, lesions in this region block the memory-enhancing effect of direct hippocampal stimulation (Roozendaal & McGaugh, 1997). Such findings provide strong evidence for McGaugh's theory that the amygdala mediates emotional memory in association with the hippocampus.

Extensive research in animals implicates stress hormones as modulators of memory consolidation for emotional events. Gold *et al.* (1975) found that post-training injections of adrenaline

enhanced memory in inhibitory-avoidance training. This was subsequently replicated in several other studies (McGaugh, 1992; McGaugh, 1996). Such effects have been proposed to be mediated by β-adrenoceptors (Intrioni-Collison, 1992). Emotional arousal also activates cortisol hormone release. A series of studies conducted by Roozendaal & McGaugh (1996, 1997) showed that memory was improved by post-training administration of low doses of corticosterone-receptor agonists. These studies highlight the importance of stress hormones in emotional memory as outlined in McGaugh's framework. Furthermore the amygdaloid and stress hormonal effects on emotional memory interact as evidenced by findings that amygdala lesions block memory-enhancing effects of adrenaline and glucocorticoids (McGaugh, 1996).

These findings suggest key interacting roles of the amygdala and stress hormones in the mediation of memory for emotional stimuli. Such biological research provides an insight into the neural underpinnings of emotional memory, a key focus of this set of studies.

6.4 The effect of emotion on memory – behavioural studies

A significant body of scientific literature supports the popular view that memory tends to be superior for emotionally arousing, rather than neutral, information (Danion, 1995; Phelps, 1997; Rubin, 1986; Christianson, 1992). Memory for emotional events has been described as more vivid, more focused and more distinct than memory for neutral events (Ochsner, 2000). Several behavioural studies have reported that performance on episodic memory tasks is influenced by the items' emotional content. A widespread finding is that recall of emotionally valenced (positive or negative) words is enhanced relative to the recall of

neutral words (Rubin, 1986; Danion, 1995; Phelps, 1997; Palomba *et al.*, 1997).

Running parallel to findings of superior memory for positive or negative stimuli are a number of studies that have focused on the arousal dimension (see Eyseneck, 1976 for reviews). In these studies, arousal has been variously operationalized as the rated arousal of the stimulus materials, the level of arousal as measured by electrodermal responses, or by the presence of a constant stimulus background (white noise). The general finding is that verbal items associated with high arousal at encoding result in better memory performance on a later memory test. Maltzman (1966) observed greater recall for high-arousal words relative to low-arousal words on an immediate memory test and a delayed test administered 30 minutes later. Bradley *et al.* (1992) investigated the free-recall of emotional slides, varying along the dimensions of valence (positive or negative) and arousal (calming or exciting). In the immediate free recall test, very arousing pictures (both pleasant and unpleasant) were remembered better than low-arousal stimuli. It was concluded that when emotion is defined by the dimensions of pleasantness and arousal, the main predictor of future memory performance is not valence but arousal. In short, the subjective intensity of the emotion evoked is more important than whether it is a positive or negative emotion.

6.5 Event-Related Potentials to emotional stimuli

Event-related potentials (ERPs) have also been employed to investigate the effect of emotion on cognitive processing. Lifshitz (1966) and Begleiter *et al.* (1967) were the first to report the influence of emotional stimuli on event-related responses. Subsequently, several studies employing pictorial (Schupp *et al.*, 2000; Kayser *et al.*, 1997; Palomba *et al.*, 1997; Johnston *et al.*, 1986, Mini, 1996; Cuthbert, 1998; Cuthbert, 2000; Ito, 1998)

and verbal (Naumann, 1992; Naumann, 1997; Stormark, 1995) stimuli have converged showing greater P300/LPC amplitudes in response to emotionally arousing relative to neutral stimuli. In support of behavioural findings, the effect of positive valenced stimuli is qualitatively similar to that of negative stimuli, such that both have been interpreted in terms of their enhanced motivational salience and arousal value (Schupp *et al.*, 2000; Kayser *et al.*, 1997; Leiphart *et al.*, 1993; Johnston *et al.*, 1986).

6.5.1 ERPs and implicit memory processing of emotional stimuli

Some studies have investigated the effect of emotion on implicit cognitive processing. When emotional affect was incidental in the task, i.e. in same-different judgements, no effect of emotional arousal on P300 amplitude was found (Carretie, 1997; Naumann 1997; Leiphart, 1993). Other studies however employing subliminal stimulation (Bernat *et al.*, 2000) or visual masking techniques (Zimmer & Schmitt, 1987) reported that emotional valence influenced ERPs from 100-400 ms post-stimulus. Thus it was proposed that only conscious processing of emotion influences P300/LPC amplitude, while unconscious processing has an earlier and more frontal influence (Bernat *et al.*, 2000). Therefore the influence of words' emotional connotation on implicit memory processes has yet to be established.

6.5.2 ERP Repetition Effect and emotion

Recent studies have shown that the ERP repetition effect for emotionally negative or positive words is significantly different from that of neutral words (Maratos *et al.*, 2000; Dietrich *et al.*, 2001; Johannes *et al.*, 1999; Windmann & Kutas, 2001).

Maratos *et al.* observed that the repetition effect for negative words was smaller in magnitude than that elicited by neutral words. However such effects of emotion on recognition memory were not attributed to the emotionality of the words *per se*. Instead it was suggested that emotionally valenced words influenced recognition memory by virtue of their strong inter-item associations (semantic cohesion), which creates a tendency for "false recollection" of new items. Dietrich (2001) and Johannes (1999) reported that the repetition effect was significantly enhanced for positive and negative items compared to neutral stimuli. As semantic cohesion was not controlled for in these studies, such results may be attributable to this confound.

In a similar paradigm, Windmann & Kutas (2001) observed that when semantic similarity was controlled for, emotional valence had a significant effect on the ERP difference to the old items and false alarms (new words considered old) – neutral items showed a large effect prefrontally, while negative items did not. A recent study published by Windmann *et al.* (2002) reported an effect of emotional content on words correctly classified as new or old, whereby neutral words elicited a reliable ERP repetition effect, whereas negative items evoked no effect. They attributed these findings to a recognition bias for negative words, possibly reflecting an adaptive cognitive function to ensure that potentially threatening events (i.e. negative stimuli) are not easily missed.

Discrepancies in the findings between these studies may also be due to the fact that the subjects did not rate the words employed in the tasks for their emotional valence or arousal themselves. Windmann and Maratos only had 50% of the words rated by a subset of participants in the study-test procedure. A group independent from the study participants rated the words in the

Dietrich and Johannes studies. As individual variation in responses to emotional words may be large, it is important that subjective ratings are measured in the participants performing the tasks. In this study, subjects were required to rate each word after ERP testing to ensure that each subject agreed with the emotional categories chosen for each word.

The aim was to investigate recognition memory for emotional words using the ERP repetition effect. As semantic interrelatedness was controlled for, any effects elicited by emotional words in this paradigm would be due to the emotionality of the word and not attributable to semantic factors. It remains unknown whether the effect of emotional valence on recognition memory is associated with explicit, recollective processes or with automatic, unconscious processes. Therefore both the direct and indirect task paradigms, believed to reflect explicit and implicit memory respectively (Rugg *et al.*, 1994), were employed in this study.

6.6 The effect of gender on memory

Behavioural studies have shown a tendency for women to outperform men on episodic memory tasks. In 1988, Bleecker *et al.* observed that men had lower scores on verbal learning and memory than women. Similarly, McGivern (1997) found superior performance in women relative to men on recognition memory tasks. Women performed better than men on the Wechsler Memory Scale and California Verbal Learning Test in another study conducted by Ragland *et al.* (2000). Sex differences in regional cerebral blood flow correlations with performance were also noted. In electrophysiological studies, evoked potential latencies are shorter and amplitudes are larger in females than in males (Allison *et al.*, 1983, Buchsbaum *et al.*, 1974; Kaneda *et al.*, 1996; Stockard *et al.*, 1979; Beagley *et al.*,

1978; McClelland *et al.*, 1979; Jerger *et al.*, 1980; Fagan *et al.*, 1986). Whether sex-related differences exist in terms of ERP recognition memory paradigms remains unclear and was analysed as part of this research.

6.6.1 The effect of gender on emotion

Sex-related differences in emotional processing have been well documented, with females more strongly influenced by emotional stimuli than males. Several studies have reported that women are better decoders of emotional stimuli (Brody, 1985; Duda & Brown, 1985; Hall, 1978; Shields, 1991; LaFrance & Banaji, 1992; Otta *et al.*, 1996; Grunwald *et al,* 1999). Furthermore, in a recent study on sex differences in judgement of facial affect, Thayer *et al.* (2000) showed that females had a higher rate of correct classification, with males having greater difficulty distinguishing one emotion from another. Furthermore, the two-factor structure of emotion (i.e. the valence and arousal dimensions) was only present for female participants.

Much evidence suggests that women experience emotion more intensely than men (Choti *et al.*, 1987; Gross & Levenson, 1993; Grunwald, 1999). Similarly, elderly women reported experiencing more intense emotions when reliving emotional memories than elderly men (Levenson, 1991). However, many other studies have not found sex differences in emotional intensity (Cupchik & Poulos, 1984; Kring & Gordon 1998; Lanzetta *et al.*, 1976; Wagner, 1993; Zuckerman *et al.*, 1984).

Recent neuroimaging studies have confirmed the behavioural findings of significant sex differences in emotional processing. George *et al.* (1996a) looked at sex differences in brain regions activated during different emotional states. 10 men and 10 women underwent PET scanning at rest and during happy, sad

or neutral states that were self-induced (recalling personal events) or by viewing happy/sad/neutral faces. Although men self-induced transient emotional states to the same degree as women, women had more extensive regional cerebral blood flow changes than men in anterior limbic regions. Another imaging study reported increased activity of the right amygdala related to emotional memory in men, and greater left amygdala activation in women (Cahill, 2001). It is possible therefore that such gender-related differences in emotional processing may be related to this gender-related lateralization of amygdala involvement in emotionally influenced memory. Gur *et al.* (2002) extended these findings in a study on sex differences in emotion in temporal and frontal brain volumes. Although men and women had identical volumes of amygdala, hippocampus and dorsal prefrontal cortex, women had larger orbital frontal cortices, a region specialised for emotional processing. This provides neuroanatomical evidence supporting behavioural findings of sex differences in emotional processing.

As is evident from the preceding review, the interactions between gender and emotional processing have been extensively researched. However, to date no study has investigated the effect of gender on behavioural or electrophysiological measures of emotional memory. Considering the apparent superiority of women in episodic memory tasks, their greater sensitivity to emotional stimuli and larger brain regions dedicated to emotional processing, one would predict that women would exhibit greater emotional memory than men. By extension, sex differences in emotional memory at an electrophysiological level would also be expected. Thus the aim was to analyse the effect of gender on emotional memory using behavioural measures such as percentage correct and free recall and ERPs as part of the ERP repetition effect paradigm.

6.7 The effect of age on memory

The large body of literature on developmental changes in memory ability is consistent in their general findings of age-related decrements in performance. For example, older people typically perform less well on tasks of free recall, cued recall, and recognition memory for lists of words or sentences (Davis *et al.*, 2001). Performance on such tasks requiring explicit recollection of material (cued recall and recognition tests) generally show a dramatic change as a function of the participant's age, whereas indirect memory task performance declines very little with age (Rugg *et al.*, 1994).

6.7.1 The effect of age on emotion

As shown above, much research documents the effect of age on various aspects of cognition. However, evidence regarding age effects on emotion is relatively sparse. Some aspects of emotional processing, for example emotional expression and perception, have revealed age-related effects. Studies examining posed facial expressions have found older participants to be less accurate than young subjects (Malatesta & Izard, 1984). Grunwald (1999) looked at the perception of lexical/verbal emotion across the adult life span and observed that older subjects perceived emotional and non-emotional stimuli with less accuracy than did younger participants. They also evaluated non-emotional stimuli as more intense. Overall, such studies suggest that emotional processing diminishes with age.

However, other studies have not found any significant age-related changes in emotional processing. Schulz (1982) concluded that an individual's ability to respond emotionally to stimuli is maintained across the lifespan. Similarly, Malatesta & Kalnok (1984) found no evidence of change in the effect of

emotional intensity with age. Furthermore, Tsai (2000) observed that old and young participants did not differ in their subjective and expressive responses to sad and amusing films. Such studies report stability in emotional response, which suggests that the advantage in memory for emotional material would not diminish with age.

Such disparate results may be attributed to methodological differences (emotional stories, faces, sentences, pictorial stories, and photographs) and the use of non-standardized affective materials. The analysis of a variety of aspects of emotion, i.e. experience, expression etc., in these studies further obscures the effect of age on emotional memory and general inferences are therefore difficult to ascertain.

A recent neuroimaging study, however, provides some support for the findings of age-related differences in emotional processing. Iidaka (2002) reported diminished activity in the left amygdala during perception of negative faces and reduced activity in the right parahippocampal gyrus in response to positive faces in older relative to younger participants. Thus ageing differentially affected the neural responses to faces with positive or negative emotional valence. Therefore this lends credence to the behavioural studies reporting age effects on emotional processing.

As well as these reports on emotional processing across the lifespan, three studies have been conducted on emotional memory in the elderly. Wallach *et al.* (1980) found that old participants retrieved fewer emotional words than the young, although they were equally proficient at recognition of neutral words leading them to conclude that the elderly were less responsive to emotional words. Similarly, Riege (1980) reported lower recognition of emotional words in the elderly but

equivalent performance for neutral words. Oscar-Berman (1990) who conducted a study on emotionality and alcoholism, observed that the elderly performed significantly worse on recognition of emotional faces and sentences than young subjects, regardless of whether or not they had a history of alcoholism. It has been suggested that deficient recognition memory in old people may reduce their ability to make use of a word's emotional content to enhance recognition performance.

However there is some opposition to this view. A study carried out on young, middle-aged and older women (Yoder *et al.*, 1987), reported that affective content (pictorial stories) had similar effects on recall at all ages. Cartensen (2000) found that the proportion of emotional versus neutral phrases recalled was similar in young and old subjects, concluding that the salience of emotion increases with age.

Although Iidaka's study mentioned earlier provides a biological plausibility for age-related differences in emotional processing, behavioural studies have yielded mixed results for emotional processing and emotional memory. This study addressed this by investigating the impact of age on memory for emotional words using percentage correct as part of a recognition memory paradigm and free recall.

Chapter 7

Emotion and cognition: methodology

7.1 Word rating study

7.1.1 Participants

60 young (aged 19 – 30) male and female medical students.

7.1.2 Procedure

A group of 60 subjects received forms containing 300 words to be rated. Each form contained 100 positive, negative and neutral stimuli selected from the Affective Norms for English Words (ANEW) (Bradley and Lang, 1999). Each sheet presented individual words in one column and the words were sequentially numbered in rows from 1 to n. For each set of words, two forms were prepared which counterbalanced the order in which any specific word was rated, and the item surrounding any specific word. Subjects received the sheets and instructions were given. Ratings were collected in a self-paced procedure, in which the subject silently read each word, and entered in their emotional rating on the sheet. Words were rated on a Likert Scale of 1 to 9 according to valence i.e. how positive or negative they thought each word was (1= very negative 5=neutral, 9=very positive) and arousal i.e. how exciting or unexciting each word was (1=unarousing, 9= very arousing). The session was completed for all subjects within 25 minutes.

7.1.3 Instructions to participants

"The study being conducted is investigating people's emotional response to different types of words. There are a total of 9 possible points along each of the two rating scales by which you can indicate the extent of your emotional response. The first scale (2nd column) is the valence scale. At one extreme of this scale (numbers 7 to 9), you feel

happy, pleased, satisfied, contented, hopeful. The other end of the scale (numbers 1 to 3) is when you feel completely unhappy, annoyed, unsatisfied, melancholic, despaired. You can describe intermediate feelings of pleasure by entering in any other number. If you feel completely neutral, neither happy or sad, enter number 5. The second scale is the arousal scale, which is a measure of how excited or calm you feel in response to a word. At one extreme of the scale (>6) you are stimulated, excited, frenzied, jittery, wide-awake or aroused. At the other end (<4) you feel relaxed, calm, sluggish, dull, sleepy, or unaroused. Again you can represent intermediate levels of excitedness or calmness by entering any numbers in between. Please work at a rapid pace and don't spend too much time thinking about each word. Rather, make your rating based on your first and immediate reaction as you read each word."

7.1.4 Statistics

The effect of gender on emotional response to words in terms of valence was statistically analyzed using an analysis of variance (ANOVA) with the factors representing word type (positive, negative or neutral) and gender status (male or female). The arousal dimension was similarly investigated using an analysis of variance with the factors representing word type (arousing or non-arousing) and gender status (male or female).

7.1.5 Word Categorization study

A word categorization study was conducted in order to ensure that the sets of positive, negative and neutral words had equivalent levels of semantic similarity. Lists of words were categorized according to their semantic theme. A form was created which presented these words belonging to two different themes at random. 10 young people categorized these words according to their semantic theme (i.e. whichever theme best described each word).

Table 7.1. *Correctly classified positive, negative and neutral words (percentage ± S.D.) employed in the direct and indirect memory tasks.*

	Direct	**Indirect**
Positive	100 (2.5)	97.5 (1.5)
Negative	97.5 (3)	95 (2.5)
Neutral	100 (1.5)	95 (3.5)

7.2 Emotion and cognition

7.2.1 Participants

The subject population consisted of four groups, namely young males and females, and elderly males and females. A total of ten young males, nine young females, seven elderly males and eleven elderly females participated in the study. The participants were recruited by advertisements in the hospital or university campus and from local active retirement groups. Informed written consent was obtained prior to the experiment and the local ethics committee approved the study. All subjects reported normal or corrected-to-normal vision. Characteristics of the participants are summarized in Table 7.2.

