Event-related potential indices of cognitive functioning in long term cannabis users

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EVENT-RELATED POTENTIAL INDICES
OF COGNITIVE FUNCTIONING
IN LONG TERM CANNABIS USERS

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the degree of Doctor of Philosophy

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ABSTRACT

This thesis investigates cognitive impairments associated with chronic use of cannabis in a series of brain event-related potential (ERP) studies of selective attention. The first experiment found few differences between users and controls in a simple auditory discrimination paradigm. In experiment two, a complex auditory selective attention task showed that users differed significantly from controls in efficiency of information processing. Subjects attended to tones that varied in location, pitch and duration and responded to long duration tones of a particular location and pitch. Cannabis users' task performance was poorer than that of controls and users showed enhanced early processing negativity (PN) to stimuli of irrelevant pitch in the attended ear. This indicates that users engaged in unnecessary pitch processing and had difficulty in filtering out irrelevant information. P300 was reduced in the user group, suggesting a dysfunction in the allocation of attentional resources and stimulus evaluation strategies. Experiment three replicated the finding of large PN to pitch irrelevant stimuli in a larger sample, and examined the effects of frequency and duration of cannabis use. The ability to focus attention and reject irrelevant information, measured by PN to irrelevant stimuli, was progressively impaired with the number of years of use but was unrelated to frequency of use. The speed of information processing, measured by P300 latency, was significantly delayed with increasing frequency of use but was unrelated to duration of use. These results suggest that a chronic build up of cannabinoids produces both short and long term cognitive impairments. Experiment four assessed the reversibility of the PN effect in ex-cannabis users. The results showed that the large PN to irrelevant stimuli partially resolved following cessation of cannabis use. There was still a significant relationship between PN and past duration of cannabis use, and ex-users' task performance was poorer than that of controls. This suggests that past exposure to cannabis continues to affect electrophysiology and cognition well after discontinuing use. The conclusion from this research is that long term cannabis use progressively impairs the ability to process information efficiently, and there is only partial recovery with cessation of use.

" what hashish gives with one hand it takes away with the other: that is to say, it gives the power of imagination and takes away the ability to profit by it. "

Charles Baudelaire (1860) *Les Paradis Artificiel*, Paris: Poulet-Malassis.

" ...unquestionably there are modifications (I do not dare use the word "lesion") in the organ which is in charge of mental functions. But these modifications are not those one would generally expect. They will always escape the investigations of the researchers seeking alleged or imagined structural changes. One must not look for particular, abnormal changes in either the gross anatomical or the fine histological structure of the brain; but one must look for any alterations of its sensibility, that is to say, for an irregular, enhanced, diminished or distorted activity of the specific mechanisms upon which depends the performance of mental functions."

Moreau de Tours, J.J. (1845) *Du Haschisch et de l'Alienation Mentale: Etudes Psychologiques*. Paris: Libraire de Fortin, Masson.

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of a university or other institute of higher learning, except where due acknowledgement is made in the text.

Nadia Solowij

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CHAPTER 1

INTRODUCTION

Cannabis (marijuana) is the most widely used illicit substance in the western world (Goldstein and Kalant, 1990). It is the most popular and widespread of the illicit drugs in Australia, having been tried by 30% of the population at some stage in their lives (Makkai and McAllister, 1993). Of those who reported having tried cannabis in a major national survey, 14% of adults and 30% of adolescents had used within the week prior to the survey (Makkai and McAllister, 1993). Clearly, its use remains highly prevalent despite law enforcement efforts to inhibit its sale and consumption.

Cannabis is a psychoactive substance with a long history in many eastern cultures, gaining popularity among young western users in the 1970s due to its mind altering properties. The "high" produced by ingestion of cannabis (almost always by smoking) is characterised by mild euphoria, relaxation, perceptual alterations including time distortion, and the intensification of ordinary sensory experiences such as listening to music and watching films. When used in a social setting the high is often accompanied by infectious laughter and talkativeness. This state of altered awareness is also marked by a disruption of cognitive functions, encompassing a loosening of associations with impaired concentration and memory function, slowed reaction time and poor motor coordination.

Much ambiguity surrounds the psychological and health hazards attributed to the use of cannabis (Hollister, 1986). The drug is known to produce adverse effects when high doses are consumed or with continual regular and frequent use, and in some individuals adverse effects manifest even with the first exposure at low doses. These effects include anxiety and panic attacks, paranoid ideation, delusions, visual or auditory hallucinations, dysphoria and depression. The incidence of such effects, together with the cognitive impairments associated with the state of intoxication provide cause for concern regarding the psychological well being of the user. Further, concerns are raised about the possible long term effects that exposure to such a substance may have. This thesis examines the long term effects of cannabis use upon a specific aspect of cognitive functioning: selective attention.

The acute effects of cannabis upon human behaviour and cognition are reasonably well documented. Numerous studies have reported the acute effects of cannabis on psychomotor and cognitive performance, and these are briefly and selectively reviewed in Chapter 3. The most frequently affected functions are those of memory and attention; the results of many behavioural studies attest that cannabis impairs short-term memory and various kinds of attention whilst intoxicated, impairing also the ability to perform complex functions requiring attention and mental coordination (Casswell and Marks, 1973; Chait and Pierri, 1992; MacAvoy and Marks, 1975; Miller and Branconnier, 1983). The long term consequences of cannabis use on memory and attentional processes are unclear. Memory and attention are inextricably linked: effective memory function is dependent upon efficient attentional processes. Impaired attentional processing in the long term would have serious implications given that such processes are required for successful work performance, learning, memory and everyday tasks such as driving a motor vehicle.

A logical starting point for examining the consequences of long term exposure to cannabis is to assess precisely those functions most consistently disrupted by acute intoxication. Relatively few studies have investigated cognitive functioning in chronic cannabis users, fewer still in any rigorous way. Many were done more than a decade ago in response to wide community concern following 1) the explosion of cannabis use in the west in the 1970s; 2) the appearance of reports in the clinical literature describing mental deterioration associated with chronic use of cannabis (eg. Kolansky and Moore, 1971; 1972); 3) the publication of a medical report of cerebral atrophy in young cannabis users (Campbell et al, 1971); and 4) the concurrent sensationalist scare mongering of "brain damage" by the media. Chapter 4 discusses the evidence pertaining to possible neurological damage as a result of exposure to cannabis.

The studies of cognitive functioning in chronic users, reviewed in depth in Chapter 5, produced essentially contradictory results, due in part to the gross measures used and to methodological difficulties. Researchers relied primarily upon the use of psychometric tests to assess the presence of dysfunction in fairly broad areas of cognition. Whilst some studies did find significant differences between cannabis users and controls on a number of cognitive tests, these could variously be attributed to acute intoxication (eg. Stefanis, Dornbush and Fink, 1977), lack of pre-standardization of test batteries for the rural subject populations used (eg. Rubin and Comitas, 1975), or the unrepresentative populations tested (eg. Soueif, 1976). Many studies were unable to replicate the findings (eg. Carlin and Trupin, 1977; Fehr and Kalant, 1983b). Positive results were often reported as nonspecifically as "impairment of cognitive functions associated with long-term heavy cannabis use" (eg. Mendhiratta et al, 1988). It is argued in Chapter 5 that the lack of specificity and sensitivity of assessment techniques led to equivocal results. It is also argued that the long term effects of cannabis, if they exist, are likely to be subtle rather than grossly debilitating. Following past research

efforts, the question as to whether chronic use of cannabis leads to any long term impairment remained unresolved and there remained considerable controversy over this issue.

The discovery and anatomical localization of a specific cannabinoid receptor in the brain (Bidaut-Russell et al, 1990; Devane et al, 1988; Gerard et al, 1991; Herkenham et al, 1990; Matsuda et al, 1990) and the recent identification of an endogenous brain molecule, named anandamide, which binds to the receptor and mimics the action of cannabinoids (Devane et al, 1992), underscored the involvement of cannabinoids in the central nervous system. Cannabinoid receptors are distributed throughout brain regions known to be involved in attention, with high densities in the cerebral cortex and hippocampus (Bidaut-Russell et al, 1990; Devane et al, 1988; Herkenham et al, 1990). The hippocampus plays a role in excluding extraneous stimuli during concentration of attention and it was suggested that cannabinoids may disinhibit septal-hippocampal inputs to the reticular activating system resulting in failure to habituate to irrelevant stimuli (Miller and Branconnier, 1983).