Table 7.2. *Characteristics of participants*

	Young		**Elderly**	
Age	Males	Females	Males	Females
Mean	23.5	24.6	66.1	66.8
Range	20-25	20-26	60-75	61-76
Education				
Mean	14	15	9	9
Range	13-18	14-18	8-10	8-14

7.2.2 Inclusion/Exclusion criteria

For the young group, participants were aged between 20-30 years and free of neurological diseases (stroke, migraine etc.) and had no psychiatric history (e.g. depression). The young female group had regular menstrual cycles (27-32 days). Those taking the oral contraceptive pill were excluded, as were those with Late Luteal Phase Dysphoric Disorder (as assessed by self-report of key symptoms according to DSM-IV). The elderly participants were aged 60-80 years, free of neurological diseases and had no psychiatric history.

7.2.3 Procedure

Subjects who met the inclusion criteria attended the Mercer's Institute for Research on Ageing for testing on a single occasion. To negate menstrual cycle effects in the young females, they were tested during the menstrual phase only (day 2-5). Task order was counterbalanced, whereby half the subjects performed the direct test first and the other half performed the indirect test initially. Each testing session lasted approximately 1 hour. The direct and the indirect tasks lasted approximately 20 minutes each, with a five-minute rest break in between. The young group carried out the direct and indirect memory tasks as part of electrophysiological testing, followed by the free recall task. The elderly group performed the behavioural tests only i.e. direct and indirect memory tasks without concurrent electrophysiological testing, as well as the free recall task.

7.2.4 Direct and Indirect Memory Task Stimuli and Structure

200 words were chosen on the basis of their normative affective ratings from the Affective Norms for English Words (ANEW) (Bradley and Lang, 1999). These stimuli were then adapted for an Irish population in the electrophysiological study. The words varied in length between three and nine letters (mean=5). The household objects had a mean frequency

of occurrence of 20 per million, and all other words had a mean frequency of 10 per million, according to the Francis and Kucera word corpus (1967). All words were semantically distinct from each other in that derivatives of words from a common root were not used. In the indirect task, 20 of the words in a list were household objects (targets), whereas in the direct test these words were replaced by 20 non-target filler words (neutral). Out of a total of 140 words per list, 20 words belonging to 3 different categories were included i.e. pleasant, unpleasant and neutral. All word categories were matched for arousal ratings (mean of 9.1 for pleasant and unpleasant words and a mean of 3.4 for the neutral words). For the two tests, these words were repeated after a mean of 6 (range 1-12) intervening words. Two sequences were constructed, each of a different pseudorandom order. Two lists were produced, one for each sequence. Therefore for each task there were two independent sequences of words. A neutral buffer word was added to the beginning and end of each list. Words were displayed on a computer monitor (white characters on a black background) in central vision. Stimulus duration was 300 milliseconds and the interstimulus interval 3.0 seconds. Stimuli were visually presented using STIM™ version 3.0.

7.2.5 Direct and Indirect Memory Task Procedure

Following application of the recording electrodes, subjects were seated in front of the display monitor and given a response pad to hold. They were informed that a series of words would be presented one at a time. For the indirect task they were instructed to respond by clicking on button 2 on the response pad whenever they saw the name of a household object (n=20), otherwise to click on button 1 for all other words (n=100). For the direct task, they were instructed to press button 1 when a word appeared for the first time (n=100) and button 2 when a repeated word (n=20) was presented. Both response speed and accuracy were emphasized. They were further instructed to maintain fixation on the centre of the screen and to blink only between trials i.e. when no words were presented on the screen. After delivery of instructions,

participants were given 10 practice trials with items different to those used in the experimental list proper. Responses faster than 200ms or slower than 2.5 s were treated as errors. Hand used for each response was alternated across participants.

7.2.6 ERP recording

Scalp EEG was recorded from 32 positions of the International 10-20 system (Jasper, 1958) via electrodes in an elastic cap (ElectroCap™). To detect eyeblink artifacts, electro-oculogram (EOG) was recorded bipolarly from electrodes placed on the outer canthus of the left eye and above the supraorbital ridge of the right eye. Electrode impedance was measured at the beginning and end of the recording and never exceeded 5 kΩ. All channels were referenced to linked mastoids. All eyeblink and movement artifacts were manually removed from the continuous files using Neuroscan's Scan™ software (Scan version 4.1). In addition, sweeps were rejected if the potential amplitude in the EOG or EEG exceeded 60μV. A 250ms prestimulus interval was used to baseline correct the recorded ERPs. The EEG signal was filtered (zero phase digital filtering) with a bandpass of 0.05-30 Hz and a digital-sampling rate of 256 Hz. Trials where the subject made an incorrect response were excluded from further analysis. The EEG 250ms before to 1250ms after each word was then averaged to produce an evoked potential. It was averaged for correct "new" words and for correct "old" words. A minimum of 16 trials per stimulus category per subject was included in the statistical analysis. The mean amplitude in the 250-1000ms latency windows in the event-related potential produced by both new and repeated words was analyzed. The accuracy of the response (percentage correct) and reaction times (milliseconds) were also recorded.

7.2.7 Free Recall

A free recall task was conducted immediately after the testing session detailed above. This allows an assessment of the effects of emotional

words on short-term memory performance. The subject was instructed to write down, in any order, as many words as they could remember from the list of words previously presented. The free recall period was 5 minutes. Correct recall was scored if the word recalled belonged to the task given earlier.

7.2.8 Statistical analysis

For the word rating study, two separate multiway ANOVAs were used to evaluate ratings given in response to emotional words in terms of both valence (positive, negative or neutral) and arousal (arousing or non-arousing). Factors of word valence (positive/negative/neutral) and gender (male/female) were entered into the valence ANOVA. Factors of word arousal status (arousing/non-arousing) and gender (male/female) were entered into the arousal ANOVA.

Behavioural parameters (percentage correct, reaction time and free recall) were statistically analysed in an analysis of variance with factors representing Valence (positive, negative or neutral word), Gender (male or female), Age (young or old) and Status (new or repeated word).

ERP parameters were statistically analysed in an analysis of variance (ANOVA) with factors representing Gender (male or female), Valence (positive, negative or neutral word), the type of Task (direct or indirect), Word ("old" or "new") and Electrode (Fz, Cz, Pz, etc.). The Greenhouse-Geisser (Winer, 1991) three-step approach to significance testing was employed when relevant (more than one degree of freedom). Post hoc t-tests were calculated to follow up significant main effects of Gender, Valence, Word, Task and Electrode site as well as respective interactions. To limit familywise Type 1 errors when degrees of freedom were 3 or greater, Hochberg's stepwise Bonferroni procedure was adopted for the post hoc contrasts (Keselman, 1998).

Chapter 8

Emotion and Cognition: Results

8.1 Emotional word rating study

Two multiway analysis of variances (ANOVAs) were conducted to analyze ratings given in response to emotional words in terms of both valence (positive, negative or neutral) and arousal (arousing or non-arousing). Analysis of the valence ANOVA revealed a significant effect of word valence on the emotionality ratings [$F(2, 13365) = 5007.8$, $p < 0.0001$]. As shown in Table 8.1.1, positive words were rated higher than neutral and negative, and neutral words were given higher ratings than negative words. An overall effect of gender was not significant, with no sex differences observed in the ratings given for emotionally valenced words [$F(1, 13365) = 1.89$, $p = 0.1$]. The gender x word valence interaction however was significant [$F(2, 13365) = 142.2$, $p < 0.0001$], showing that males rated negative words more negatively (gave them a lower score) than females, whereas females rated positive words as being more positive (gave them a higher score) than males.

In the arousal ANOVA analysis, a significant effect of word arousal was found, with participants rating arousing words more highly than non-arousing words [$F(1, 13573) = 4427$, $p < 0.0001$]. As illustrated in Table 8.1.2, a significant effect of gender was observed, whereby females rated all words (arousing and non-arousing) as more arousing (gave them a higher score) than males [$F(1, 13573) = 85.7$, $p < 0.0001$]. As revealed by the gender x word arousal interaction [$F(1, 13573) = 21.9$, $p < 0.0001$], females rated arousing words as more arousing than males, and also rated non-arousing words as more arousing than males.

Table 8.1.1 *Word ratings (mean ± SD) in terms of valence for positive, negative and neutral words in male and female participants*

Valence	Males	Females
Positive	5.1 ± 1.3	5.5 ± 1.5
Neutral	4.8 ± 1.3	4.8 ± 1.3
Negative	3.6 ± 1.3	4 ± 1.5

Table 8.1.2 *Word ratings (mean and SD) in terms of arousal for arousing and non-arousing words in male and female participants*

Arousal	Males	Females
Arousing	4.9 ± 1.3	5.3 ± 1.4
Non-Arousing	4.8 ± 1.3	5.2 ± 1.4

8.2 The effect of emotionally positive, negative and neutral words on behavioural measures of recognition memory

8.2.1 Behavioural performance (percentage correct) in young and old groups

The percentage correct data was evaluated using a multiway ANOVA with factors of word valence (positive, negative, neutral), gender (male/female), age (young/old) and word status (new/repeated). See Table 8.2.1 for illustration of these results. An effect of valence on percentage correct was not observed [$F(2, 447) = 0.5$, $p = 0.5$]. An overall effect of gender was observed, whereby females performed significantly better than males [$F(1, 447) = 5.9$, $p = 0.01$]. The age effect was also significant, revealing that the young group performed significantly better than the old group [$F(1, 447) = 47$, $p < 0.0001$]. Furthermore, the analysis revealed a significant interaction between gender and age. This showed that whilst no sex difference in performance was found in the young group, older females performed

better than older males [$F(1, 447) = 23$, $p < 0.0001$]. As expected, word status effect was observed, whereby more new than old words were correctly identified [$F(1, 447) = 5.4$, $p < 0.01$].

Table 8.2.1 *Percentage correct scores (mean ± SD) for positive, negative and neutral words for both sexes and age groups*

% Correct	Young males	Young females	Old males	Old females
Positive	96.4 ± 6.3	95.5 ± 7.5	84.4 ± 16.7	91.6 ± 12
Negative	96.4 ± 6.3	95.6 ± 7.4	84.8 ± 16.7	92.2 ± 11.7
Neutral	96.5 ± 6.3	95.9 ± 7.2	85 ± 16.8	92.5 ± 11.6

8.2.2 Reaction time data in young and old groups

Factors of word valence (positive, negative, neutral), gender (male/female), (young/old) and word status (new/repeated) were entered into an ANOVA to evaluate the reaction time results. As can be seen in Table 8.2.2, no significant difference in reaction time was found for new and old items belonging to either the positive, negative or neutral category, valence: [$F(2, 447) = 0.03$, $p = 0.9$]. No effect of gender was observed [$F(1, 447) = 0.02$, $p = 0.8$]. However a significant effect of age revealed that the old group performed significantly slower than the young group by 140 ms [$F(1, 447) = 70.6$, $p < 0.0001$].

Table 8.2.2. *Reaction times for positive, negative and neutral words for both sexes and age groups*

Reaction time	**Young males**	**Young females**	**Old males**	**Old females**
Positive	909 ± 208	902 ± 206	1036 ± 286	955 ± 143
Negative	908 ± 225	901 ± 206	1025 ± 290	996 ± 143
Neutral	904 ± 223	900 ± 206	1014 ± 293	996 ± 143

8.2.3 Free recall in young and old groups

Another ANOVA was employed to analyze free recall data with factors of word valence (positive, negative, neutral), gender (male/female) and age (young/old). Such results are shown in Table 8.2.3. A significant valence effect on free recall was observed [$F(2, 453) = 4.7$, $p < 0.001$]. This revealed that significantly more positive than neutral words were recalled. Females performed significantly better on this task than males, as indicated by the gender effect: [$F(1, 453) = 53$, $p < 0.0001$]. An age effect was found, whereby the young group recalled significantly more words than the old participants. A gender x age interaction revealed that the sex difference noted above (females better than males) was exacerbated in the elderly [$F(1, 453) = 20$, $p < 0.0001$], i.e. the superior performance effect in elderly women relative to elderly men was greater than the performance difference between young women and men. The valence effect reported earlier (more positive than neutral words recalled) was present in females only, as indicated by the gender x valence effect [$F(2, 453) = 5.7$, $p < 0.001$]. The age x valence interaction [$F(2, 453) = 10$, $p < 0.0001$] further reveals that this valence effect was present in the young group only. Thus no effect of valence was observed in the old group.

Table 8.2.3. *Free recall scores of positive, negative and neutral words for both sexes and age groups*

Free recall	Young males	Young females	Old males	Old females
Positive	6.1 ± 1.5	6.5 ± 1.4	1.7 ± 1.5	3.6 ± 2.2
Negative	6.1 ± 1.5	6.4 ± 1.4	1.7 ± 1.5	3.6 ± 2.2
Neutral	6 ± 1.5	6.3 ± 1.4	1.8 ± 1.5	3.5 ± 2.2

8.3 Electrophysiological data

8.3.1 Mean amplitude differences in the 250-1000ms latency window (repetition effect)

Evoked potentials produced in response to whether the word was seen previously ("old") or not ("new") in the memory test were analyzed. The effects of repetition were quantified by measurement of the 250-1000ms latency region. Such effects were also studied in relation to the three different word categories i.e. positive, negative and neutral across gender and the two different task types (direct and indirect). For topographical illustration see Figures 8.1 to 8.6. The mean amplitudes of the ERP repetition effect for positive, negative and neutral words in the direct task for males and females are shown in Tables 8.3.1 and 8.3.2 respectively. The data for the indirect task for males and females are given in Tables 8.7 to 8.12. For the sake of brevity the mean amplitudes obtained for 5 channels (Fz, Cz, Pz, C3 and C4) are shown in these tables.

The data was evaluated using a multiway ANOVA with factors of word type (new/old), valence (positive, negative or neutral), gender (male/female), task type (direct/indirect), and electrode site (Fz, Pz etc.). Mean amplitude analysis of the 250-1000 ms latency region revealed a very reliable word repetition effect [$F(1,6840) = 318.3$, $p < 0.0001$]. This was due to the fact that the mean amplitude of the ERP to repeated

words was more positive by 1.4 μV on average. An overall effect of valence was observed [F (2, 6840) = 8.93, p = 0.0001], whereby both neutral and positive words elicited greater positivity than negative words, though they were not different from each other. The valence x task interaction reveals that while these valence differences were present in both direct and indirect tasks, they were more pronounced in the direct than the indirect test [F(2, 6840) = 44, p < 0.0001]. A three-way interaction (valence x word x task) revealed that emotional valence had a significant effect on the ERP repetition effect in the direct task only [F(2, 6840) = 77.5, p < 0.001]. This means that in the direct task, the ERP repetition effect was greater for neutral and positive words than for negative words.

The effect of gender was also significant [F (1, 6840) = 158.25, p < 0.0001], such that females had a more positive going ERP amplitude than males by 0.98μV. The gender x valence interaction was significant [F(2, 6840) = 6.7, p > 0.001], reflecting the fact that females had more positive amplitude than males for each word valence type (greatest for negative words, followed by neutral and then positive words). A significant main effect of gender on the word category effect was found [F(1,6840) = 3.9, p > 0.05], reflecting that the repetition effect was larger in females than in males. The gender x task interaction reflected the fact that the enhanced amplitude in females relative to males was more pronounced in the direct than the indirect task [F(1,6840) = 22.7, p < 0001].

As expected, the repetition effect was greater in the direct than in the indirect test, as revealed by the task x word interaction [F(1,6840) = 7.36, p = 0.006]. The ANOVA performed across both tasks confirmed that overall mean amplitudes were maximal at Pz, electrode: [F(29, 6840) = 3.27, p < 0.0001]. An overall effect of task was not observed [F(1, 6840) = 0.29, p = 0.58].

8.3.2 P300 Analysis (250-500 ms)

P300 Amplitude

P300 amplitude was defined as the maximum positive peak between 250 and 500 ms post-stimulus. P300 latency was measured from the stimulus onset to the peak within this interval. Identification of P300 waves was determined independently by two observers who had to agree before measurement of latency and amplitude could take place. The latency intervals for the P300 and LPC components were chosen based on visual inspection of the ERP responses obtained in the present experiments. The mean amplitudes and latencies of the P300 and LPC in response to positive, negative and neutral words for the direct and indirect tasks in males and females displayed in Tables 8.3.5 to 8.3.8. Analysis of variance with repeated-measures factors representing word type (new/old), valence (positive, negative or neutral), gender (male/female), task type (direct/indirect) was carried out.

A reliable effect of word on P300 amplitude was observed, with old words eliciting a more positive going amplitude than new words [$F(1,6838) = 47.7$, $p < 0.0001$]. An overall effect of valence was observed [$F(2, 6838) = 7.2$, $p = 0.0008$], whereby both neutral and positive words elicited greater positivity than negative words, though they were not different from each other. A word x valence interaction was significant [$F(2, 6838) = 14.2$, $p < 0.0001$], whereby the word repetition effect was greater for neutral than positive words, with no word effect for negative words. Post-hoc analysis revealed that this effect was carried by the greater positivity of the old neutral words compared to old negative and old positive words.

The effect of gender was also significant [$F(1, 6838) = 120.4$, $p < 0.0001$], whereby females had a higher P300 amplitude than males by 1.2μV. The gender x valence interaction was significant [$F(1, 6838) = 5.24$, $p=0.005$]. This reflected the fact that females had more positive

amplitude than males for positive words, followed by neutral and then negative words. The gender x task interaction suggests that the enhanced amplitude in females relative to males is more pronounced in the direct than the indirect task [$F(1,6838) = 17.9$, $p < 0.0001$].