In this thesis, the integrity of attentional processes in long term cannabis users was assessed using a combination of performance and event-related potential (ERP) measures, which together can provide insight into the nature of cognitive dysfunction (Ward et al, 1991). Event-related potentials are scalp recorded electrical responses of the brain to a particular event or stimulus, usually recorded during the performance of a cognitive task. ERP components are sensitive markers of specific stages of information processing, reflecting the nature, timing and duration of cognitive processes (Hillyard and Kutas, 1983; Näätänen, 1990). In ERP studies of auditory selective attention, reviewed in Chapter 6, directing attention to a particular channel of information results in the onset of a negative shift of the ERP waveform, which is referred to as processing negativity (PN) (Hansen and Hillyard, 1983; Näätänen, 1982). Processing negativity is

evident in the auditory system as early as 60 to 80 ms post-stimulus, reflecting the selection of relevant from irrelevant sources of information. Ongoing negativity beyond 600 ms in the ERP waveform to attended stimuli is referred to as late PN and reflects the maintenance and rehearsal of the attentional trace (Näätänen, 1982). The other component of interest is the P300, a large positive peak which is elicited by infrequent stimuli in the attended channel when a response is required (Donchin, 1981; Pritchard, 1981). The latency of the P300 component reflects the time taken to evaluate a stimulus, while its amplitude reflects the nature of stimulus evaluation processes. It is these two components that are of particular interest in the series of studies reported in this thesis.

In the first study, presented in Chapter 7, a small group of cannabis users was compared with a group of nonuser controls on a simple auditory oddball paradigm and then a complex selective attention task. The results of this study were then followed up by attempting a replication with a larger sample and assessing the effects of frequency and duration of cannabis use. This is presented in Chapter 8. Finally, the extent of reversibility of the impairments observed was assessed in a group of long term cannabis users who had given up (Chapter 9). Some descriptive and qualitative data over all samples is presented in Chapter 10. The thesis concludes with a discussion of the implications of its findings and recommendations for future research.

CHAPTER 2

CANNABIS THE DRUG

Cannabis is the material derived from the herbaceous plant Cannabis sativa which grows vigorously throughout many regions of the world. It occurs in male and female forms with both sexes having large leaves which consist of 5 to 11 leaflets with serrated margins. A sticky resin which covers the flowering tops and upper leaves is secreted most abundantly by the female plant and this resin contains the active agents of the plant. While the cannabis plant contains more than 60 cannabinoid compounds, such as cannabidiol and cannabinol, the primary psychoactive constituent is delta-9-tetrahydrocannabinol or THC (Gaoni and Mechoulam, 1964), the concentration of which largely determines the potency of the cannabis preparation. Most of the other cannabinoids are either inactive or only weakly active, although they may increase or decrease potency by interacting with THC (Abood and Martin, 1992).

Previously cannabis had been erroneously classified as a narcotic, as a sedative and most recently as a hallucinogen. While the cannabinoids do possess hallucinogenic properties, together with stimulant and sedative effects, they in fact represent a unique pharmacological class of compounds. Unlike many other drugs of abuse, cannabis acts upon specific receptors in the brain and periphery. The recent discovery of the receptors and the naturally occurring substances in the brain that bind to these receptors, is of great importance in that it signifies an entirely new pathway system in the brain.

2.1 The cannabinoid receptor

The desire to identify a specific biochemical pathway responsible for the expression of the psychoactive effects of cannabis has prompted a prodigious amount of cannabinoid research (Martin, 1986). Early studies found that radioactively labelled THC would nonspecifically attach to all neural surfaces, suggesting that it produced its effects by perturbing cell membranes (Martin, 1986). However, the work of Howlett and colleagues (Howlett et al, 1986; 1987; 1988) showed that cannabinoids inhibit the enzyme that synthesizes cyclic AMP in cultured nerve cells, and that the degree of inhibition was correlated with the potency of the cannabinoid. Since many receptors relay their signals to the cell interior by changing cellular cyclic AMP, this finding strongly suggested that cannabinoids were not just dissolving nonspecifically in membranes. After eliminating all the known receptors that act by inhibiting adenylate cyclase, it was concluded that cannabinoids acted through their own receptor. The determination and characterisation of a specific cannabinoid receptor in brain followed soon after (Devane et al, 1988), paving the way for its distribution in brain to be mapped (Bidaut-Russell et al, 1990; Herkenham et al, 1990).

It is now accepted that cannabis acts on specific cannabinoid receptors in the brain, conclusive evidence being provided by the cloning of the gene for the cannabinoid receptor in rat brain (Matsuda et al, 1990). A cDNA which encodes the human cannabinoid receptor was also cloned (Gerard et al, 1991) and the human receptor was found to exhibit more than 97% identity with the rat receptor. Cannabinoid receptors have also been found in the nervous system of lower vertebrates, including chickens, turtles and trout (Howlett et al, 1990) and there is preliminary evidence that they exist in low concentration in fruit flies (Bonner quoted in Abbott, 1990; Howlett, Evans and Houston, 1992). This phylogenetic distribution suggests that the gene must have been

present early in evolution, and its conservation implies that the receptor serves an important biological function.

The localisation of cannabinoid receptors in brain has elucidated the pharmacology of the cannabinoids. Herkenham and colleagues (Herkenham, et al 1990; 1991a; 1991b; 1992) used autoradiography to localise receptors in fresh cut brain sections of a number of species, including human. Dense binding was detected in the cerebral cortex, hippocampus, cerebellum and in outflow nuclei of the basal ganglia, particularly the substantia nigra pars reticulata and globus pallidus. Few receptors were present in the brainstem and spinal cord. Bidaut-Russell and colleagues (Bidaut-Russell et al, 1990) located cannabinoid receptors in greatest abundance in the rat cortex, cerebellum, hippocampus and striatum, with smaller but significant binding in the hypothalamus, brainstem and spinal cord.

High densities of receptors in the hippocampus and cortex suggest roles for the cannabinoid receptor in cognitive functions. This is consistent with evidence in humans that the dominant effects of cannabis are cognitive: loosening of associations, fragmentation of thought, and confusion on attempting to remember recent occurrences (Hollister, 1986; Miller and Branconnier, 1983). High densities of receptors in the basal ganglia and cerebellum suggested a role for the cannabinoid receptor in movement control, a finding which is also consistent with the ability of cannabinoids to interfere with coordinated movements. Recent research has also determined a role for the cerebellum in cognition (eg. Fiez et al, 1992; Petersen et al, 1989), and particularly in the switching of attention (Akshoomoff and Courchesne, 1992). The globus pallidus, rich in cannabinoid receptors, has also been shown to be activated in positron emission tomography (PET) studies of selective attention (Corbetta et al, 1991).

Cannabis has a mild effect on cardiovascular and respiratory function in humans

(Hollister, 1986) which is consistent with the observation that the lower brainstem area has few cannabinoid receptors. The absence of sites in the lower brainstem may in fact explain why high doses of THC are not lethal. Cannabinoid receptors do not appear to reside in the dopaminergic neurons once thought to constitute the "reward" system of the brain. This was at first taken to imply that the euphoric effects of cannabinoids are produced by a different mechanism than the euphoria produced by cocaine and morphine that directly act on the dopamine "reward" system. However, recent conceptualisations of the role of the mesolimbic dopamine neurons in drug-taking behaviour have changed from the view that these neurons are a substrate whose activation produces the euphoric or hedonic effects of a drug, to one in which the cells are thought to mediate incentive motivational processes or sensitization to drugs (Corrigall, personal communication; Robinson and Berridge, 1993). The absence of cannabinoid receptors in the mesolimbic dopamine projection is thus of obvious speculative interest in terms of the dependence liability of cannabis.

These mappings of receptors have been broadly confirmed in recent work by Matsuda and colleagues (1992, 1993) using a histochemistry technique to neuroanatomically localise cannabinoid receptor mRNA. Labelling intensities were highest in forebrain regions (olfactory areas, caudate nucleus, hippocampus) and in the cerebellar cortex; the role of the cerebellum in cognition has been referred to above. Clear labelling observed in the rat forebrain suggests several potential sites in the human brain that could mediate an impairment of memory function (Miller and Branconnier, 1983), such as the hippocampus, medial septal complex, lateral nucleus of the mamillary body, and the amygdaloid complex. Similarly, labelling was detected clearly in rat forebrain regions that correspond to those that could mediate cannabis-induced effects on human appetite and mood, namely, the hypothalamus, amygdaloid complex, and anterior cingulate cortex. Interestingly, the anterior cingulate cortex has been consistently implicated in human PET studies of attention (Pardo et al, 1990; Posner et al, 1988;

Posner and Petersen, 1990; Petersen et al, 1989), particularly divided attention (Corbetta et al, 1991) and lesion data suggest that the anterior cingulate plays an important role in aspects of attention such as neglect (Mesulam, 1981). It should also be borne in mind that the regions where cannabinoid receptors occur may have long projections to other areas, contributing to the multiplicity of effects of the cannabinoids.

Since THC is not a naturally occurring substance within the brain, the existence of a cannabinoid receptor suggested the existence of an endogenous cannabinoid-like substance. Devane and colleagues (1992) recently identified a brain molecule which binds to the receptor and mimics the action of cannabinoids. The molecule, arachidonylethanolamide, which is fat soluble like THC, has been named "anandamide" from a Sanskrit word meaning "bliss". Anandamide has been found to act on cells that express the cannabinoid receptor, but has no effect on identical cells which lack the receptor. Research has established that anandamide exhibits the essential criteria to be classified as a genuine neurotransmitter for the cannabinoid receptor (Felder et al, 1993; Vogel et al, 1993). Further research is necessary to determine which neurons are responsible for producing anandamide molecules and to determine their role.

The unique psychoactivity of cannabinoids may be described as a composite of numerous effects which would not arise from a single biochemical alteration, but rather from multiple actions (Martin, 1986). Thus, the diverse pharmacological actions of the various cannabinoids implies the existence of receptor subtypes. Cannabinoid receptor cDNA can be used to search for other members of the hypothesised receptor family (Snyder, 1990). If the receptors with the potential for mediating the therapeutic uses of cannabis are different from those responsible for their psychoactive effects, cannabinoid receptor cDNA cloning and new synthetic cannabinoids modelled on anandamide may help to uncover the receptor subtypes and develop drugs to target them, thus fulfilling the ancient promise of "marijuana as medicine". However, if it were the case that there

was only one type of cannabinoid receptor, then the psychoactive and therapeutic effects would be inseparable. The evidence against this proposition mounts with the recent cloning of a receptor in spleen that does not exist in brain (Munro, Thomas and Abu-Shaar, 1993).

2.2 Forms of cannabis

The concentration of THC varies with the forms in which cannabis is prepared for ingestion, the most common of which are marijuana, hashish and hash oil. Marijuana is prepared from the dried flowering tops and leaves of the harvested plant. Its potency depends upon the growing conditions, the genetic characteristics of the plant and the proportions of plant matter. The flowering tops and bracts (known as "heads") are highest in THC concentration, with potency descending through the upper leaves, lower leaves, stems and seeds. Some varieties of the cannabis plant contain little or no THC, such as the hemp varieties used for making rope, while others have been specifically cultivated for their high THC content, such as "sinsemilla".

Marijuana may range in colour from green to grey or brown, depending on the variety and where it was grown, and in texture from a dry powder or finely divided tea-like substance to a dry leafy material. The concentration of THC in a batch of marijuana containing mostly leaves and stems may range from 0.5% to 5%, while the "sinsemilla" variety with "heads" may result in concentrations from 7% to 14%. The potency of marijuana preparations being sold has probably increased in the past decade (Jones, 1987), although the evidence for this has been contested (Mikuriya and Aldrich, 1988).

Hashish or "hash" consists of dried cannabis resin and compressed flowers. It ranges in colour from light blonde/brown to almost black, and is usually sold in the form

of hard chunks or cubes. The concentration of THC in hashish generally ranges from 2% to 8%, although it can be as high as 10% to 20%. Hash oil is a highly potent and viscous substance obtained by using an organic solvent to extract THC from hashish (or marijuana), concentrating the filtered extract, and, in some cases, subjecting it to further purification. The colour may range from clear to pale yellow/green, through brown to black. The concentration of the THC in hash oil is generally between 15% and 50%, although samples as high as 70% have been detected.

2.3 Routes of administration

Almost all possible routes of administration have been used, but by far the most common method is smoking (inhaling). Marijuana is most often smoked as a hand-rolled "joint", the size of a cigarette or larger and often thicker. Tobacco is often added to marijuana to assist burning and "make it go further", and a filter may be inserted. Hashish may be mixed with tobacco and smoked as a joint, but is more often smoked through a pipe, either with or without tobacco. A water pipe known as "bong" is a popular implement for all cannabis preparations because the water cools the hot smoke before it is inhaled and there is little loss of the drug through sidestream smoke. Hash oil is used sparingly because of its extremely high psychoactive potency; a few drops may be applied to a cigarette or a joint, to the mixture in the pipe, or the oil may be heated and the vapours inhaled. Whatever method is used, smokers inhale deeply and hold their breath for several seconds in order to ensure maximum absorption of THC by the lungs.

Hashish or marijuana may also be baked in foods and eaten. When ingested orally the onset of the psychoactive effects is delayed by about an hour. In clinical and experimental research, THC has often been prepared in gelatine capsules and

administered orally. In India, a popular method of ingestion is in the form of a tea-like brew of the leaves and stems, known as "bhang". The "high" is of lesser intensity but the duration of intoxication is longer by several hours. It is easier to titrate the dose and achieve the desired level of intoxication by smoking than ingestion since the effects are more immediate.

Crude aqueous extracts of cannabis have on very rare occasions been injected intravenously. THC is insoluble in water, and so little or no drug is actually present in these extracts, and the injection of tiny undissolved particles may cause severe pain and inflammation at the site of injection and a variety of toxic systemic effects. Injection of cannabis is ineffective as a route of cannabis administration, but has been used for administering THC extract in research to investigate pharmacokinetics.

Different routes of administration give rise to differing pharmacokinetics. For the remainder of this thesis the reader may assume that the method of ingestion is by smoking unless explicitly stated otherwise.

2.4 Dosage

A typical joint contains between 0.5 and 1.0 g of cannabis plant matter, which varies in THC content between 5 and 150 mg (i.e. typically between 1% and 15% THC). Not all of the available THC is ingested; the actual amount of THC delivered in the smoke has been estimated at 20 to 70% of that in the cigarette (Hawks, 1982), with the rest being lost through combustion or escaping in sidestream smoke. The bioavailability of THC from marijuana cigarettes (the fraction of THC in the cigarette which reaches the bloodstream) has been reported to range between 5% and 24% (mean 18.6%) (Ohlsson et al, 1980). For all these reasons, the actual dose of THC that is

absorbed when cannabis is smoked is not easily estimated.

In general, only a small amount of smoked cannabis (e.g. 2 to 3 mg of available THC) is required to produce a brief pleasurable high for the occasional user, and a single joint may be sufficient for two or three individuals. A heavy smoker may consume five or more joints per day, while heavy users in Jamaica, for example, may consume up to 420 mg THC per day (Ghodse, 1986). In clinical trials designed to assess the therapeutic potential of THC, single doses have ranged up to 20 mg in capsule form. In human experimental research, THC doses of 10, 20 and 25 mg have been administered as low, medium and high doses (Barnett et al 1985; Perez-Reyes et al 1982).