The repetition effect was greater in the direct than in the indirect test, as revealed by the task x word interaction [$F(1,16) = 13.2$, $p = 0.0003$]. An overall effect of task was observed [$F(1, 16) = 5.13$, $p = 0.02$] , whereby the direct task gave rise to larger P300 amplitudes than the indirect task.

P300 Latency

A significant valence effect was observed [$F(2, 6838) = 6.8$, $p = 0.003$], where positive words gave rise to longer latencies than neutral words and negative words, and negative words elicited longer latencies than neutral words. Valence also interacted significantly with task [$F(2, 6838) = 31.7$, $p < 0.0001$]. This reflects the fact that the valence effect (positive words gave rise to longer latencies than neutral words and negative words, and negative words elicited longer latencies than neutral words) was more pronounced in the direct than the indirect task. A significant effect of gender on P300 latency was also found [$F(1, 6838) = 494.3$, $p < 0.0001$]. This means that males had a longer P300 latency than females by 26.6 ms. A gender x valence interaction was found [$F(2, 6838) = 20$, $p < 0.0001$]. This is attributable to the fact that in females, neutral words gave rise to longer latencies than positive, whereas in males, positive words elicited longer latencies than neutral words. A significant effect of word [$F(1, 6838) = 4.4$, $p = 0.03$] reveals that new words evoked longer P300 latencies than old words. A gender x word interaction [$F(1, 6838) = 75.4$, $p < 0.0001$] showed that in females, old words elicited longer latencies than new words while in males, new words elicited longer latencies than old words. A significant effect of task was also found, whereby the direct task gave rise to longer latencies than the indirect task (4ms) [$F(1, 6838) = 8.3$, $p = 0.004$]. A task x word interaction was observed [$F(1, 6838) = 10.4$, $p = 0.0012$], whereby old

words gave rise to longer latencies than new words in the indirect task. This was not the case however for the direct task.

8.3.3 LPC (P600) Analysis (500-700 ms)

LPC Amplitude

LPC amplitude was defined as the maximum positive peak between 500 and 700 ms post-stimulus. A reliable effect of word on LPC amplitude was observed, with old words eliciting a more positive going amplitude than new words [$F(1,6838) = 333.76$, $p < 0.0001$]. An overall effect of valence was not observed [$F(2, 6838) = 1.12$, $p = 0.3$]. However a valence x word interaction was significant [$F(2, 6838) = 9.17$, $p = 0.0001$], whereby the repetition effect was greater for neutral than positive or negative words. Similar to the P300 amplitude analysis, post-hoc analysis of this interaction revealed that this effect was carried by the greater positivity of the old neutral words compared to old negative and old positive words.

The effect of gender was also significant [$F(1, 6838) = 571.4$, $p < 0.0001$], whereby females had a higher LPC amplitude than males by 2.4 μV. An overall effect of task was observed [$F(1, 6838) = 5.13$, $p = 0.02$], whereby the direct task gave rise to larger LPC amplitudes than the indirect task. The gender x task interaction suggests that the enhanced amplitude in females relative to males is more pronounced in the direct than the indirect task [$F(1,6838) = 62.8$, $p < 0.0001$].

LPC Latency

A valence effect was observed [$F(2, 6838) = 10.4$, $p < 0.0001$], suggesting that positive words gave rise to longer latencies than neutral words. A significant effect of word was also noted [$1, 6838] = 3.3$, $p < 0.0001$], whereby new words elicited longer latencies than old words. A valence x word interaction was significant [$F(2, 6838) = 23.9$, $p <$

0.0001], reflecting the fact that the word effect (new words elicited longer latencies than old words) is more pronounced for positive than for negative or neutral words. A valence x gender interaction also was found [$F(2, 6838) = 20$, $p < 0.0001$]. This is attributable to the fact that in males, neutral words gave rise to longer latencies than positive words. Task also interacted significantly with valence [$F(2, 6838) = 22.8$, $p < 0.0001$]. This reflects the fact that the valence effect (positive words gave rise to longer latencies than neutral words and negative words, and negative words elicited longer latencies than neutral words) is more pronounced in the direct than the indirect task. No significant effect of gender on LPC latency was found [$F(1, 6838) = 1.7$, $p = 0.2$]. However, a gender x word interaction was observed [$1, 6838) = 22.4$, $p < 0.0001$], whereby in males, new words elicited longer latencies than old words. Gender also interacted significantly with task [$F(1, 6838 = 61.9$, $p < 0.0001$]. In males, P300 latency was longer in the direct than in the indirect task, while in females, P300 latency was prolonged in the indirect task. A task x word interaction was observed [$F(1, 6838) = 6.7$, $p = 0.009$], whereby old words gave rise to longer latencies than new words in the direct task. This was not the case however for the indirect task.

Table 8.3.1. *Mean Amplitude (μV) of the ERP Repetition Effect in the Direct Task for the 250-1000 ms latency region for positive, negative and neutral words in male subjects*

	Fz	**Cz**	**Pz**	**C3**	**C4**
Positive					
Mean (SD)	1.3 (3.2)	1.2 (3.2)	0.19 (3.2)	1.2 (3.2)	0.9 (3.2)
Negative					
Mean (SD)	0.3 (3.2)	0.5 (3.2)	0.3 (3.2)	0.1 (3.2)	0.1 (3.2)
Neutral					
Mean (SD)	4.23 (3.2)	2.9 (3.2)	2.6 (3.2)	2.4 (3.2)	2.8 (3.2)

Table 8.3.2. *Mean Amplitude (μV) of the ERP Repetition Effect in the Direct Task for the 250-1000 ms latency region for positive, negative and neutral words in female subjects*

	Fz	**Cz**	**Pz**	**C3**	**C4**
Positive					
Mean (SD)	2.4 (3.8)	4.1 (3.8)	4.6 (3.8)	4.5 (3.8)	4.3 (3.8)
Negative					
Mean (SD)	0.2 (2.5)	0.1(2.5)	0.2 (2.5)	0.1 (2.5)	0.1 (2.5)
Neutral					
Mean (SD)	2.6 (3.7)	2.2 (3.7)	2.1 (3.7)	1.5 (3.7)	1.1 (3.7)

Table 8.3.3. *Mean Amplitude (μV) of the ERP Repetition Effect in the Indirect Task for the 250-1000 ms latency region for positive, negative and neutral words in male subjects*

	Fz	**Cz**	**Pz**	**C3**	**C4**
Positive					
Mean (SD)	0.9 (3.1)	1 (3.1)	1.4 (3.1)	1.5 (3.1)	1.9 (3.1)
Negative					
Mean (SD)	1.5 (3.2)	2.2 (3.1)	1.8 (3.2)	1.8 (3.2)	2 (3.2)
Neutral					
Mean (SD)	1.2 (3.4)	1.5 (3.4)	0.7 (3.3)	0.7 (3.4)	0.5 (3.4)

Table 8.3.4. *Mean Amplitude (μV) of the ERP Repetition Effect in the Indirect Task for the 250-1000 ms latency region for positive, negative and neutral words in female subjects*

	Fz	**Cz**	**Pz**	**C3**	**C4**
Positive					
Mean (SD)	-1.4 (3.5)	-0.7 (3.5)	-0.7 (3.5)	-1 (3.5)	-1.1 (3.5)
Negative					
Mean (SD)	2.74 (2.7)	3.2 (2.7)	2.9 (2.7)	2.9 (2.7)	3.1 (2.7)
Neutral					
Mean (SD)	1.9 (2.8)	1.5 (2.9)	1.2 (2.7)	1.6 (2.8)	1.4 (2.8)

Table 8.3.5. *P300 Amplitude (μV), P300 Latency, LPC Amplitude and LPC Latency in the Direct Task for positive, negative and neutral words in male subjects*

Males - Direct	**Positive Mean (S.D.)**	**Negative Mean (S.D.)**	**Neutral Mean (S.D.)**
P300 Amplitude -New	4.2 (3.4)	5.3 (3.4)	4.5 (3.7)
Old	5.6 (3.9)	5.2 (3.8)	6.8
P300 Latency - New	362.8 (59.9)	350.0 (59)	347.8 (56.8)
Old	366.3 (59)	351.1 (57.9)	327.2
LPC Amplitude - New	3.9 (3.5)	4.5 (4)	3.6 (4.1)
Old	1.4 (4)	5.4 (4.1)	6.9
LPC Latency - New	603.0 (88.4)	639.9 (88.2)	647.3 (93.2)
Old	562.8 (87.6)	638.6 (90.2)	636.4

Table 8.3.6. *P300 Amplitude (μV), P300 Latency, LPC Amplitude and LPC Latency in the Direct Task for positive, negative and neutral words in female subjects*

Females - Direct	**Positive** Mean (S.D.)	**Negative** Mean (S.D.)	**Neutral** Mean (S.D.)
P300 Amplitude -New	5.1 (4.3)	6.6 (4.3)	5.6 (4.3)
Old	7.3 (4.3)	5.4 (4.3)	7.3 (4.3)
P300 Latency - New	291.6 (34.8)	280.2 (36.3)	270.7 (36.6)
Old	277.4 (35.6)	282.9 (36.9)	287.2 (37.4)
LPC Amplitude - New	5.5 (4.2)	7.2 (4.1)	6.6 (4.1)
Old	8.1 (4.2)	7.2 (4.1)	9.6 (3.9)
LPC Latency - New	564.6 (75.8)	548.6 (77)	548.7 (76.4)
Old	555.3 (76.5)	507.6 (76)	558 (77)

Table 8.3.7. *P300 Amplitude (μV), P300 Latency, LPC Amplitude and LPC Latency in the Indirect Task for positive, negative and neutral words in male subjects*

Male - Indirect	**Positive** Mean (S.D.)	**Negative** Mean (S.D.)	**Neutral** Mean (S.D.)
P300 Amplitude -New	6.1 (4.8)	4.9 (4.5)	5.4 (4.1)
Old	4.8 (4.7)	5.5 (4.3)	6.1 (3.9)
P300 Latency - New	344.0 (50.2)	350.8 (48.8)	351.4 (47.6)
Old	347.0 (49.1)	330.4 (48.2)	338 (46.8)
LPC Amplitude - New	4.1 (3.8)	3.9 (3.6)	3.9 (3.2)
Old	5.8 (3.7)	5.7 (3.4)	4.7 (3.2)
LPC Latency - New	632.6 (73.4)	615.5 (73.4)	592.7 (73.8)
Old	586.1 (73.3)	539.9 (73.9)	526.2 (73.9)

Table 8.3.8. *P300 Amplitude (μV), P300 Latency, LPC Amplitude and LPC Latency in the Indirect Task for positive, negative and neutral words in female subjects*

Female - Indirect	**Positive Mean (S.D.)**	**Negative Mean (S.D.)**	**Neutral Mean (S.D.)**
P300 Amplitude -New	6.1 (5.1)	4.6 (5.2)	5 (5.2)
Old	6.1 (5.2)	5.6 (5.2)	6.1 (5.2)
P300 Latency - New	283.7 (47.4)	286.7 (46.8)	284.2 (45.8)
Old	293.2 (47.1)	307 (46.5)	317.9 (44.7)
LPC Amplitude - New	6.4 (5)	3.9 (5)	4 (5)
Old	6.7 (5.1)	6.7 (5.2)	6.2 (5.3)
LPC Latency - New	554 (90.2)	557.3 (89.6)	545.9 (90.4)
Old	557 (89.9)	552.2 (89.6)	585 (90.2)

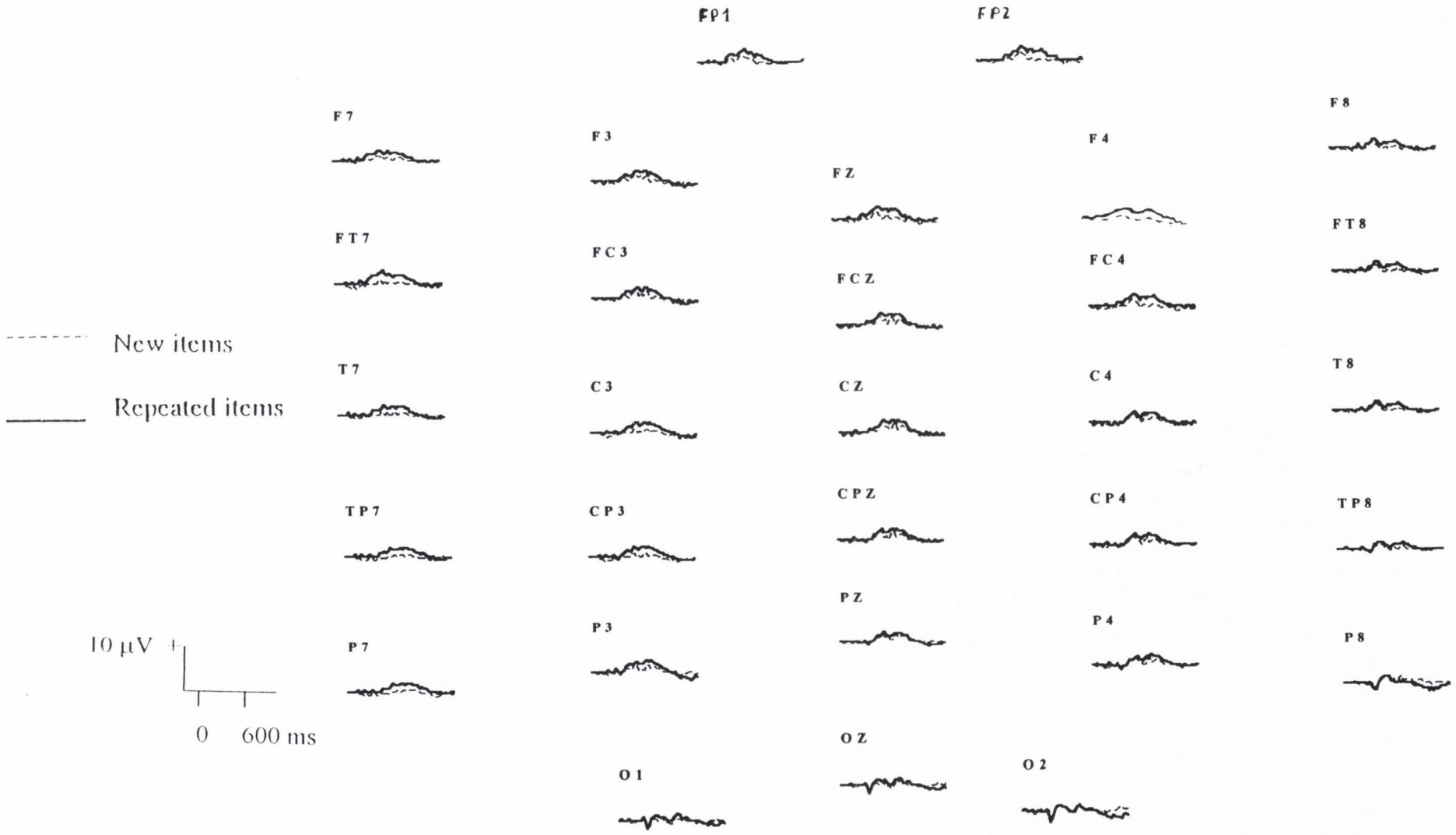

Figure 8.1. Grand average waveforms from the direct task for first presentations (new) and repeated (old) positive words in male subjects.

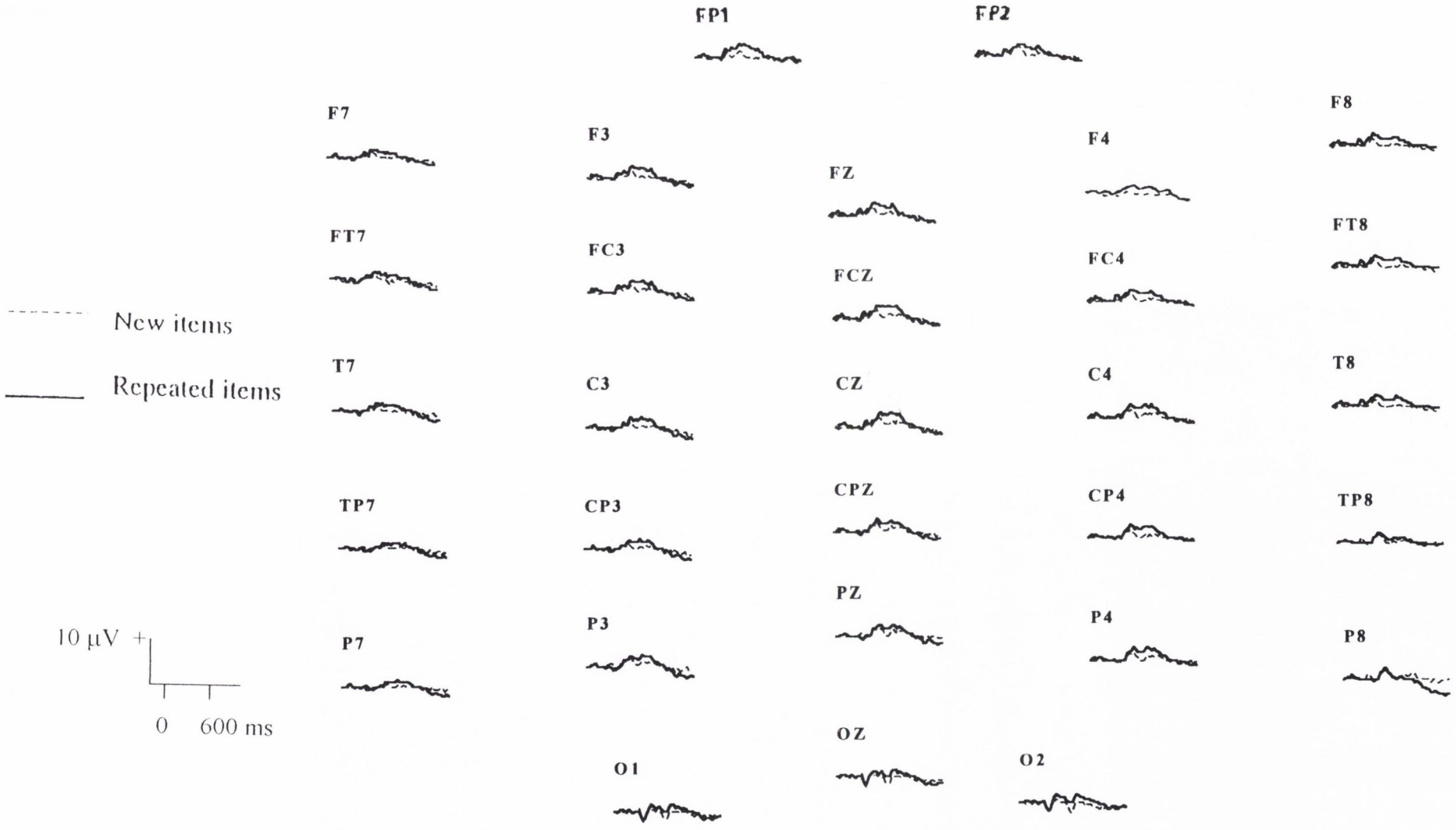

Figure 8.2. Grand average waveforms from the direct task for first presentations (new) and repeated (old) negative words in male subjects.