Perez-Reyes et al (1974) determined the amount of THC required to produce the desired effects by slow intravenous administration. They estimated that the threshold for perception of an effect was 1.5 mg (i.e. the dose delivered averaged 21 ng/kg), while a peak social "high" required 2-3 mg THC (an average of 37 ng/kg). These levels did not differ between frequent and infrequent users so Perez-Reyes et al concluded that tolerance or sensitivity to the perceived high does not develop.

2.5 Patterns of Use

Cannabis is the most widely used illicit drug in Australia, having been tried by a third of the adult population, and by the majority of young adults between the ages of 18 and 25 (Donnelly and Hall, 1993). The most common route of administration is by smoking, and the most widely used form of the drug is marijuana.

The majority of cannabis use is "experimental". That is, most users use the drug on a small number of occasions. Most of those who have tried cannabis either

discontinue their use after a small number of occasions, or if they continue to use, do so intermittently and episodically whenever the drug is available. Only a very small proportion of those who ever use cannabis become regular cannabis users. The best estimate from the available survey data is that about 10% of those who ever use cannabis become daily users, and a further 20% to 30% use on a weekly basis (Queensland Criminal Justice Commission, 1993; Donnelly and Hall, 1993). Among those who continue to use cannabis, the majority discontinue their use in their mid to late 20s.

Because of uncertainties about the dose of THC contained in illicit marijuana, there is no information on the amount of THC ingested by regular Australian cannabis users. "Heavy" cannabis use is typically defined in terms of the frequency of use rather than average dose of THC received. Daily or near daily use probably places users at greatest risk of experiencing negative long term health and psychological consequences. Such users are more likely to be male and less well educated, and are more likely to regularly consume alcohol, and to have experimented with a variety of other illicit drugs, such as, amphetamines, hallucinogens, psychostimulants, sedatives and opioids.

2.6 Metabolism of cannabinoids

"Cannabinoids" is the collective term for a variety of compounds which can be extracted from the cannabis plant or are produced within the body after ingestion and metabolism of cannabis. Some of these compounds are psychoactive, that is, they have an effect upon the mind of the users; others are pharmacologically or biologically active, that is, have an effect upon cells or the function of other bodily tissues and organs but are not psychoactive. Animal and human experimentation indicates that delta-9-tetrahydrocannabinol (THC) is the major psychoactive constituent of cannabis.

THC is rapidly and extensively metabolised in humans. Different methods of ingesting cannabis give rise to different patterns of absorption, metabolism and excretion of THC. Upon inhalation, THC is absorbed within minutes from the lungs into the bloodstream. Absorption of THC is much slower after oral administration, entering the bloodstream within 1 to 3 hours, and delaying the onset of psychoactive effects.

After smoking, the initial metabolism of THC takes place in the lungs, followed by more extensive metabolism by liver enzymes which transform THC to a number of metabolites. The most rapidly produced metabolite is 9-carboxy-THC (or THC-COOH) which is detectable in blood within minutes of smoking cannabis. It is not psychoactive. Another major metabolite of THC is 11-hydroxy-THC, which is approximately 20% more potent than THC, and which penetrates the blood-brain barrier more rapidly than THC. 11-hydroxy-THC is only present at very low concentrations in the blood after smoking, but at high concentrations after the oral route (Hawks, 1982). THC and its hydroxylated metabolites account for most of the psychoactive effects of the cannabinoids.

Peak blood levels of THC are reached very rapidly, usually within 10 minutes of smoking and before the joint is fully smoked, and decline rapidly to about 5% to 10% of their initial level within the first hour. This initial rapid decline reflects the rapid conversion of THC to its metabolites, as well as the distribution of THC to lipid-rich tissues, including the brain (Fehr and Kalant, 1983; Jones, 1980; 1987). THC and its metabolites are highly fat soluble and may remain for long periods of time in the fatty tissues of the body from which they are slowly released back into the bloodstream. This phenomenon slows the elimination of cannabinoids from the body.

The time required to clear half of the administered dose of THC from the body has been found to be shorter for experienced or daily users (19 to 27 hours) than for

inexperienced users (50 to 57 hours) (Agurell, et al 1986; Hunt and Jones, 1980; Lemberger et al, 1970; 1978; Ohlsson, et al, 1980). Recent research using more sensitive detection techniques suggests that the half-life in chronic users may be closer to 3 to 5 days (Johansson et al, 1988). It is the immediate and subsequent metabolism of THC that occurs more rapidly in experienced users (Blum, 1984). Given the slow clearance, repeated administration of cannabis results in the accumulation of THC and its metabolites in the body. Because of its slow release from fatty tissues into the bloodstream, THC and its metabolites may be detectable in blood for several days, and traces may persist for several weeks.

While blood levels of THC peak within a few minutes, 9-carboxy-THC levels peak approximately 20 minutes after commencing smoking and then decline slowly. The elimination curve for THC crosses the 9-carboxy-THC curve around the time of the peak of the latter and subjective intoxication also peaks around this time (i.e. 20 to 30 minutes later than peak THC blood levels), with acute effects persisting for approximately 2 to 3 hours.

2.7 Detection of cannabinoids in body fluids

Cannabinoid levels in the body, which depend on both the dose given and the smoking history of the individual, are subject to substantial individual variability. Plasma levels of THC in humans may range between 0-500 ng/ml, depending on the potency of the cannabis ingested and the time since smoking. For example, blood levels of THC may decline to 2 ng/ml one hour after smoking a low potency cannabis cigarette, a level that may be achieved only 9 hours after smoking a high potency cannabis cigarette. In habitual and chronic users such levels may persist for several days after use because of the slow release of accumulated THC.

The detection of THC in blood above 10-15 ng/ml provides presumptive evidence of "recent" consumption of cannabis but it is not possible to determine how recently it was consumed. A somewhat more precise estimate of the time of consumption may be obtained from the ratio of THC to 9-carboxy-THC: similar concentrations of each in blood could be an indication of use within the last 20 to 40 minutes, and would predict a high probability of the user being intoxicated. When the levels of 9-carboxy-THC are substantially higher than those of THC, ingestion can be estimated to have occurred more than half an hour ago (Hawks, 1982; Perez-Reyes et al, 1982). However, such an interpretation is probably only applicable to the naive user who has resting levels of zero. Background levels of cannabinoids (particularly 9-carboxy- THC) in habitual users make the estimation of time of ingestion almost impossible. Since it is very difficult to determine the time of administration from blood concentrations of THC and its metabolites (even if the smoking habits of the individual and the exact dose consumed are known), the results of blood analyses indicate, at best, the "recent" use of cannabis.

Urinary cannabinoid levels provide an even weaker indicator of current cannabis intake. In general, the greater the level of cannabinoid metabolites in urine, the greater the possibility of recent use but again it is impossible to be precise about how "recent" use has been (Hawks, 1982). Only minute traces of THC itself appear in the urine due to its extensive metabolism and most of the administered dose is excreted in the form of metabolites in faeces and urine (Hunt and Jones, 1980). 9-carboxy-THC is detectable in urine within 30 minutes of smoking. This and other metabolites may be present for several days in first time or irregular cannabis users, while frequent users may continue to excrete metabolites for weeks or months after last use because of the accumulation and slow elimination of these compounds (Dackis et al, 1982; Ellis et al, 1985). As with blood levels, there is substantial human variability in the metabolism of THC and no

simple relationship between urinary levels of THC metabolites and time of consumption. Hence, urinalysis results cannot be used to distinguish between use within the last 24 hours and use more than a month ago.

Several studies have examined measures of cannabinoids in fat and saliva. Analyses of human fat biopsies confirm an accumulation of the drug for at least 28 days (Johansson, et al, 1987). Detection of cannabinoids in saliva holds more promise for forensic purposes, since it has the capacity to reduce the time frame of "recent" use from days and weeks to hours (Hawks, 1982; Gross et al 1985; Thompson and Cone, 1987). Salivary THC levels have also been shown to correlate with subjective intoxication and heart rate changes (Menkes, Howard, Spears and Cairns, 1991).

2.8   Intoxication and levels of cannabinoids

Ingestion of cannabis produces a dose related impairment on a wide range of cognitive and behavioural functions. Since there is evidence that cannabis intoxication adversely affects skills required to drive a motor vehicle (see Chapter 3), it would be desirable to have a reliable measure of impairment due to cannabis intoxication that was comparable to the breath test of alcohol intoxication.

While the degree of impairment due to alcohol proved possible to determine from a single blood alcohol estimate, a clear relationship between blood levels of THC or its metabolites and degree of either impairment or subjective intoxication has not been demonstrated (Agurell et al, 1986). The estimation of the degree of intoxication from a single value of blood THC level is difficult, not only because of the time delay between subjective high and blood THC, but also because of large individual variations in the effects experienced at the same blood levels. The difficulty is compounded by the

distribution of THC to body tissues, and its metabolism to other psychoactive compounds.

Blood levels of THC metabolites, such as 11-hydroxy-THC, correlate temporally with subjective effects but are not readily detectable in blood after smoking cannabis, while blood levels of THC correlate only modestly with cannabis intoxication, in part because of its lipid solubility (Barnett, Licko and Thomson, 1985; McBay 1988; Ohlsson et al 1980). The level of intoxication could only realistically be related to the total sum of all the psychoactive cannabinoids present in body fluids and in the brain and various tissues.

Due to large human variability, no realistic limit of cannabinoid levels in blood has been set which can be related to an undesirable level of intoxication. Tolerance also develops to many of the effects of cannabis. Hence, a given dose consumed by a naive individual may produce greater impairment on a task than the same dose consumed by a chronic heavy user. THC may also be active in the nervous system long after it is no longer detectable in the blood so there may be long term subtle effects of cannabis on the cognitive functioning of chronic users even in the unintoxicated state. To date, there is no consistently demonstrated correlation between blood levels of THC and its effect on human mind and performance. Thus, no practical method has been developed as a forensic tool for determining levels of intoxication based on detectable cannabinoids. A consensus conference of forensic toxicologists has concluded that blood concentrations of THC which cause impairment have not been sufficiently established to provide a basis for legal testimony in cases concerning driving a motor vehicle while under the influence (Consensus Report, 1985).

2.9   Passive inhalation

In the United States, urine testing for drug traces and metabolites is increasingly used to identify illicit drug users in the workplace (Hayden, 1991). A technical concern raised by the opponents of this practice has been the possibility of a person having a urine positive for cannabinoids as the result of the passive inhalation of marijuana smoke at a social event immediately prior to the provision of the urine sample. A number of research studies have attempted to determine the relationship between passive inhalation of marijuana smoke and consequent production of urinary cannabinoids (Hayden, 1991).

In one of the first studies on passive inhalation, Perez-Reyes and colleagues (1983) found that nonsmokers who had been confined for over an hour in a very small unventilated space containing the smoke of at least 8 cannabis cigarettes over 3 consecutive days had insignificant amounts of urinary cannabinoids. Law and colleagues (1984) and Mule et al (1988) also showed that passive inhalation produced urinary cannabinoid concentrations well below the detection limit of 20 ng/ml 9-carboxy-THC used in workplace drug screens.

Morland et al (1985) produced urinary cannabinoid levels above 20 ng/ml in nonsmokers but the conditions were extreme, namely, confinement in a space the size of a packing box with exposure to the smoke of 6 cannabis cigarettes. The studies of Cone and colleagues (1986; 1987a, 1987b) confirmed the necessity to apply extreme experimental conditions which they claimed nonsmokers were unlikely to submit themselves to for the long periods of time required to produce urinary metabolites above 20 ng/ml. They also showed that nonsmokers with significant amounts of cannabinoids in their urine experienced the subjective effects of intoxication.

CHAPTER 3

ACUTE EFFECTS OF CANNABIS ON COGNITIVE FUNCTIONING

The acute effects of cannabis on cognitive functioning have been reasonably well researched. The literature, though, is so vast that any attempt to summarise the findings will necessarily be an oversimplification. This review will selectively focus on those aspects of cognitive functioning that are of relevance to the research of this thesis. The substance of this thesis concerns the long term cognitive effects of cannabis and accordingly the review of the chronic literature in Chapter 5 is very thorough. While the premise that knowledge of the acute effects of a drug may provide the basis for research into possible long term consequences of use is reasonable, the acute and chronic effects of a drug need not necessarily be the same (Block, Farinpour and Braverman, 1992; Block and Ghoneim, in press) and can in fact be markedly different (Pomara et al, 1983). Also to be borne in mind is the fact that many factors impinge upon the effects experienced by the user when acutely intoxicated. These include the dose, the mode of administration, the user's prior experiences with the drug, any concurrent drug use, the "set and setting", that is, the complex of user's expectations, attitudes towards drug effects and mood state, and the social environment in which the drug is used (Jaffe, 1985). A number of the effects of cannabis are also subject to the development of tolerance (Jones, 1983) and thus naive users may show a greater decrement in performance than experienced users..

The acute intoxication

The major motive for the widespread recreational use of cannabis is the experience of a subjective "high", an altered state of consciousness which is characterised by emotional changes, such as mild euphoria and relaxation, and by perceptual alterations, such as time distortion, and the intensification of ordinary sensory experiences, such as eating, watching, films, listening to music, and engaging in sex (Jaffe, 1985; Tart, 1970). When used in a social setting, the high is often accompanied by infectious laughter, talkativeness and increased sociability.

Not all the effects of cannabis intoxication are welcomed by users, Some users report unpleasant psychological reactions, ranging from a feeling of anxiety to frank panic reactions, and depressed mood to a fear of going mad (Smith, 1968; Weil, 1970; Thomas, 1993). These effects are most often reported by naive users who are unfamiliar with the effects of cannabis, and by some patients given THC for therapeutic purposes. More experienced users may also report these effects on occasion, especially after the oral ingestion of cannabis when the effects may be more pronounced and of longer duration than those usually experienced after smoking cannabis. If such effects develop they can usually be managed by reassurance and support.

Cognitive changes are usually marked during acute intoxication. These include an impaired short term memory, and a loosening of associations, which make it possible for the user to become lost in pleasant reverie and fantasy, while making it difficult to sustain goal-directed mental activity. Motor skills, reaction time and motor coordination are also affected, so many forms of skilled psychomotor activity are impaired while the user is intoxicated (Jaffe, 1985). As with most recreational drugs, cannabis is valued for effects which remove the user from mundane concerns, produce relaxation, and enhance experiences which would normally interfere with concentration on a skilled task.

Perceptual abilities

A multitude of studies have shown that cannabis disrupts performance on a variety of cognitive and psychomotor tasks. Various mechanisms have been proposed to explain the effects of cannabis on such tasks. Alterations in all sensory modalities and the subjective distortion of space and time perception suggest that sensory and perceptual disturbances may underly many of the functions required to successfully perform complex neuropsychological tests and laboratory tasks used in research. For instance, the perceptual identification of simple geometric figures embedded within complex designs has been shown to be impaired by cannabis (eg. Carlin et al, 1972). Emrich et al (1991) demonstrated a strong cannabis-induced impairment of binocular depth inversion, suggesting that the central nervous system is unable to correct implausible perceptual information during acute intoxication.

The perception of time has been studied using two methods: time production or time estimation. In time production tasks, the subject is asked to indicate when an interval of a duration specified by the experimenter has passed. In time estimation, the subject is asked to estimate the duration of a certain interval of time generated by the experimenter. Both methods have reliably produced significant effects of cannabis on the perception of time, with subjects overestimating the amount of elapsed time in the estimation method (eg. Cappell and Pliner, 1973; Jones and Stone, 1970), and producing shorter than requested intervals with the production method (eg. Chait, Fischman and Schuster, 1985; Tinklenberg et al, 1972; Vachon, Sulkowski and Rich, 1974; Webb et al, 1992; 1993). This indicates that subjects experience time as passing more quickly relative to real time, that is, cannabis increases the subjective time rate.