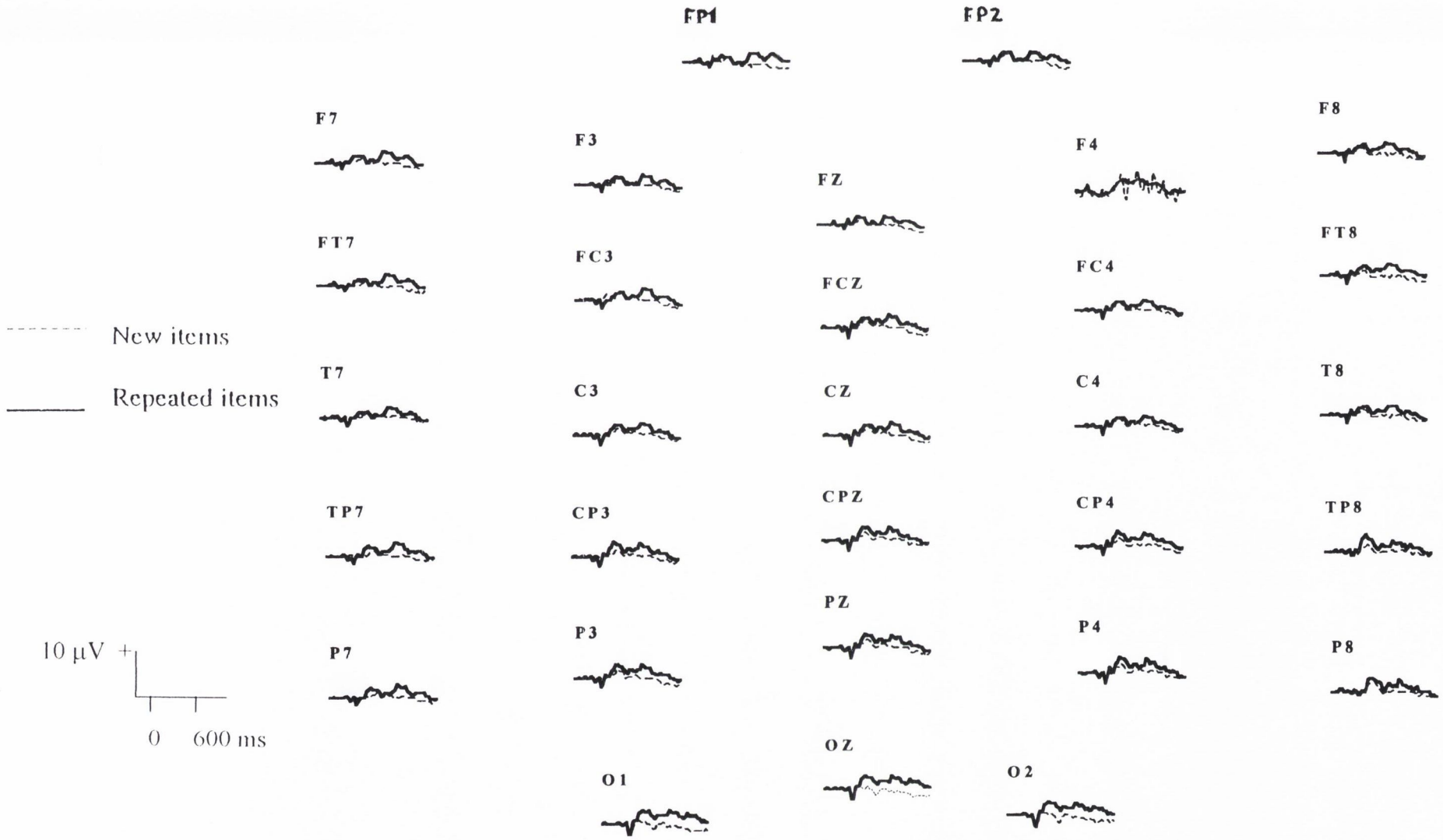

Figure 8.3. Grand average waveforms from the direct task for first presentations (new) and repeated (old) neutral words in male subjects.

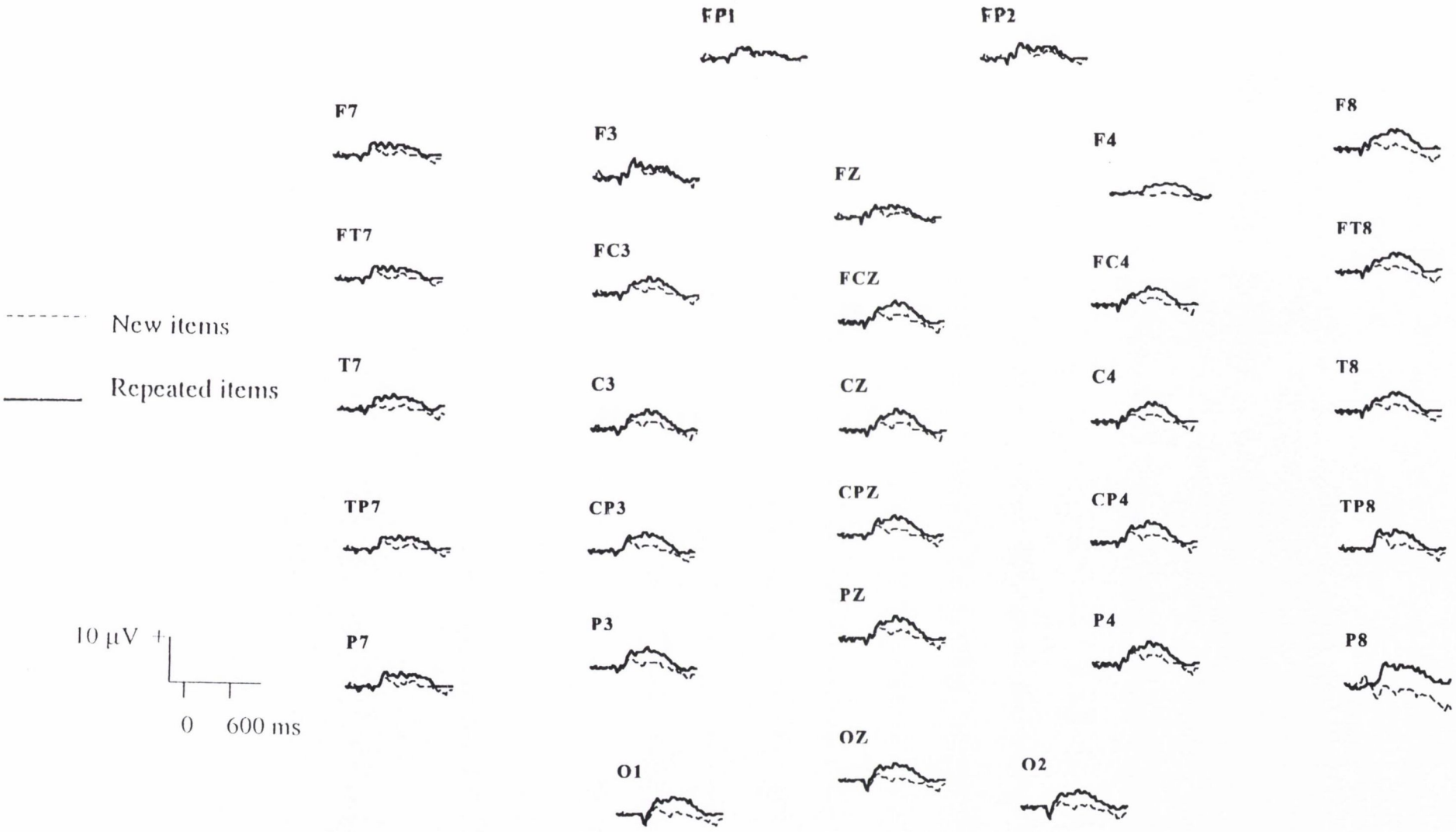

Figure 8.4. Grand average waveforms from the direct task for first presentations (new) and repeated (old) positive words in female subjects.

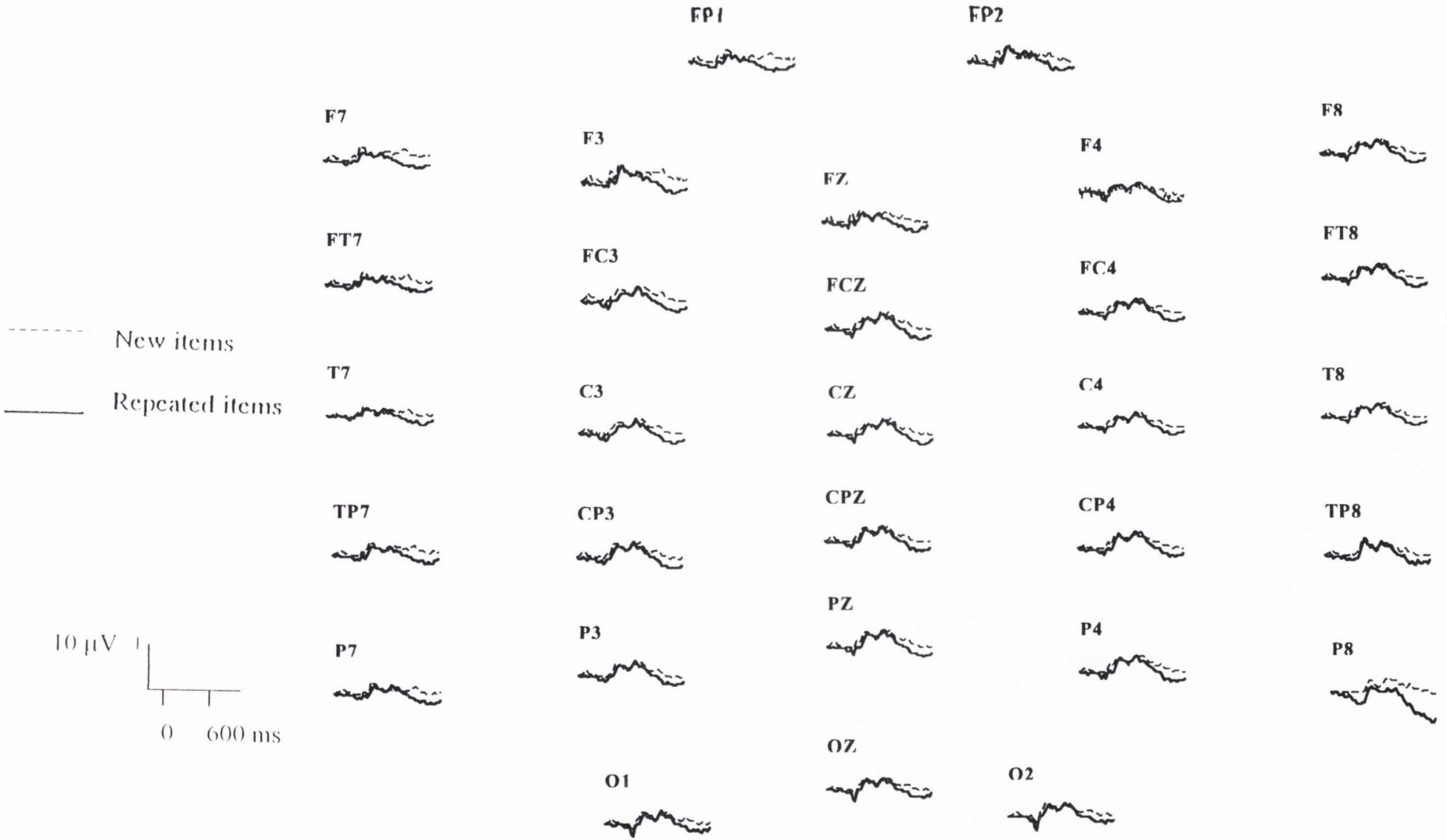

Figure 8.5. Grand average waveforms from the direct task for first presentations (new) and repeated (old) negative words in female subjects.

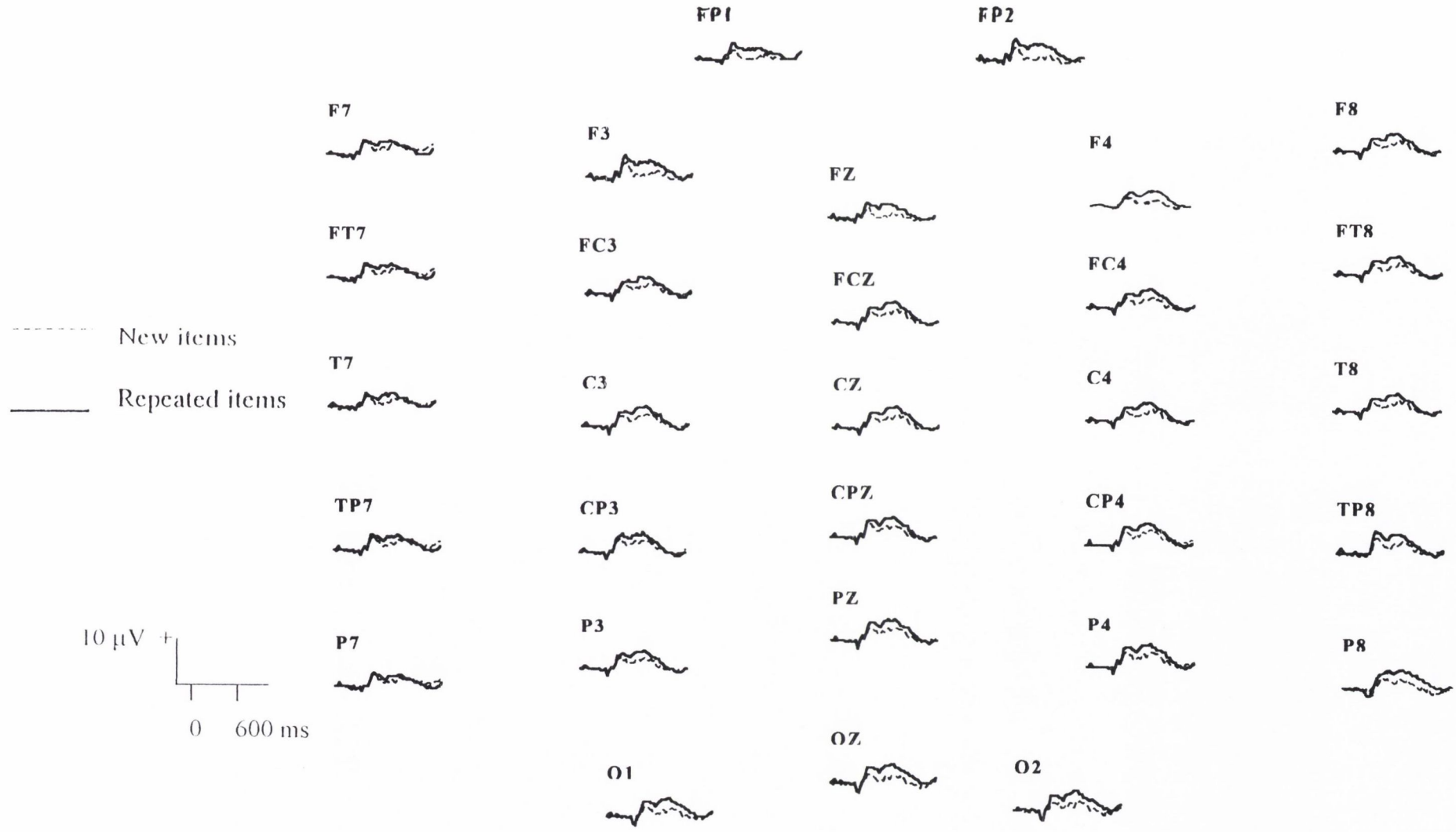

Figure 8.6. Grand average waveforms from the direct task for first presentations (new) and repeated (old) neutral words in female subjects.

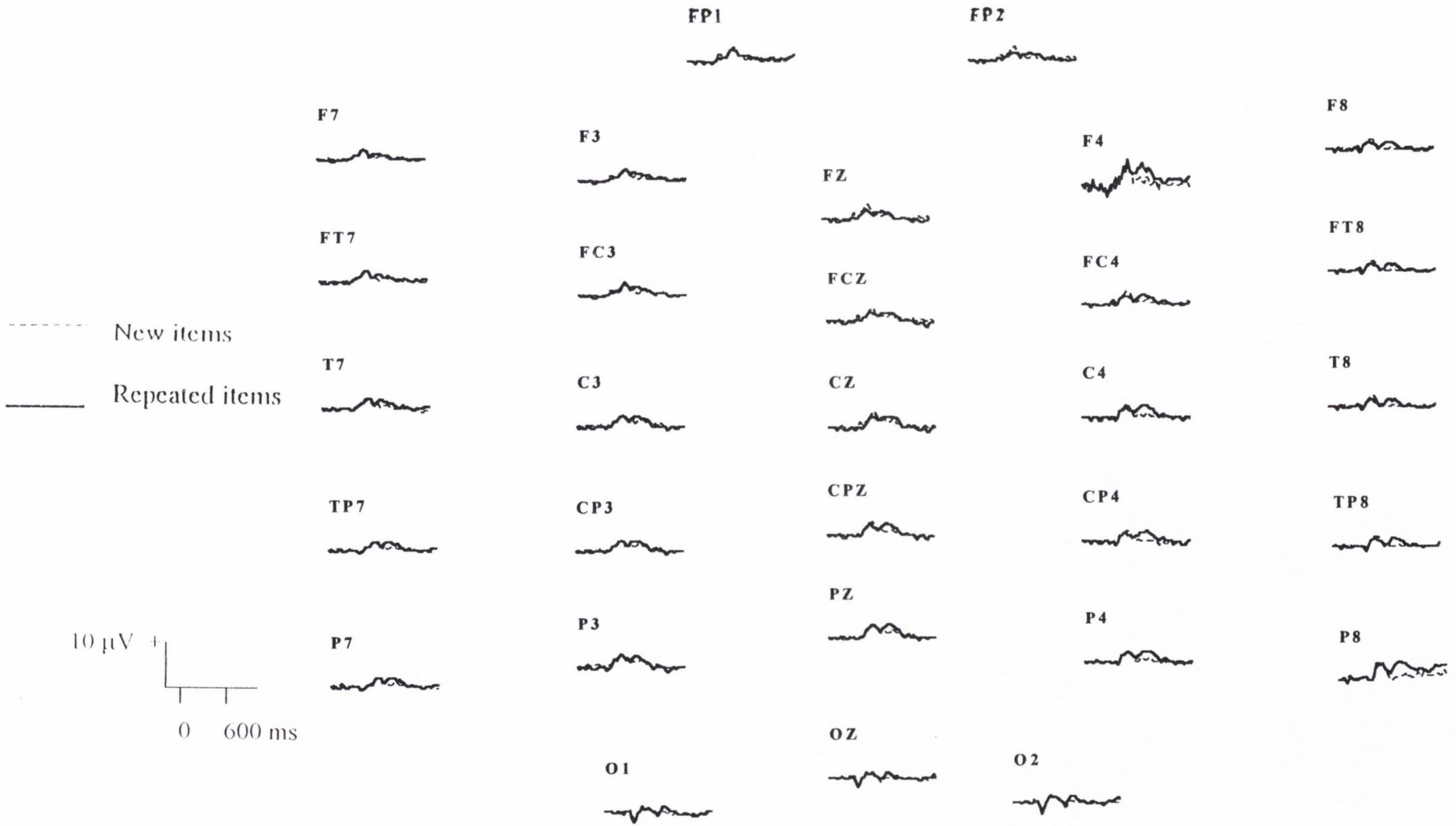

Figure 8.7. Grand average waveforms from the indirect task for first presentations (new) and repeated (old) positive words in male subjects.

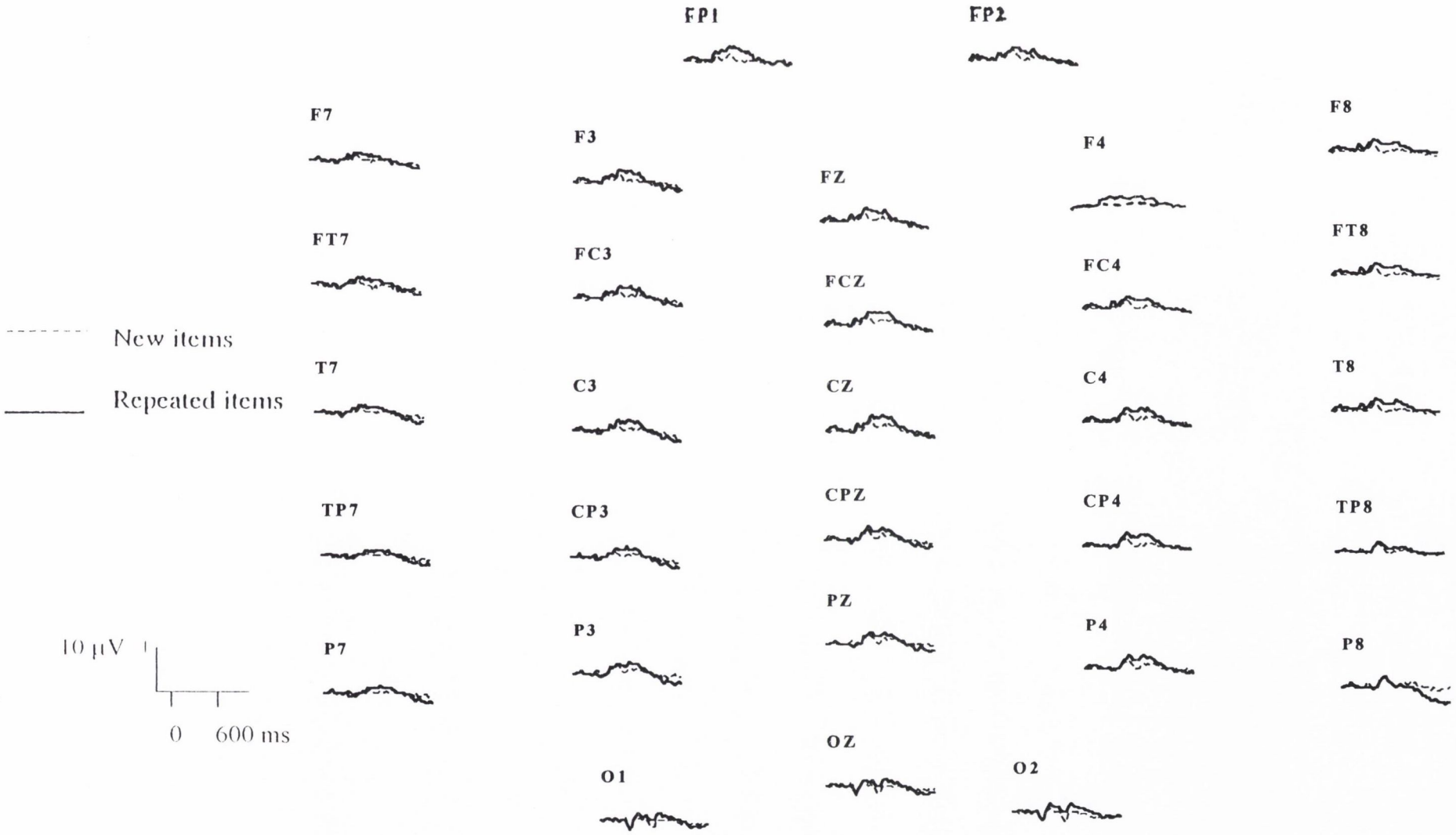

Figure 8.8. Grand average waveforms from the indirect task for first presentations (new) and repeated (old) negative words in male subjects.

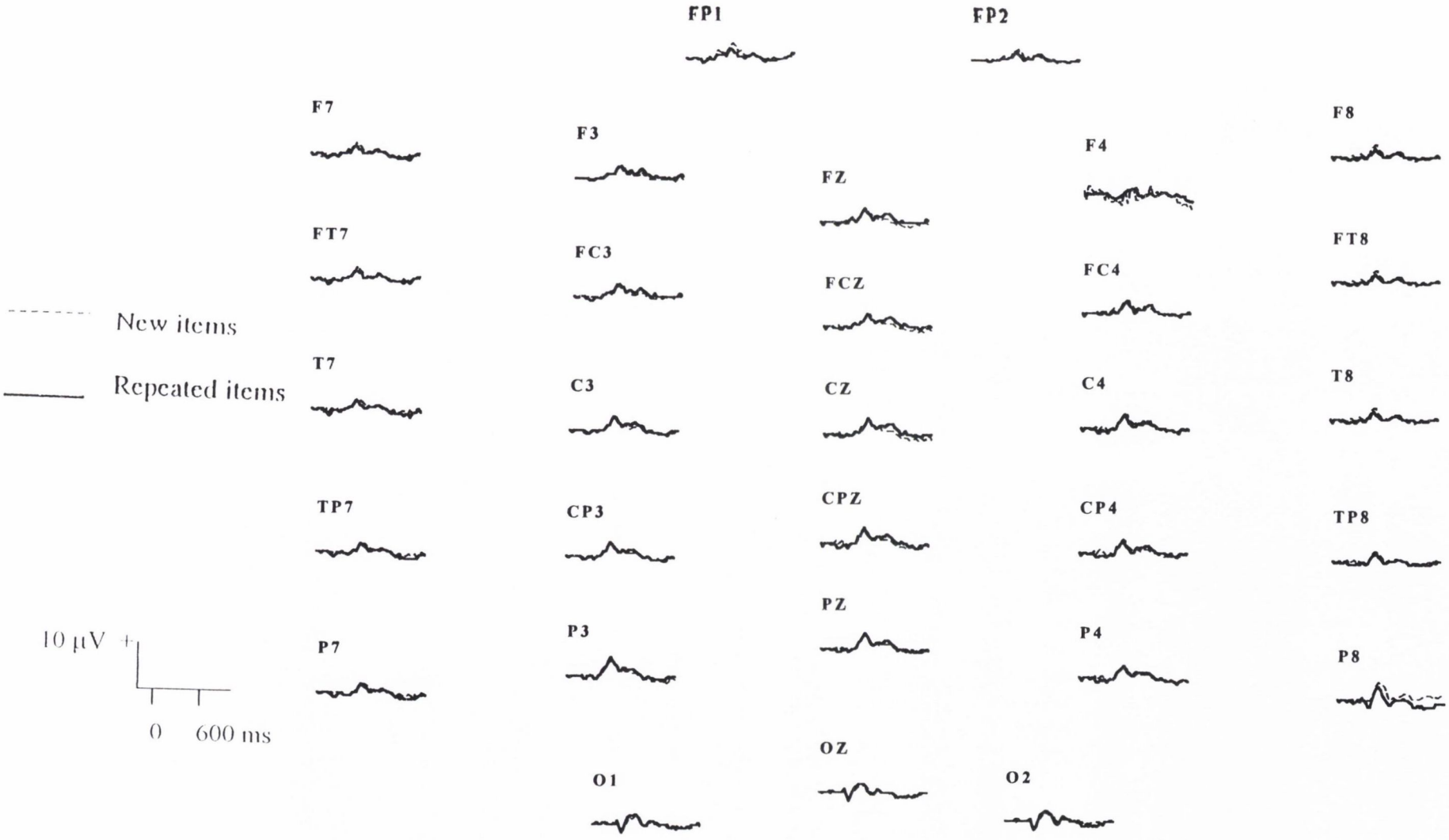

Figure 8.9. Grand average waveforms from the indirect task for first presentations (new) and repeated (old) neutral words in male subjects.

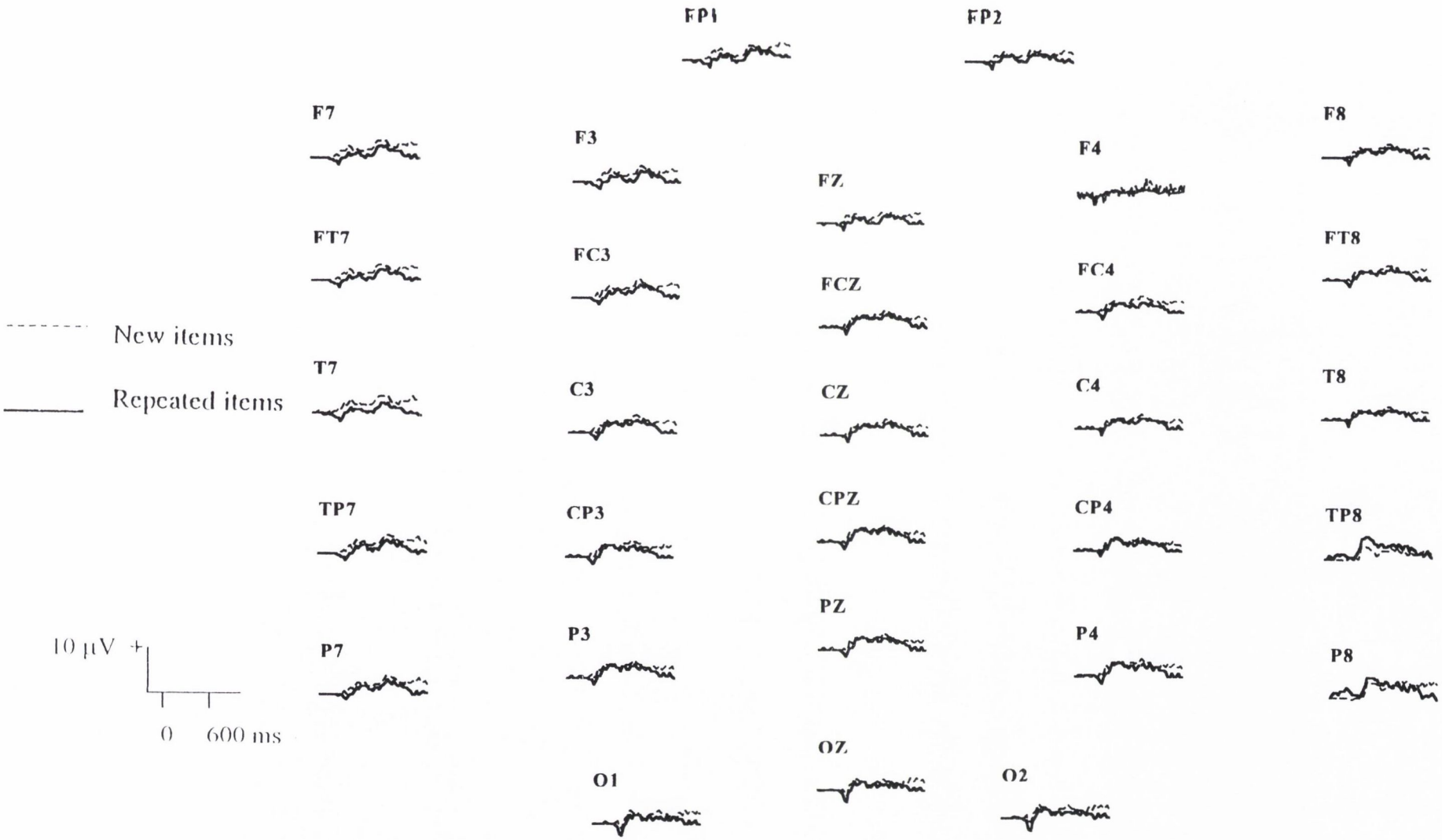

Figure 8.10. Grand average waveforms from the indirect task for first presentations (new) and repeated (old) positive words in female subjects.

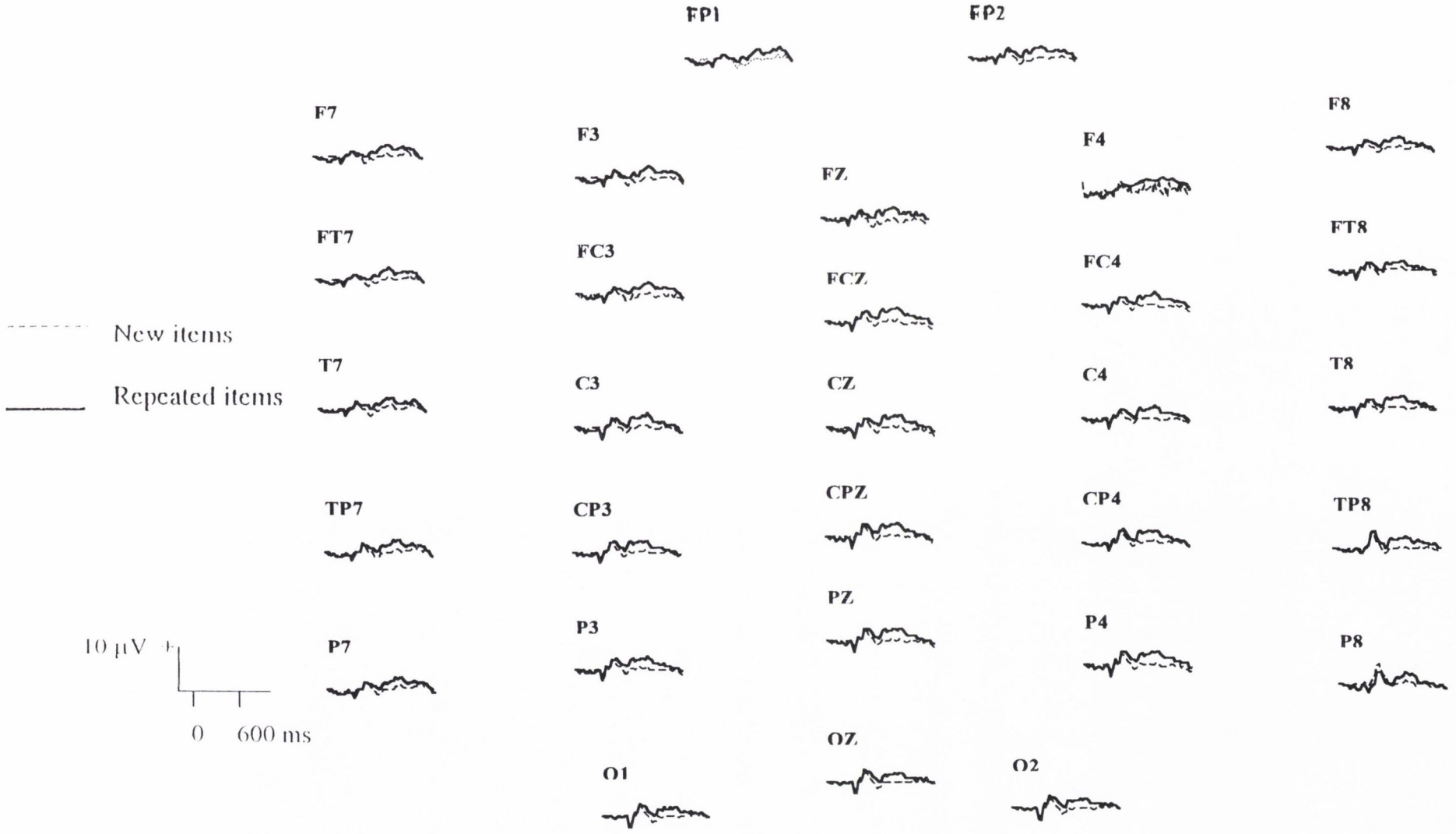

Figure 8.11. Grand average waveforms from the indirect task for first presentations (new) and repeated (old) negative words in female subjects.