Attention and task accuracy

The subjective effects of cannabis might be expected to decrease performance in situations where both perceptual accuracy and attention are important. The Digit Symbol Substitution Test, a component of the Wechsler Adult Intelligence Scale, is a speed based task of associative ability which requires subjects to copy symbols which correspond to particular digits. This test has been shown to be consistently disrupted by acute cannabis intoxication (eg. Carlin et al, 1972; Heishman, Stitzer, and Bigelow, 1989; Heishman, Stitzer and Yingling, 1989; Vachon, Sulkowski and Rich, 1974). The results of some studies suggested that heavy users may develop tolerance to the effects of the drug on this task (eg. Chait, Fischman and Schuster, 1985; Jones and Stone, 1970).

Few studies have systematically compared the effects of cannabis with other substances, such as alcohol. An exception is the study by Heishman, Stitzer and Bigelow (1989) who compared performance on the digit symbol substitution test following placebo, two different doses of smoked THC, and two different doses of alcohol. They found stronger dose-related impairment following alcohol than THC, but the two doses of THC were both relatively low (1.3% and 2.7%) and would be unlikely to be differentiated. The impairment due to both THC doses was equivalent to the low dose of alcohol (0.6 g/kg).

The administration of the Stroop Color Word Test, which measures aspects of attention and in particular the ability to inhibit an automatic response, has produced mixed results (eg. Carlin et al, 1972; Hooker and Jones, 1987; Miller, Drew and Kiplinger, 1972), although various versions of the task were employed and a variety of measures analysed.

Braff et al (1981) reported that cannabis impaired the speed of visual information processing in a backward masking task of letter matching. The interval between the target and mask necessary for the conscious registration of the stimulus was longer following cannabis than placebo, and the authors interpreted this finding as a slowed speed of information processing from labile iconic memory to more permanent registration and processing.

Reaction time and motor control

Whilst early in the phase of intoxication (and at low doses), cannabis produces a mild stimulant effect upon the central nervous system, this soon becomes a CNS depression (at moderate to high doses). This general depressant effect might contribute to slowed reaction times, inability to maintain concentration and lapses in attention. This occurs with other CNS depressants such as alcohol, but the large and reliable depressant effects of moderate doses of alcohol, and the relatively inconsistent effects obtained with moderate doses of cannabis suggest that this effect of cannabis is the not the primary mediator of performance changes.

Fine motor control and manual dexterity are generally adversely affected, although simple reaction time may or may not be (Chait and Pierri, 1993). Choice or complex reaction time is more likely to be affected, with reaction time consistently (and sometimes error rate) increasing with the difficulty of the task (eg. Block and Wittenborn, 1984; 1986; Low et al, 1973; Moskowitz, Shea and Burns, 1974).

Sustained and divided attention

Sustained attention, or vigilance, refers to the ability to maintain concentration over an extended period of time, particularly on a task that is relatively simple and boring.

Cannabis has been shown to affect sustained attention on simple visual and auditory tasks of particularly long duration (in excess of 50 minutes), impairing accuracy by increasing the number of errors of omission and commission (eg. Moskowitz and McGlothlin, 1974; Moskowitz, Sharma and McGlothlin, 1972; Sharma and Moskowitz, 1974). No drug effects were found in studies using short versions of less than 10 minutes of the Continuous Performance Test (CPT) (eg. Vachon, Sulkowski and Rich, 1974).

A number of studies have utilised dual or concurrent tasks, where one task requires almost continuous attention, typically tracking, and the other involves the detection of an infrequent stimulus from a variety of sporadically occurring stimuli, often presented in the periphery of vision. These tasks are often referred to as the central and peripheral task respectively, and the paradigm referred to as a dual-task or divided attention paradigm. This paradigm has been one of the most widely studied in the field of research into acute effects of cannabis, possibly due to its presumed relevance to driving-related skills. Performance on such tasks is almost always adversely affected by cannabis, although the effects on the component tasks are not consistent. The number or proportion of peripheral targets missed (MacAvoy and Marks, 1975; Marks and MacAvoy, 1989; Casswell and Marks, 1973a; Moskowitz, Sharma and McGlothlin, 1972), the proportion of hits (Moskowitz, Sharma and McGlothlin, 1972), the number of false alarms (MacAvoy and Marks, 1975; Moskowitz and McGlothlin, 1974), reaction time to peripheral targets (Perez-Reyes et al, 1988; Moskowitz, Hulbert and McGlothlin, 1976) and tracking errors (Barnett, Licko and Thompson, 1985) have all been shown to reflect impaired performance, but no interpretable pattern of decrements has consistently emerged. It seems to be the case that overall performance on divided attention tasks is impaired during cannabis intoxication, and the differences between studies are merely task dependent. There is no consistency either as to whether it is the performance of the central or peripheral task that is mainly affected by cannabis.

Impairments are more likely to be seen in more complex or demanding tasks of divided attention, and complex or choice reaction time tasks.

Driving and flying

A major societal concern about cannabis intoxication is its potential to impair psychomotor performance in ways which may directly affect the well-being of nonusers of cannabis. The prototype outcome is an automobile accident caused by a cannabis user driving while intoxicated. It is well known that individuals who drive while intoxicated with alcohol are dangerous to others in proportion to their level of intoxication. Is there evidence that intoxication with cannabis produces impaired psychomotor performance of a nature and degree sufficient to warrant restrictions upon its use by automobile drivers?

There is considerable evidence, as reviewed above, that cannabis intoxication has some negative effects upon performance which become more pronounced with increasing task difficulty. Motor vehicle driving is a complex task, particularly in conditions of heavy traffic or poor road or weather conditions, and as such, might be expected to be adversely affected by cannabis. Simulated driving tasks require skills which are similar to those involved in driving, which can be performed under controlled laboratory conditions. Smiley (1986) critically reviewed the research on the effects of cannabis intoxication on simulated driving. She reported that early studies found less impairment than more recent studies, but that this was due to the unrealistic car dynamics employed. Later studies demonstrated impairments of lane control after cannabis use, but also showed reductions in risk-taking as manifested in slower speeds, and the maintenance of a larger distance from the vehicle in front.

Studies of actual on-road driving performance have been relatively uncommon due to ethical and safety concerns. Generally, such studies have been carried out on a closed

course, although a few have actually been conducted in city traffic (eg. Klonoff, 1974). The measures in such studies have generally been the number of lane-defining markers hit, speed, manoeuvrability, observer ratings and various measures used in actual driving tests. Generally, cannabis has impaired performance more on closed courses than in real traffic, and the mechanism proposed for this phenomenon is an ability of users to compensate for the impairing effects of cannabis in more serious situations (eg. Robbe and O'Hanlon, 1993). Previous experimental evidence suggested also that cannabis users can voluntarily compensate for some of the impairing effects of the drug (eg. Cappell and Pliner, 1973).

The effects of cannabis have also been found to be generally less impairing than those due to alcohol intoxication (Smiley, 1986); for example, cannabis users tend to drive more slowly, whereas those under the influence of alcohol tend to drive faster and more dangerously than normal. However, the few studies that have tested the response of cannabis intoxicated drivers in situations that require emergency decision making have found that this is in fact impaired regardless of the ability to compensate under more normal driving circumstances (Smiley, 1986).

The relatively small impairment of driving skills associated with cannabis intoxication appears to be at odds with the predictions from results of laboratory divided attention tasks. While the combination of performance abilities which is tapped by the typical divided attention task, such as concurrent pursuit tracking and visual discrimination, is plausibly related to driving, the tracking task is usually a much more difficult task than driving under normal conditions. Greater attentional resources must be allocated to the central task in most divided attention tests, for example, leading to a substantial decrease in performance when drugs such as cannabis are ingested. Thus, the findings of laboratory tasks are difficult to extrapolate to actual driving.

The tasks relevant to flying an aircraft have also been investigated in the laboratory using flight simulators, and have generally been found to be impaired by cannabis (Janowsky et al, 1976; Leirer, Yesavage and Morrow, 1989; 1991; Yesavage et al, 1985). The latter two studies found performance to be impaired in experienced pilots for as long as 24 hours after smoking without any subjective awareness of the drug's influence. The impairment in flight simulators appears to be greater than in motor vehicle driving. This may be due to the greater complexity involved in manoeuvring an aircraft, with a greater number of controls to be monitored. It may be that flight simulators are more similar to the laboratory tasks of divided attention.