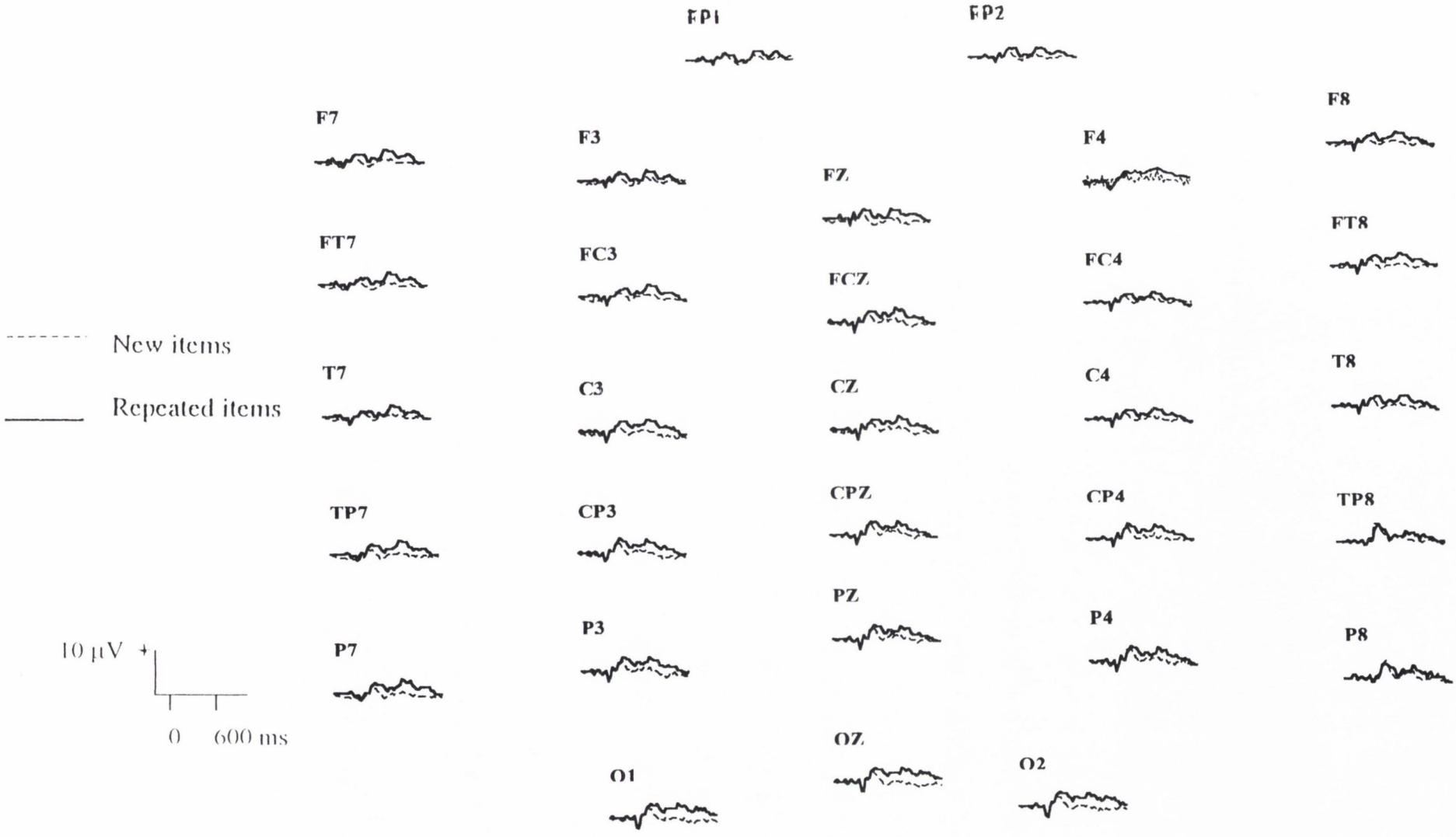

Figure 8.12. Grand average waveforms from the indirect task for first presentations (new) and repeated (old) neutral words in female subjects.

Chapter 9

Emotion and Cognition: discussion

9.1 Overall findings

Results from the word rating study revealed that both word valence and arousal had significant effects on the response ratings, showing that the participants agreed with the designated emotional word categories, thereby validating the emotional words employed in the memory tasks in terms of valence and arousal. Furthermore this study showed an effect of gender on the emotional ratings in terms of valence, whereby males gave more negative scores to negative words while females rated positive words more positively. Gender also had an influence on the arousal ratings, with females rating words as significantly more arousing than males.

As regards behavioural performance, females performed significantly better than males on the percentage correct scores for the direct and indirect tasks. As expected, the elderly group had significantly lower scores relative to the young subjects. These effects interacted such that the sex difference (superior memory performance in females) was more pronounced in the elderly. The free recall data showed a word valence effect, whereby positive words were recalled more than neutral or negative words. This effect was present in the young female participants only. Similar to the percentage correct results, females showed superior performance relative to men and the young group had higher scores than the old. Once again, women's enhanced recall scores compared to males was more pronounced in the elderly. No effect of valence on memory performance in direct memory or free recall tasks was observed in the elderly group.

The electrophysiological data revealed a reliable ERP word repetition effect. The emotional content of the words had a significant influence on

the ERP repetition effect in the 250-1000 ms latency region, being greater for neutral and positive words than for negative words, though they were not different from each other. This effect was only present in the direct task and in females only. No valence effect was present in males. Overall, females had higher ERP amplitudes and had a greater ERP repetition effect relative to males. This sex difference was more pronounced for the direct task than the indirect task.

P300 analysis revealed an effect of word valence on P300 amplitude, whereby neutral and positive words elicited greater positivity than negative words. P300 and LPC analysis also reveals an effect of word valence (emotional content) on the word repetition effect in these more constrained latency regions, with greater ERP repetition effects for neutral and positive words than for negative words, though they were not different from each other. Gender had a consistent influence on the P300 and the LPC, with greater positivity evoked in females relative to males. Such findings were more pronounced in the direct relative to the indirect task.

Cumulatively, emotional content had consistent effects on emotional response and on recognition memory processes, at a behavioural and electrophysiological level. Gender exerted a significant influence on emotional processing and emotional memory in electrophysiological terms. The emotional memory effect present in the young participants was absent in the elderly, suggesting that age had a considerable impact on memory for emotional stimuli.

9.2 Word rating study

Our first approach in setting up this series of studies was to create a standardized set of emotional stimuli validated by a young Irish population. Analysis showed that subjects reliably discriminated between words in terms of their valence (positive, negative, and neutral) and arousal (exciting or unexciting) properties. Investigation of the

impact of gender gave rise to some interesting results. As regards valence, males were more sensitive to negative words, whilst females were more sensitive to positive words. A recent imaging study (Schneider *et al.*, 2000) found brain activity in the male amygdala during negative affect, with no activity in women. They concluded that men underwent greater processing of sadness than women, thereby agreeing with our finding of greater sensitivity to negative valence in males. The differential responsiveness in females to positive words has not been previously documented in behavioural studies. This dissociation in response to positive and negative stimuli across gender requires further research.

The finding of women's greater intensity of emotion in response to emotional words is supported by a variety of studies (Choti, 1987; Gross & Levenson, 1993; Grunwald, 1999; Levenson, 1991; Thayer, 2000). These findings suggest that women experience emotions more intensely than men. For example, Fujita *et al.* (1991) reported that women experienced greater emotional intensity than men, with gender accounting for over 13% of the variance in affect intensity. In 1999 Grunwald carried out a study on the perception of emotional stimuli in 14 men and 14 women. Participants made intensity ratings of emotional and non-emotional stimuli from the New York Emotion Battery. When gender was examined, emotional stimuli were rated more intensely by female than male participants. In the present study, women not only rated arousing words higher than males, but also rated non-arousing words as more arousing than males. This suggests that emotional elicitation gives rise to a reactive inhibition in males, and an elaboration of the emotional response in females. Such results may be explained using the findings of neuroimaging studies, several of which have reported sex differences in emotional processing (George *et al.*, 1996a; Cahill *et al.*, 2002; Gur *et al.*, 2002). Gur *et al.* 2002 reported that although men and women had identical volumes of amygdala, hippocampus and dorsal prefrontal cortex, women had larger orbital frontal cortices (a region important in emotional processing, see Section

6.3). They postulated that the larger volume of cortex devoted to emotional modulation may underlie behavioural evidence for sex differences in emotional processing.

This study served to provide a set a standardised emotional verbal material. These words were taken from the Affective Norms of Emotional Word (ANEW) system (Bradley & Lang, 1999) developed in the United States. To ensure that the words' emotional rating as designated and ratified by this system was not related or unique to the American context in which they were originally standardized, words were selected from this corpus to establish the words' emotionality for an Irish population. For example the word "prairie" may give rise to more positive scores in America than in Ireland. Thus this method negated any potential confounds due to cultural influences on word meaning and emotionality. Words rated as being emotionally positive, negative or neutral and arousing or non-arousing were then employed in the direct and indirect tasks in the recognition memory studies, as discussed below.

9.3 The effect of emotional words on behavioural measures of memory

No effect of emotional content was observed on recognition memory accuracy, as measured by percentage correct scores. However, a significant effect of emotional valence on memory as measured by free recall was found. Greater recall for positive than negative or neutral words was observed. It is noteworthy that this valence effect was present only in the female participants. The finding that memory in females was more sensitive to positive than negative valence may reflect the word rating results, whereby women rated positive words more positively than males. Thus the sensitivity of women to positive words may extend to their superior memory advantage for positive words, as found in this study. Although it has received little attention, research on memory for pleasant stimuli had produced evidence for increased memorability

relative to neutral events (Matlin & Stang, 1978). While no difference in recall between positive and negative words has been found (Bradley & Baddeley, 1990), three reports have observed an advantage for positive relative to negative stimuli (Bradley *et al.*, 1992; Danion *et al.*, 1995; Palomba *et al.*, 1997).

It has been suggested that emotionally charged words are accompanied not only by more correct recognition than neutral words, but also by a higher probability of incorrect recognition (false alarms) (Windmann & Kruger, 1998). Therefore the absence of a valence effect in the recognition task and its presence in the free recall task may be due to the tendency of emotionally valenced words to produce false alarms in the recognition task, thus offsetting the tendency for a higher accuracy rate for emotional words. Two studies have reported that the well-documented free recall advantage for emotional words does not extend to recognition memory tests. Danion *et al.* 1995 found that discrimination between new and old words was lower for emotional than for neutral words. Furthermore Leiphart *et al.* 1993 showed that emotional words were associated with a higher hit rate but, because this effect was offset by an equivalent increase in the false alarm rate, recognition accuracy did not differ between the emotional and neutral words.

No effect of emotion on reaction times was observed. However, other studies (Maratos *et al.*, 2001; Simpson, 2000; Dahl, 2001) reported prolonged reaction times to new negative words relative to neutral words. Such results however may be explained in terms of the false memory effect elicited by semantically similar word sets, whereby negative words are more semantically cohesive than neutral words. Thus negative words give rise to a greater tendency for false memories than neutral words. It is well documented that false recollection of stimuli invokes longer reaction times than correctly classified stimuli (Nessler, 2001). Thus negative stimuli were more difficult to discriminate than

neutral words. The absence of this effect in this study may be due to the elimination of semantic effects in the word lists employed.

In line with previous studies (Bleecker *et al.*, 1988; McGivern, 1997), regardless of emotional content, females performed significantly better on both the recognition memory task and the free recall task than males. Women performed better than men on the Wechsler Memory Scale and California Verbal Learning Test in a study conducted by Ragland *et al.* (2000). They reported a relationship between this enhanced performance and greater regional cerebral blood flow in the temporal region in women. Another study (Herlitz *et al.*, 1997) demonstrated that women (n=530) consistently performed at a higher level than did men (n=470) on episodic memory tasks. Thus both behavioural and imaging evidence support the present findings of superior performance in women relative to men.

This sex difference (superior memory performance in females) was more pronounced in the elderly group i.e. there was a greater difference in memory performance between old males and females than between young males and females. This pattern was present in both the recognition task and the free recall task. This concurs with two neuroimaging studies investigating the effects of age and sex on brain structure and volume. Cowell *et al.* (1994) conducted Magnetic Resonance Imaging (MRI) scans on 96 young and 34 old men and women and observed that age-related reductions in the frontal and temporal lobes were greater in men than in women. It is noteworthy that both these regions are important in episodic memory (see Chapter 2). In a study of young adults (aged 18-49), men experienced greater volume decrement across age-groups than women, particularly in prefrontal regions (Gur *et al.*, 2002). Thus these findings support MRI evidence that neuroanatomical structures may change more rapidly with age in males compared with females.

It was suggested that different levels of education between elderly males and females may have accounted for superior memory performance in elderly females relative to elderly males. This is unlikely however as only three of the female participants had third level education, whilst the remaining females and the male group were all educated to a secondary level.

As expected, the elderly participants performed significantly worse on both the direct/indirect memory task and the free recall task than the young group. A recent study conducted by Davis *et al.* (2001) found that the elderly were significantly impaired on both recognition memory and free recall tasks. This agrees with an extensive body of literature on age-related decrements in memory performance (for a review, see Friedman *et al.*, 1995). Furthermore, elderly subjects were significantly slower to respond to word stimuli than the young participants. This finding is in agreement with an extensive body of literature (for a review, see Friedman *et al.* 1995). This effect may be due to the slower motor skills and impaired cognitive processing associated with old age.

No valence effect was found in the elderly participants in either the recognition memory or free recall tasks. Thus the emotional memory effect present in the young group was absent in the older participants. This finding supports previous behavioural studies introduced in Chapter 6 (Grunwald, 1999; Wallach *et al.*, 1980; Riege *et al*, 1980; Oscar-Berman *et al.*, 1990). Another study reported that the elderly were significantly less accurate in identifying facial affective valence (McDowell *et al.*, 1994). Neuroanatomical evidence lends further credence to this finding, whereby diminished activity in the amygdala was observed during perception of emotional faces in older relative to younger participants (Iidaka *et al.*, 2002). Thus is possible that impaired recognition memory in old people may reduce the ability to profit from the words' emotional content to enhance recognition performance.

9.4 The effect of emotional words on electrophysiological correlates of memory

Between 250 and 1000 ms post-stimulus ERPs were modulated by both the repetition status and valence of the words. ERPs to words correctly identified as "old" were more positive than those to words correctly identified as "new" from 250 to 1000 ms post word onset. This is the typical ERP repetition effect observed in ERP studies of recognition memory (Allan *et al.*, 1998; Johnson, 1995; Rugg, 1995). This involves modulation of the N400 component. The N400 is an index of associative processing activity and is negative in response to new words. When a word is repeated, less activity is required to process this word with the context in which it was first presented. Thus a smaller N400 is elicited, and this difference between the greater activity in response to new relative to repeated words is known as the ERP repetition effect.

In the 250-1000 ms latency range, negative words elicited an ERP repetition effect that was significantly smaller in magnitude that that elicited by neutral and positive words. Analysis of the P300 and LPC amplitudes also revealed similar effects of emotional content. This effect was due to the smaller amplitude (greater negativity) of the old negative words compared to old neutral words. This suggests that negative words, when presented for the second time, were treated as if they were new i.e. greater cognitive processing was required for negative words than neutral words when repeated in a recognition task. The greater negativity in response to repeated negative words is a measure of the greater activity elicited.

The false memory theory could be offered to account for the emotional effects reported in this project. According to this account, the probability of falsely classifying a new item as "old" in a memory test increases dramatically when the new item is strongly (semantically, thematically) related to actually studied items (Roediger *et al.*, 1998). Several mechanisms such as semantic priming have been offered to account for

this phenomenon. Thus, if the negative words in this study were more interrelated than the neutral ones, it could be argued that the effects attributed to negative valence were due to this factor. However, in this study every effort was made to equate the positive, negative and neutral word lists for interrelatedness. An equivalent number of semantically related words were included in the neutral list (e.g. discuss, describe, articulate) as in the positive and negative lists.