Memory and higher cognitive functions

"The single, most consistently reported, behavioral effect of cannabinoids in humans is an alteration in memory functioning" (Miller, 1984). Memory is one of the most frequently cited functions to be impaired by cannabis acutely, and numerous studies have investigated the processes of acquisition, storage and retrieval in a variety of tasks. State-dependent effects of cannabis on memory have been demonstrated (eg. Stillman et al, 1974).

One of the simplest measures of short term memory function is the digit span test, in which subjects are required to reproduce increasingly longer strings of digits in the order presented or reversed. The effects of cannabis on this task have been inconsistent but impairment appears to be highly dose-dependent (eg. Casswell and Marks, 1973b; Heishman, Stitzer and Yingling, 1989; Hooker and Jones, 1987; Melges et al, 1970; Tinklenberg et al, 1970).

Similarly, effects on recognition memory have been inconsistent, but generally indicate a greater number of intrusion errors, seen as errors of commission (eg. Abel,

1971a; 1971b; Dornbush, 1974; Miller et al, 1977; Miller and Branconnier, 1983). Almost all studies utilising free recall tasks have demonstrated impairment following cannabis administration. These tasks usually involve the presentation of a list of words (or other items), which the subject must then recall (repeat or write down) either immediately or following some delay. The number of items recalled is invariably fewer, and the next most consistent effect is an increase in the number of intrusion errors (eg. Cappell and Pliner, 1973; Chait, Fischman and Schuster, 1985; Dornbush, 1974; Dornbush, Fink and Freedman, 1971; Miller and Branconnier, 1983; Miller, Cornett and McFarland, 1978; Miller et al, 1977a; 1977b). Intrusion errors are items recalled by subjects which were not present in the original list. Miller and Branconnier (1983) suggested that the mechanism behind the large number of intrusion errors generated by subjects acutely intoxicated with cannabis, may be due to a failure to habituate to irrelevant stimuli which results in an inability to exclude extraneous information. Similarly, the effects of cannabis on the number of errors and out-of-sequence distortions in the recall of prose or narrative material were greater than the effects on the number of factual elements recalled (Hooker and Jones, 1987; Miller, Drew and Kiplinger, 1972). Remote memory of previously learned material does not appear to be affected by cannabis (Dornbush, 1974; Hooker and Jones, 1987). The cumulative data from the studies reviewed above, suggests that particularly under conditions of distraction or interference, cannabis may affect the acquisition of information by dysfunction in the processes of focussing attention and maintaining concentration. Further, cannabis may interfere with the transfer from short to long term memory storage.

A number of other higher cognitive functions are affected by acute cannabis intoxication. Among these is the ability to perform mental arithmetic. This has been examined in a number of studies demonstrating impairment in addition, subtraction, goal-directed serial alternation and numerous other variations (Casswell and Marks,

1973b; Chait and Pierri, 1993; Melges et al, 1970; Tinklenberg et al, 1972). Many of these tasks involve holding some information in memory while manipulating other information. A number of studies have attempted to verify empirically the claim that cannabis can promote creative thought processes and enhance artistic creativity but the results have been equivocal (eg. Carlin et al, 1972). Block and Wittenborn (1984) reported that cannabis decreased the vividness of visual imagery when instructed to use this in a paired-associate learning task, contrary to previous subjective reports that imagery is enhanced by cannabis. More recently, Block, Farinpour and Braverman (1992) reported that cannabis intoxication altered associative processes, encouraging more uncommon associations. This study also compared the acute effects of cannabis on a test battery which assessed learning and memory, abstraction and psychomotor performance, with the chronic effects of cannabis on the same test battery. The acute effects were far more pervasive, but there were some similarities between acute and chronic impairments.

The possibility that cannabis detrimentally affects planning and organisational strategies and a multitude of frontal lobe functions is becoming increasingly apparent in clinical observations (see Chapter 5), but has not been investigated in any rigorous manner.

Cannabis and alcohol

Cannabis is often used in combination with alcohol. Alcohol and cannabis have a number of effects in common although the mechanisms of these actions appear to be different, with the activity of cannabinoids being receptor-mediated (see Chapter 2). Low doses of cannabis and alcohol in combination are perceived to enhance the intoxication (Chesher et al, 1976), while large doses are reported to be aversive (Chesher et al, 1986). Chesher and colleagues (1976; 1977; 1986) studied the effects of orally

administered THC and alcohol and their interaction on psychomotor performance on a

battery of tests. They found that their combination is approximately additive, but at low

doses there is a less than additive effect. After approximately two hours, the effects of

THC alone were more detrimental than were those of THC plus alcohol, suggesting an

antagonism of the effects of THC by alcohol (Chesher et al, 1977). A further study

(Belgrave et al, 1979) found no antagonism when cannabis was administered an hour

earlier than the alcohol , but demonstrated that performance decrements of THC were

slower in onset and lasted longer than those induced by alcohol. Perez-Reyes et al

(1988) administered alcohol prior to smoked cannabis and found that the decrements due

to alcohol in the performance of skills necessary to drive a motor vehicle were

significantly enhanced by cannabis in an additive and possibly synergistic manner. The

prior administration of alcohol did not affect subjective ratings of intoxication, heart rate

acceleration or THC plasma concentrations.

Conclusions

In summary, there is no doubt that cannabis adversely affects the performance of a

number of cognitive and psychomotor tasks, and that the effects are dose-dependent, and

larger, more consistent and persistent in complex and unfamiliar tasks. The acute effects

on performance of doses of cannabis which are comparable to those subjects report

using recreationally, are similar to, if smaller than, those of intoxicating doses of

alcohol.

Most of the studies reviewed above reported that the effects on cognition and

psychomotor performance persisted no longer than four hours, although many did not

measure performance beyond this period. At least two studies have reported dysfunction

to persist for longer, up to 24 hours after smoking in one instance (Barnett, Licko and

Thompson, 1985; Yesavage et al, 1985). Maximal impairment was generally reported to coincide with the peak level of intoxication, approximately 40 minutes after smoking (longer after oral administration of THC). Memory impairment is the most consistently reported effect associated with acute cannabis intoxication. However, the most robust explanation for the mechanism of memory impairment is in reduced attention because of increased competition by the intrusion of irrelevant associations (Miller and Branconnier, 1983).

In recent years, there has been a shift away from further research into the acute effects of cannabis on cognitive functioning, since it is now reasonably well established that cannabis affects a wide range of psychomotor and cognitive tasks at doses that produce moderate levels of intoxication. It has been considered of greater importance to investigate possible long term effects of chronic cannabis use. Nevertheless, the acute effects of cannabis do have practical significance in terms of impaired learning, driving and operating complex machinery whilst intoxicated, and further research might aim to elucidate the mechanisms of impairment with greater specificity. It is beyond the scope of this thesis to evaluate the possible mechanisms of cognitive impairment associated with acute cannabis intoxication, particularly since the acute and chronic effects may be quite different.

CHAPTER 4

EVIDENCE FOR BRAIN DAMAGE ASSOCIATED WITH THE LONG TERM USE OF CANNABIS

A major concern about the recreational use of cannabis has been whether it may lead to functional or structural neurotoxicity, or "brain damage" in ordinary language. Fehr and Kalant (1983) defined neurotoxicity as "functional aberrations qualitatively distinct from the characteristic usual pattern of reversible acute and chronic effects, and that may be caused by identified or identifiable neuronal damage" (p. 27). On this definition an enduring impairment of cognitive functioning may be interpreted as a manifestation of neurotoxicity. This chapter, however, will concentrate on direct investigations of neurological function and structural brain damage arising from exposure to cannabinoids. The review begins with an examination of the evidence for behavioural neurotoxicity from animal studies. Neurochemical, electrophysiological and brain substrate investigations of functionality follow, and the chapter concludes with the findings of more invasive examinations of brain structure and morphology in animals, and of less invasive techniques for imaging the human brain.