These results are partly consistent with results of similar studies carried out by Maratos *et al.* (2000), Windmann & Kutas (2001) and Windmann *et al.* (2002). The first study reported a reduced ERP repetition effect for correctly recognized negative words compared to the repetition effect for neutral words. Such results however were attributed to the influence of semantic cohesion discussed above, which was not controlled for in their experiment. According to this hypothesis, emotionally valenced words have stronger inter-item association than do sets of neutral words. Such cohesiveness leads to a tendency for "false recollection" of new items. Thus emotional words act like "related lures" that elicit high false alarm rates in studies of false recollection. High levels of inter-items association between members of negative words means that these items tend to prime each other semantically. This effect is manifest in the greater positivity elicited by new negative words, leading to an attenuated N400 and a reduced ERP repetition effect.

Windmann & Kutas (2001) examined the effects of valence on ERPs to words classified as "old" when they were actually "new" and also found no repetition effect for negative words. They postulated that this arose from a greater tendency to classify words as "old" more often when these words have a negative valence as opposed to neutral ones, whether or not the words are actually new or old (Ehlers *et al.*, 1988; Leiphart *et al.*, 1993; Windmann & Kruger, 1998; Windmann & Kutas, 2001; Windmann *et al.*, 2002). This induced a larger ERP positivity to the new negative words which elicited a false alarm response. They concluded that the emotion-related influence on the bias to respond "old" was

related to an adaptive cognitive function, whereby the brain assigns greater priority to the processing of potentially threatening stimuli.

A previous study by the same authors (Windmann & Kruger, 1998) suggested that negative valence can "misdirect" information processing at preattentive stages. Furthermore, negative stimuli may encourage the orbitofrontal regions to relax the tendency to suppress currently irrelevant memories (Schnider *et al.*, 2000). Thus, by this mechanism, the brain ensures that biologically relevant stimuli are not missed or forgotten as readily as neutral stimuli (Gunther *et al.*, 1996; Le Doux, 1996; Schnider & Ptak, 1999; Windmann & Kruger, 1998).

This finding is further supported by Windmann *et al.* (2002) who replicated the 2001 study using panic disorder patients. For the healthy control group, neutral words elicited ERPs to correctly recognized old words, whereas words with negative connotations were associated with significantly smaller ERP repetition effects. These findings were again interpreted in terms of the brain's adaptive function of heightened sensitivity to potentially negative stimuli in the environment.

Many similarities exist between the Windmann studies and the present findings. Semantic cohesion was controlled for and reduced repetition effects were found for negative compared to neutral words. However, Windmann's results were attributed to the greater positivity of the new negative words and the negative recognition bias. In this study, the reduced positivity (more negativity) for old negative words was underlying the results. This suggests that negative stimuli were subject to greater processing than neutral or positive words.

The present findings may reflect the automatic withdrawal of inhibitory control exerted by the prefrontal cortex over limbic structures during memory retrieval upon presentation of negative stimuli (Windmann *et al.*, 2002). As the ERP repetition effect indexes the engagement of higher order control functions by the prefrontal cortex during memory

retrieval (Allan *et al.*, 1998), this explains the attenuated repetition effect for negative words. When a negative word is presented, inhibitory control is removed so that the memory system becomes sensitive to such salient stimuli. Since semantic cohesion was removed as a factor in this experiment and no difference in ERPs to new negative, positive or neutral words were observed, false recollection, arising from either semantic interrelatedness of negative words or negative-induced recognition bias, cannot be used to explain the present findings. The P300 latency results lend weight to these findings, whereby both positive and negative words gave rise to longer P300 latencies, thus indicating a greater allocation of processing resources to emotionally relevant stimuli. Thus these findings may reflect the greater processing assigned to negative stimuli, due to the removal of top-down inhibition of memory retrieval usually in place for irrelevant i.e. neutral stimuli. This lack of inhibition means that memory for stimuli of survival value in the environment is enhanced.

The presence of this emotional effect in female participants only is also noteworthy. This finding parallels the word rating study results, whereby females rated emotional words as being more arousing than males. Together this suggests that females have a greater propensity for this negative memory bias effect than males.

Regardless of valence, gender also had an important influence on electrophysiological processing. Specifically, females elicited a higher overall ERP amplitude, particularly the P300 and LPC. This agrees with several studies (Allison, 1983, Buchsbaum, 1974; Kaneda, 1996; Rodin, 1965; Stockard, 1979; Beagley, 1978; McClelland, 1979; Jerger, 1980; Fagan, 1986). This effect was more pronounced in the direct than the indirect task. This suggests that the influence of gender on cognitive processing is mediated at the level of explicit rather than implicit processing.

A significant finding of this research was the greater ERP repetition effect in females compared to males. Although this not been previously documented, this result is consistent with the behavioural findings (percentage correct and free recall) in this study of greater memory performance in females relative to males. As discussed earlier, this is further supported by several behavioural studies. Again this effect was exacerbated in the direct compared to the indirect task, supporting the hypothesis made earlier that gender has a greater impact on explicit than implicit memory processes.

Finally, emotional content had no effect on implicit memory processes as measured by the indirect memory task. This supports the behavioural finding of Danion *et al.*, (1995) who investigated explicit and implicit memory for emotional words in depressed and healthy participants. They observed that word-stem completion performance was insensitive to emotional valence. This suggests that emotionality influences memory only when controlled, conscious recollection is required (as found above), and not when no reference is made to the previous learning episode, as in the indirect task. Memory measured by the direct task is determined by conscious, effort-demanding processes, whilst memory assessed by the indirect task is determined by automatic integrative processes. Taken together this suggests that memory as measured by the indirect task is impervious to the emotional content of words.

Cumulatively, emotional content had consistent effects on emotional response and on recognition memory processes, at a behavioural and electrophysiological level. These findings may reflect the greater processing assigned to negative stimuli. The influence of gender on emotional processing suggests that females have a greater propensity for this negative memory bias. The lack of an emotional memory effect in the elderly may reflect impaired memory function due to the ageing process.

Chapter 10

Conclusions and Implications for Future Research

10.1 Sex hormones and cognition

This research investigated the effect of the menstrual cycle on a broad range of cognitive functions, namely verbal memory as assessed by behavioural and electrophysiological methods, mood and attention and visual memory as measured by the CANTAB battery.

The failure to find an effect of the menstrual cycle on behavioural or electrophysiological correlates of verbal memory suggests that this cognitive domain was insensitive to cyclic sex hormonal fluctuations. The finding of an interaction between the menstrual cycle and electrophysiological measures of verbal processing suggests that the ERP response to verbal stimuli varied as a function of menstrual cycle phase. Thus menstrual cycle effects are dependent on the type of processing and the cognitive domain under investigation. Although the functional significance of this effect, including their cerebral generators, remains unclear, the present results suggest that the menstrual cycle can modulate brain activity associated with verbal processing. The finding of enhanced mood at mid-cycle relative to start-cycle suggests that the menstrual cycle also exerts a reliable influence on mood.

The current results require replication and extension. Future studies should address which sex hormones are responsible for these positive findings. Although correlational analysis was conducted to investigate oestrogen and progesterone levels with behavioural and ERP measures, the sample size was probably too small for any significant correlations to emerge. Thus, greater sample sizes should be employed to allow correlational analysis of electrophysiological and mood effects with these hormones. The period of investigation should be extended to include several menstrual cycles and more regular hormonal sampling

should be carried out to allow a more precise delineation of hormonal changes concomitant with cognitive changes. Furthermore, experimental manipulation of hormone levels, for example using a gonadotrophin agonist to suppress hormone production, would enable a more direct analysis of the contribution of systemic hormones to changes in ERP measures and mood. In addition, women taking oral contraceptives should be included in subsequent studies as control subjects (Hampson & Kimura, 1985), since their menstrual cycles are not characterized by the same fluctuations in oestrogen and progesterone.

The current findings of increased P300 and LPC amplitude at start-cycle and mid-cycle could be further explored by comparing ERPs in response to neutral and emotional words presented once i.e. not within the ERP repetition effect paradigm but within a continuous verbal task. This would permit investigation of verbal processing rather than verbal memory, the latter of which was unresponsive to hormonal variation in this study. Such research would help to clarify the double dissociation between ERP measures of non-emotional verbal processing and emotional pictorial processing across the menstrual cycle suggested by the present findings and those from previous studies (Johnston & Wang, 1993; Krug, 2000).

This research, by offering electrophysiological and behavioural evidence that the hormonal milieu modulates verbal processing and mood, provides impetus for future work to determine the exact mechanisms underlying these findings and their implications for cognitive function.

10.2 Electrophysiological and behavioural measures of recognition memory for emotional words

Emotional content had a significant influence on emotional response ratings and on recognition memory processes, at both a behavioural and an electrophysiological level. The present finding of a greater ERP repetition effect for neutral and positive than negative words may be

attributable to an adaptive system whereby memory is biased towards negative stimuli of survival value in the environment. Future studies should explore this hypothesis by employing stimuli which are of great personal salience to the individual participant. This would allow an insight into the effect of words' subjective emotionality on memory. Furthermore, concurrent measurements of physiological arousal by skin conductance techniques would complement rating studies to further verify the arousing properties of the stimuli employed.

Gender exerted consistent effects on emotional processing and emotional memory in electrophysiological terms. This sex difference could be due to sex hormonal factors. Future research could clarify this by investigating the effect of hormonal fluctuations across the menstrual cycle on emotional memory using a similar ERP paradigm.

The emotional memory effect present in the young participants, was absent in the elderly, suggesting that age had a considerable impact on memory for emotional stimuli. The mechanisms underlying this finding could be further explored by investigating the effect of manipulating neurotransmitters systems involved in emotional memory. For example, a great deal of research from animal and human studies has documented a facilitatory effect of corticosteroids on memory performance (Roozendaal, 2000; Buchanan & Lovallo, 2001). Thus the administration of cortisol to elderly subjects would be expected to counteract or reverse the effect found in this research, with emotional memory being maintained in old age. Similarly, acetylcholine has been implicated in emotional processes (Passani *et al.*, 2001; Nail-Boucherie *et al.*, 2000), with fear conditioning being associated with an increase in acetylcholine release. Therefore treatment of elderly participants with cholinesterase inhibitors may counteract or reverse the impairment of emotional memory processes with increasing age.

This paradigm could also be employed to investigate emotional memory in depression. A recent study (Dietrich *et al.*, 2000) reported that relative

to a control group, depressed patients displayed greater ERP positivity to negative items. This was attributed to the smaller N400 due to the negative words being less distinctive than positive or neutral words, as a result of the negative cognitive schemata of the depressive patients (Blaney, 1986). These findings are questionable however due to the failure to control for semantic similarity in the word lists employed. As a greater tendency for negative bias is associated with depression (Dietrich *et al.*, 2000), a greater attenuation of the ERP repetition effect to negative words in depressed patients relative to healthy controls would be predicted in light of the present findings. Furthermore, an investigation of the effect of antidepressant drugs would further clarify the functional significance of this emotional bias effect in both healthy and pathological populations.

The current finding provides evidence that the emotional content of an item has a major influence on electrophysiological concomitants of recognition. This paradigm appears to be feasible not only for the investigation of age and sex differences, but potentially for the examination of the mechanisms underlying such effects by pharmacological manipulation.

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Appendix A

Diagnostic and Statistical Manual of Mental Disorders

American Psychiatric Association 4th Edition

Diagnostic criteria for Late Luteal Phase Dysphoric Disorder

A. In most menstrual cycles during the past year, symptoms in B occurred during the last week of the luteal phase and remitted within a few days after onset of the follicular phase. In menstruating females, these phases correspond to the week before, and a few days after, the onset of menses. (In nonmenstruating females who have had a hysterectomy, the timing of luteal and follicular phases may require measurement of circulating reproductive hormones.)

B. At least five of the following symptoms have been present for most of the time during each symptomatic late luteal phase, at least one of the symptoms being either (1), (2), (3), or (4):

(1) marked affective lability, e.g., feeling suddenly sad, tearful, irritable, or angry
(2) persistent and marked anger or irritability
(3) marked anxiety, tension, feelings of being "keyed up," or "on edge"
(4) markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
(5) decreased interest in usual activities, e.g., work, friends, hobbies
(6) easy fatigability, or marked lack of energy
(7) subjective sense of difficulty in concentrating
(8) marked change in appetite, overeating, or specific food cravings
(9) hypersomnia or insomnia
(10) other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," weight gain

C. The disturbance seriously interferes with work or with usual social activities or relationships with others.

D. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as Major Depression, Panic Disorder, Dysthymia, or a Personality Disorder (although it may be superimposed on any of these disorders).

E. Criteria A, B, C, and D are confirmed by prospective daily self-ratings during at least two symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

Note: For coding purposes, record: 300.90 Unspecified Mental Disorder (Late Luteal Phase Dysphoric Disorder).

Appendix B

Paragraph Recall test (Wechsler Memory Scale, 1987)

Session 1, Paragraph A, (Story 8)

Barry / Smith / planned / to / bake / a chocolate / cake / on Wednesday / to / celebrate / his / parent's / 35th / wedding / anniversary. / The page / on which / the recipe / was printed / had / a stain / over / the number / of eggs / needed. / He / was / an inexperienced / cook, / and guessed / that 10 / seemed / about / right. / When he / looked / in the oven / after / an hour, / the cake / had spilled, / covering / the bottom / of the oven. /

Prompt: " A man who wanted to cook something. " Given ?_____

Session 1, Paragraph B, (Story 17)

Marjorie / Waters / was asked / by her / employer / to / mail / 8 / large / packages / and an overseas / letter / by the end / of Monday. / At 4 / o'clock / she / went / to the mailbox / in her / building. / but the box's / door / was / too / small. / She / rushed / down / the street / to the main / post / office / and arrived / out / of breath. / She / was relieved / to / get / there/ just / before / they / closed. /

Prompt: " A woman who did a job." Given ?_____

Delay Start _____ Delay End_____

Session 2, Paragraph A, (Story 9)

Randy / Jackson / was **arrested / one / morning /** in **front /** of **his / Park / Avenue / apartment /** for **32 / unpaid / parking / tickets. /** The **police / escorted / him /** to the **station /** where **they / fingerprinted /** and **photographed / him, /** and **locked / him /** in a **jail / cell. / His / concerned / wife / paid / his / bail / that / afternoon. / He / went /** to **court /** the **next / week, / pleaded / guilty, /** and was **fined / 250 / dollars. /**

_____

_____

_____

_____

_____

_____

_____

_____

Prompt: " A man who got into trouble. " Given ?_____

Session 2, Paragraph B, (Story 21)

Maria's / child / Ricky / played / soccer / every / Monday / at **3:30. / He / liked / going /** to the **field / behind / their / house /** and **joining /** the **game. / One / day, / he / kicked /** the **ball /** so **/ hard /** that **it / went / over /** the **neighbor's / fence /** where **three / large / dogs / lived. /** The **dog's / owner / heard / loud / barking, / came / out, /** and **helped / them / retrieve /** the **ball . /**

_____

_____

_____

_____

_____

_____

_____

_____

Prompt: " A boy who did a sport.. " Given ?_____
Delay Start _____ Delay End_____

Appendix C

Profile of Mood States (POMS)

NAME_____ DATE_____

Below are words that describe feelings and moods people have. Please read EVERY word carefully. Then fill in ONE space under the answer which best describes how you have been feeling DURING THE PAST WEEK INCLUDING TODAY.

Suppose the word is *happy*. Mark the one answer which is closest to how you have been feeling DURING THE PAST WEEK INCLUDING TODAY.

The numbers refer to these phrases.

0 = Much unlike this
1 = Slightly unlike this
2 = Slightly like this
3 = Much like this

IDENTIFICATION

	0	1	2	3
1. Composed				
2. Angry				
3. Cheerful				
4. Weak				
5. Tense				
6. Confused				
7. Lively				
8. Sad				
9. Friendly				
10. Tired				
11. Strong				
12. Clearheaded				
13. Untroubled				
14. Grouchy				
15. Playful				
16. Timid				
17. Nervous				
18. Mixed-up				
19. Vigorous				
20. Dejected				
21. Kindly				
22. Fatigued				
23. Bold				
24. Efficient				
25. Peaceful				
26. Furious				
27. Lighthearted				
28. Unsure				
29. Jittery				
30. Bewildered				
31. Energetic				
32. Lonely				
33. Sympathetic				
34. Exhausted				
35. Powerful				
36. Attentive				
37. Serene				
38. Bad tempered				
39. Joyful				
40. Self-doubting				
41. Shaky				
42. Perplexed				
43. Active				
44. Downhearted				
45. Agreeable				
46. Sluggish				
47. Forceful				
48. Able to concentrate				
49. Calm				
50. Mad				
51. Jolly				
52. Uncertain				
53. Anxious				
54. Muddled				
55. Ready-to-go				
56. Discouraged				
57. Good-natured				
58. Weary				
59. Confident				
60. Businesslike				
61. Relaxed				
62. Annoyed				
63. Elated				
64. Inadequate				
65. Uneasy				
66. Dazed				
67. Full of pep				
68. Gloomy				
69. Affectionate				
70. Drowsy				
71. Self-assured				
72. Mentally alert				

Appendix D

Paired Associate Tests (Wechsler Memory Scale, 1987)

A. First Presentation

Metal – Iron

Baby – Cries

Crush – Dark

North – South

School – Grocery

Rose – Flower

Up- Down

Obey – Inch

Fruit – Apple

Cabbage – Pen

First Recall

North –

Fruit –

Obey –

Rose –

Baby –

Up-

Cabbage –

Metal –

School –

Crush –

B. Second Presentation

Rose – Flower

Obey – Inch

North – South

Cabbage – Pen

Up- Down

Fruit – Apple

School – Grocery

Metal – Iron

Crush - Dark

Baby – Cries

Second Recall

Cabbage –

Baby –

Metal –

North –

School –

Up-

Rose –

Obey –

Fruit –

Crush –

C. Third Presentation

Baby – Cries

Obey – Inch

North – South

School – Grocery

Rose – Flower

Cabbage – Pen

Up – Down

Fruit – Apple

Crush – Dark

Metal – Iron

Third Recall

Obey –

Fruit –

Baby –

Metal –

Crush –

School –

Rose –

North –

Cabbage –

Up –

Appendix E

Direct and Indirect Memory Task word lists – Sex hormones and cognition study

Stimulus codes: 1 =short lag new, 2 = short lag old, 3 = long lag new, 4 = long lag old, 5 = control word, 6 = control words

Direct A – words and stimulus codes

alley	6
applause	3
useless	1
cabinet	3
useless	2
gangrene	1
dentist	3
gangrene	2
secure	3
kettle	5
torture	6
kindness	3
kettle	5
torture	6
applause	4
cabinet	4
dentist	4
coward	5
heaven	6
lion	1
secure	4
lion	2
kindness	4
laughter	3
peace	1
hatred	1
peace	2
hatred	2
depressed	1
coward	6
depressed	2
alert	1
bus	3
alert	2
heaven	5
wagon	6
laughter	4
brutal	5
loser	6
brutal	5
loser	6
bus	4
mischief	1
column	3
mischief	2
holiday	3
soothe	1
assault	1
soothe	2
assault	2

storm	5
glory	6
diamond	3
column	4
storm	5
glory	6
holiday	4
illness	5
village	6
illness	5
village	6
diamond	4
truck	3
salute	3
spray	5
watch	6
headache	1
execution	1
headache	2
execution	2
cake	5
happy	6
truck	4
lightning	3
trauma	1
salute	4
trauma	2
cake	5
happy	6
comedy	1
sphere	1
comedy	2
sphere	2
alone	3
lightning	4
waterfall	1
museum	1
waterfall	2
museum	2
obsession	1
mistake	3
obsession	2
putrid	3
plain	5
seat	6
alone	4
bird	3
magical	5
alien	6
magical	5
alien	6
honest	5
violin	6
mistake	4
putrid	4
measles	3
bird	4
honest	5
violin	6
violent	5
cheer	6
passage	3
pleasure	3
sunrise	6
measles	4
violent	5
cheer	6

bomb	1
sunrise	6
bomb	2
slum	1
passage	4
slum	2
pleasure	4

Direct B

arches	1
errand	3
arches	2
dwell	3
castle	6
hazel	1
fate	3
hazel	2
shovel	1
flap	3
shovel	2
errand	4
muse	1
bout	3
muse	2
dwell	4
flat	3
fate	4
flap	4
brood	5
update	6
climax	5
utter	6
twig	1
bout	4
twig	2
flat	4
lotion	6
trader	1
devise	1
trader	2
devise	2
puff	5
thresh	6
potato	1
gully	3
potato	2
disk	5
clash	6
core	5
equal	6
garlic	5
dismal	6
barb	3
gully	4
tool	5
fathom	6
deck	3
ugly	3
tent	5
wart	6
clump	5
behalf	6
thrift	5
bother	6

barb	4
cancel	1
choke	1
cancel	2
choke	2
deck	4
ugly	4
anchor	3
horn	6
expel	5
buzz	6
trot	1
rouse	1
trot	2
rouse	2
throne	5
addict	6
anchor	4
gear	5
toss	6
flavour	1
dive	3
flavour	2
vanish	3
gospel	5
pirate	6
taxi	5
gasp	6
barge	5
cargo	6
hook	3
infer	5
abbot	6
dive	4
fare	3
bleep	3
vanish	4
clove	1
vice	1
clove	2
vice	2
dwarf	5
fluent	6
hook	4
bleep	4
fare	4
napkin	3
betray	5
bend	6
weaver	1
heed	3
weaver	2
clinic	3
cradle	6
manage	1
napkin	4
manage	2
insure	3
diet	5
chain	6
rely	1
heed	4
rely	2
greet	1
clinic	4
greet	2
easter	1

insure	4
easter	2

Indirect A

eagle	5
blank	6
grouse	5
outing	6
clock	3
leaf	1
pond	1
leaf	2
pond	2
dash	3
swim	3
cockroach	5
subway	6
cliff	1
clock	4
cliff	2
sock	3
spider	5
sofa	6
swim	4
bead	3
knot	1
dash	4
knot	2
attic	3
camel	5
query	6
sock	4
goose	5
stair	6
bead	4
shed	6
sunset	3
cough	3
lizard	5
barber	6
attic	4
hyena	5
mash	6
deer	5
lorry	6
sunset	4
deed	6
trophy	1
cough	4
trophy	2
wool	3
bacon	1
flag	3
bacon	2
token	1
straw	1
token	2
straw	2
abolish	1
globe	1
abolish	2
globe	2
wool	4
toad	5

oven	6
flag	4
clap	1
cable	3
clap	2
anchor	1
comb	3
anchor	2
soup	1
cake	3
soup	2
motel	1
boil	3
motel	2
acorn	1
cable	4
acorn	2
comb	4
cake	4
yacht	1
feast	3
yacht	2
boil	4
honey	1
dial	6
honey	2
ribbon	1
wrist	3
ribbon	2
irony	3
feast	4
velvet	6
peacock	5
gold	6
terrapin	5
bake	6
wrist	4
pearl	3
walrus	5
tulip	6
irony	4
armadillo	5
campus	6
buffalo	5
banana	6
turkey	5
sauce	6
paste	3
otter	5
storm	6
pearl	4
bait	3
diary	1
arcade	1
diary	2
arcade	2
puffin	5
ridge	6
mink	5
coach	6
paste	4
worm	5
pest	6
bait	4

Indirect B

fairy	1
locker	3
fairy	2
cube	3
craft	6
dish	1
wart	3
dish	2
bride	1
oasis	3
bride	2
locker	4
crate	1
linen	3
crate	2
cube	4
flock	3
wart	4
oasis	4
dolphin	5
fancy	6
crocodile	5
usher	6
shield	1
linen	4
shield	2
flock	4
bush	6
bulb	1
verse	1
bulb	2
verse	2
skunk	5
exit	6
doll	1
charm	3
doll	2
pigeon	5
circus	6
tiger	5
roast	6
monkey	5
jelly	6
stamp	3
charm	4
kangaroo	5
brass	6
vapour	3
plate	3
turtle	5
basin	6
squid	5
clown	6
ostrich	5
loaf	6
stamp	4
mail	1
banker	1
mail	2
banker	2
vapour	4
plate	4
brand	3
layer	6
gibbon	5

dusk	6
stitch	1
abject	1
stitch	2
abject	2
clam	5
crown	6
brand	4
cobra	5
bomber	6
album	1
tower	3
album	2
herb	3
python	5
atlas	6
duck	5
marsh	6
mosquito	5
width	6
hobby	3
rabbit	5
maze	6
tower	4
cage	3
grill	3
herb	4
lamp	1
lace	1
lamp	2
lace	2
bull	5
apple	6
hobby	4
grill	4
cage	4
glue	3
cuckoo	5
curl	6
sailor	1
hedge	3
sailor	2
alarm	3
admire	6
twist	1
glue	4
twist	2
shell	3
parrot	5
cycle	6
scrap	1
hedge	4
scrap	2
heaven	1
alarm	4
heaven	2
pint	1
shell	4
pint	2

Appendix F

Word rating study

	Valence (Unpleasant/Pleasant)	Arousal (Calming/Exciting)
alley		
applause		
hell		
cabinet		
gangrene		
flirt		
pamphlet		
kettle		
torture		
beautiful		
starving		
heaven		
prestige		
laughter		
ship		
hatred		
joke		
salad		
bus		
wagon		
brutal		
bloody		
column		
stove		
holiday		
christmas		
assault		
killer		
glory		
shadow		
millionaire		
village		
truck		
disaster		
spray		
watch		
poster		
execution		
affection		
happy		
despise		
trauma		
comedy		
sphere		
whistle		
museum		
passion		
terrified		
putrid		
plain		
seat		
fabric		
caress		
magical		

devil		
quiet		
cash		
violent		
burn		
pleasure		
sunrise		
bomb		
detail		
passage		
umbrella		
fun		
stool		
circus		
excellence		
joy		
danger		
trumpet		
adorable		
crash		
bland		
phase		
barrel		
detest		
radiant		
casino		
basket		
deceit		
bench		
reserved		
traitor		
context		
chair		
clock		
chin		
scissors		
lucky		
cruel		
loved		
owl		
horror		
nightmare		
beast		
curtains		
wedding		
fork		
miracle		
toxic		
patent		
bath		
slaughter		
dazzle		
cancer		
ectasy		
journal		
drown		
imagine		
hay		
kiss		
circle		
leprosy		
destroy		
golfer		

runner		
hairdryer		
riches		
icebox		
jug		
scalding		
kettle		
fame		
lamp		
hammer		
puppy		
lantern		
abuse		
slave		
lightbulb		
ace		
bathroom		
bankrupt		
metal		
idol		
patriot		
romantic		
wasp		
vandal		
fur		
victory		
abortion		
suffocate		
adult		
taxi		
gold		
tumour		
month		
building		
star		
ink		
sunlight		
crime		
marvel		
cloth		
triumph		
fabric		
material		
glamour		
nylon		
glory		
texture		
weave		
murder		
woollen		
tartan		
tailor		
key		
whip		
flannel		
knitting		
engine		
yarn		
frightening		
formulate		
inform		
hilarious		
verbalize		

terrorize		
reveal		
display		
glee		
plague		
delight		
devastate		
estimate		
desire		
delineate		
torment		
intimate		
visualize		
vest		
bowl		
exhibit		
illuminate		
compare		
giggle		
impart		
elucidate		
plunder		
articulate		
merriment		
agony		
describe		
clarify		
ravage		
evil		
putrid		
interpret		
scream		
strangle		
revere		
pencil		
mutilate		
success		
thread		
garment		
linen		
discuss		
cotton		
sewing		

Appendix G

Word Categorization Study

This study is being conducted to establish if there is a common link in the meanings of some words. On the following page you will see a table with a list of words running down the left hand side of the table. Along the top of the table are two "themes". Please indicate which theme comes closest to describing the words on the left hand side of the page by placing a tick in the relevant box. Please see the example below.

	Farmyard animals	Emotions
Chicken	√	
Love		√
Sadness		√
Goat	√	

Table I

	Description/ Classification	'Household activity'
Designate		
Consign		
Cook		
Draft		
Clean		
Bake		
Illustrate		
Iron		
Vacuum		
Signify		
Versify		
Allegorise		
Prepare		
Tidy		
Paraphrase		
Polish		
Launder		
Wash		
Feature		
Collate		
Neaten		
Wipe		
Edit		
Denote		
Revise		
Scrub		
Rinse		
Sweep		
Tabulate		
Adjust		
Modulate		
Shine		
Boil		
Adapt		
Roast		
Grill		
Dine		
Compose		
Assemble		
Fry		
Update		

Table II

	Describe/Communicate	Management
Formulate		
Interpret		
Direct		
Lead		
Inform		
Guide		
Govern		
Control		
Discuss		
Verbalize		
Authorise		
Reveal		
Clarify		
Dictate		
Display		
Describe		
Administrate		
Assign		
Organise		
Articulate		
Impart		
Manoeuvre		
Handle		
Elucidate		
Compare		
Minister		
Estimate		
Invigilate		
Exhibit		
Visualize		
Delineate		
Regulate		
Command		
Oversee		
Superintend		
Order		

Table III

	Fame/Adulation	Relaxation
Marvel		
Applause		
Leisure		
Holiday		
Triumph		
Vacation		
Idol		
Prestige		
Rest		
Ease		
Repose		
Fame		
Comfort		
Excellence		
Patriot		
Peace		
Glamour		
Tranquil		
Refresh		
Glory		
Victory		
Respite		
Millionaire		
Lull		
Success		
Carefree		
Riches		
Content		
Recuperate		
Gold		
Revere		
Radiant		
Restore		
Relieve		
Dazzle		
Sleep		
Prize		
Unwind		

Table IV

	Pleasure	**Wealth**
Fun		
Laughter		
Prosperity		
Joy		
Success		
Luxury		
Wedding		
Affluence		
Comedy		
Intimate		
Prestige		
Hilarious		
Joke		
Profit		
Fortune		
Ecstasy		
Riches		
Glee		
Bonanza		
Plush		
Merriment		
Kiss		
Delight		
Opulent		
Glitzy		
Giggle		
Moneyed		
Casino		
Bliss		
Afford		
Passion		
Privilege		
Desire		
Caress		
Gold		
Diamonds		
Heaven		
Jewellery		
Romantic		

Table V

	Torture/Pain	Humiliation
Traitor		
Gangrene		
Humiliate		
Demean		
Torture		
Degrade		
Shame		
Terrified		
Starving		
Insult		
Demoralize		
Danger		
Chasten		
Hatred		
Brutal		
Bloody		
Humble		
Deflate		
Assault		
Killer		
Disrespect		
Embarrass		
Murder		
Snub		
Offend		
Criticize		
Condescend		
Execution		
Mutiliate		
Whip		
Disgrace		
Violent		
Reprimand		
Despise		
Mortify		
Burn		
Mortify		
Dishonour		
Scorn		
Trauma		
Strangle		

Table VI

	Fear	Anger
Scream		
Resent		
Bitter		
Frightening		
Evil		
Putrid		
Acrimonious		
Rancorous		
Spiteful		
Cruel		
Devil		
Malevolent		
Ravage		
Vindictive		
Ravage		
Terrorize		
Cross		
Wrathful		
Beast		
Nightmare		
Irate		
Agony		
Peeved		
Infuriate		
Plague		
Incensed		
Rage		
Vex		
Devastate		
Plunder		
Annoy		
Cancer		
Drown		
Exasperate		
Leprosy		
Torment		
Irascible		

Appendix H

Direct and Indirect Memory Task word lists –Emotion and cognition study

Stimulus codes: 1 = positive new, 2 = positive old, 3 = negative new, 4 = negative old, 5 = neutral new, 6 = neutral old

Direct Task – words and stimulus codes

metal	7
marvel	1
designate	5
marvel	2
egg	7
consign	5
applause	1
traitor	3
applause	2
traitor	4
bench	7
triumph	1
gangrene	3
designate	6
idol	1
draft	5
consign	6
draft	6
barrel	7
prestige	1
idol	2
illustrate	5
triumph	2
torture	3
signify	5
gangrene	4
signify	6
rent	7
versify	5
illustrate	6
terrified	3
prestige	2
terrified	4
allegorize	5
torture	4
allegorize	6
seat	7
fame	1
starving	3
danger	3
paraphrase	5
versify	6
paraphrase	6
excellence	1
ink	7
excellence	2

fame	2
danger	4
patriot	1
starving	4
patriot	2
trumpet	7
feature	5
hatred	3
glamour	1
hatred	4
lawn	7
collate	5
brutal	3
collate	6
brutal	4
glory	1
bloody	3
glory	2
bloody	4
feature	6
building	7
glamour	2
revise	5
hat	7
revise	6
victory	1
assault	3
victory	2
tabulate	5
millionaire	1
killer	3
millionaire	2
month	7
denote	5
success	1
denote	6
murder	3
assault	4
murder	4
tabulate	6
killer	4
cord	7
edit	5
riches	1
edit	6
success	2
execution	3
adjust	5
execution	4
cellar	7
modulate	5
gold	1
modulate	6
despise	3
riches	2
key	7
mutilate	3
whip	3
mutilate	4
whip	4
adjust	6
gold	2
pencil	7
violent	3
adapt	5
revere	1
despise	4

revere	2
locker	7
radiant	1
violent	4
compose	5
burn	3
dazzle	1
burn	4
radiant	2
adapt	6
compose	6
engine	7
dazzle	2
trauma	3
assemble	5
wonder	1
assemble	6
wonder	2
strangle	3
finger	7
prize	1
butter	7
prize	2
strangle	4
trauma	4
update	7

Indirect task

context	8
fun	1
scream	3
fun	2
scream	4
cabinet	7
laughter	1
frightening	3
formulate	5
frightening	4
kettle	7
joy	1
evil	3
joy	2
laughter	2
fork	7
scalding	3
interpret	5
scalding	4
inform	5
formulate	6
inform	6
stove	7
evil	4
wedding	1
discuss	5
wedding	2
discuss	6
interpret	6
hilarious	1
putrid	3
stool	7
cruel	3
verbalize	5
joke	1
verbalize	6
comedy	1
devil	3
chair	7
devil	4
putrid	4
ravage	3
hilarious	2
cruel	4
joke	2
comedy	2
terrorize	3
clock	7
terrorize	4
reveal	5
ecstasy	1
nightmare	3
ecstasy	2
clarify	5
ravage	4
table	7
display	5
describe	5
glee	1
describe	6

beast	3
reveal	6
beast	4
nightmare	4
clarify	6
agony	3
basket	7
agony	4
glee	2
display	6
plate	7
merriment	1
verbalize	5
kiss	1
verbalize	6
kiss	2
scissors	7
plague	3
articulate	5
delight	1
articulate	6
delight	2
merriment	2
hairdryer	7
impart	5
devastate	3
giggle	1
plunder	3
elucidate	5
plunder	4
plague	4
iron	7
impart	6
compare	5
bliss	1
devastate	4
bliss	2
giggle	2
elucidate	6
cancer	3
estimate	5
jug	7
estimate	6
passion	1
lamp	7
illuminate	5
compare	6
desire	1
illuminate	6
exhibit	5
cancer	4
hammer	7
caress	1
drown	3
caress	2
passion	2
heaven	1
desire	2
leprosy	3
bowl	7
drown	4
visualize	5
exhibit	6
lightbulb	7
romantic	1
torment	3
romantic	2

torment	4
heaven	2
leprosy	4
icebox	7
delineate	5
visualize	6
delineate	6
suffocate	3
intimate	1
suffocate	4
lantern	7
intimate	2
vest	8