4.1 Behavioural neurotoxicity in animals

Animal research provides the ultimate degree of control over extraneous variables; it is possible to eliminate factors known to influence research findings in humans, e.g. nutritional status, age, sex, previous drug history, and concurrent drug use. The results,

however, are often difficult to extrapolate to humans because of between-species differences in brain and behaviour and in drug dose, patterns of use, routes of administration and methods of assessment.

Animal research into the effects of cannabis on brain function has typically administered known quantities of cannabinoids to animals for an extended period of time and then examined performance on various tasks assessing brain function, before using histological and morphometric methods to study the brains of the exposed animals. In general, the results of studies with primates produce results that most closely resemble the likely effects in humans; the monkey is physiologically similar to humans, while rats, for example, metabolise drugs in a different way, and monkeys are able to perform complex behavioural tasks. Nevertheless, every animal species examined to date has been found to have cannabinoid receptors in the brain. In animal models, non-targeted staring into space following administration of cannabinoids is suggestive of psychoactivity comparable to that in humans. The most characteristic responses to cannabinoids in animals are mild behavioural aberrations following small doses, and signs of gross neurotoxicity manifested by tremors and convulsions following excessively large doses. Where small doses are given for a prolonged period of time, evidence of behavioural neurotoxicity has emerged (see Rosenkrantz, 1983). Chronic exposure produces lethargy, sedation and depression in many species, and/or aggressive irritability in monkeys.

A clear manifestation of neurotoxicity in rats, which has been called the "popcorn reaction" (Luthra, Rosenkrantz and Braude, 1976), is a pattern of sudden vertical jumping in rats exposed to cannabinoids for 5 weeks or longer. It is also seen in young animals exposed to cannabinoids in utero and then given a small dose challenge at 30 days of age. Several studies of prenatal exposure indicate that the offspring of cannabis treated animals show small delays in various stages of post-natal development, such as

eye opening, various reflexes and open field exploration, although after several weeks or months their development is indistinguishable from normal (e.g. Fried and Charlebois, 1979). This means that either the developmental delay was not chronic, the remaining damage is too subtle to be detected by available measures, or the "plasticity of nervous system organisation in the newborn permitted adequate compensation for the loss of function of any damaged cells" (Fehr and Kalant, 1983, p. 29).

Behavioural tests in rodents have included conventional and radial arm maze learning, operant behaviour involving time discriminations, open field exploration and two-way shuttle box avoidance learning. Correct performance on these tests is dependent on spatial orientation or on response inhibition, both of which are believed to depend heavily on intact hippocampal functioning. Some studies have found decreased learning ability on such tasks several months after long term treatment with cannabinoids (see Fehr and Kalant, 1983). For example, Stiglick and Kalant (1982a, 1982b) reported altered learning behaviour in rats 1 to 6 months after a 3-month oral dosing regimen of marijuana extract or THC. They claimed that the deficits were reminiscent of behavioural changes seen after damage to the hippocampus. Long lasting impairment of learning ability and hippocampal dysfunction suggests that long-lasting damage may result from exposure to cannabis. However, some studies have been carried out too soon after the final drug administration to exclude the possibility that the observed effects are residual effects, that is, due to the continued action of accumulated cannabinoids.

Memory function in monkeys has often been assessed by delayed matching-to-sample tasks. In a recent study (Slikker et al, 1992), rhesus monkeys were trained for one year to perform 5 operant tasks before one year of chronic administration of cannabis commenced. One group was exposed daily to the smoke of one standard joint, another on weekends only and control groups received sham smoke exposure (N = 15 or 16 per group). Performance on the tasks indicated the induction of an "amotivational

syndrome" during chronic exposure to cannabis as manifested in a decrease in motivation to respond, regardless of whether the monkeys were exposed daily or only on weekends. This led the authors to suggest that motivational problems can occur at relatively low or recreational levels of use (in fact, the effect was maximal with intermittent exposure). Task performance was grossly impaired for more than a week following last exposure, although performance returned to baseline levels two to three months after cessation of use. Thus, the effects of chronic exposure were slowly reversible with no long term behavioural effects. The authors concluded that persistent exposure to compounds that are very slowly cleared from the brain could account for their results. This hypothesis is consistent with the long half life of THC in the body.

One of the problems with studies such as these is that animals are often only exposed for a relatively short period of time, for example, one year or less. Slikker and colleagues acknowledge that it remains to be determined whether longer or greater exposures would cause more severe or additional behavioural effects. It may be that chronic dysfunction becomes manifest only after many years of exposure. Although it is of concern that behavioural impairments have been shown to last for several months after exposure, it is reassuring that they have generally resolved over time.

A further difficulty with animal studies is a consequence of differences between animals and humans in route of cannabinoid administration. In humans, the most common route of exposure to THC is via the inhalation of marijuana smoke whereas most animals studies have relied upon the oral administration or injection of THC because of the difficulty in efficiently delivering smoke to animals and the concern about the complications introduced by carbon monoxide toxicity. While it may well be impossible to evaluate the pharmacological and toxicological consequences of exposure to the hundreds of compounds in cannabis simultaneously, it is arguably inappropriate to assess the long-term consequences of human cannabis smoking by administering THC

alone. Hundreds of additional compounds are produced by pyrolysis when marijuana is smoked, which may contribute either to acute effects or to long-term toxicity. Future studies need to address these issues for comparability to human usage. Appropriate controls, including those which mimic the carbon monoxide exposure experienced during the smoking of marijuana may be necessary.

4.2 Neurochemistry

The discovery of the cannabinoid receptor and its endogenous ligand anandamide revolutionized previous conceptions of the mode of action of the cannabinoids. However, much further research is required before the interactions between ingested cannabis, anandamide and the cannabinoid receptor are fully understood. Nor should the anandamide pathways be seen as responsible for all of the central effects of the psychoactive cannabinoids. There is good evidence that cannabinoids affect the concentration, turnover, or release of endogenous substances (Pertwee, 1988). Much research has been devoted to examining the interactions between cannabinoids and several neurotransmitter receptor systems (e.g. norepinephrine, dopamine, 5-hydroxytryptamine, acetylcholine, gamma-aminobutyric acid (GABA), histamine, opioid peptides, and prostaglandins). The results suggest that all these substances have some role in the neuropharmacology of cannabinoids, although little is known about the precise nature of this involvement. Cannabinoids may alter the activities of neurochemical systems in the central nervous system by altering the synaptic concentrations of these mediators through an effect on their synthesis, release, or metabolism, and/or by modulating mediator-receptor interactions. There have been numerous reports of neurotransmitter perturbations in vitro and after short-term administration (Martin, 1986; Pertwee, 1988).

Domino (1981) demonstrated in cats that large doses of THC elevate brain acetylcholine and reduce its turnover by producing a decrease in acetylcholine release from the neocortex. At large doses, THC may depress the brain stem activating system. With lower doses, brain acetylcholine utilisation was reduced primarily only in the hippocampus. Some of the potential undesirable side effects of cannabinoids may be related to a decrease in acetylcholine release and turnover. Domino also reported that THC decreased EEG activation and induced slow wave activity: high voltage slow waves in neocortical EEG were produced in frontal regions and tended to be exaggerated by small doses but reduced by larger doses. These findings support the general observation made in a variety of studies, that low doses of THC stimulate while high doses depress the noradrenergic and dopaminergic system.

Bloom (1984) reported that cannabinoids increase the synthesis and turnover of dopamine and norepinephrine in rat and mouse brain while producing little or no change in endogenous levels of catecholamines. However, THC and other cannabinoids were reported to alter functional aspects of catecholaminergic neurotransmission. THC was found to increase the utilisation of the catecholamine neurotransmitters, to alter the active uptake of biogenic amine neurotransmitters and their precursors into synaptosomes, and to alter transmitter release from synaptosomes. Further, THC was reported to alter the activity of enzymes involved in the synthesis and degradation of the catecholamines. THC and other cannabinoids can selectively alter the binding of ligands to several different membrane bound neurotransmitter receptors.

Relatively few studies have examined whether long-term exposure to cannabinoids results in lasting changes in brain neurotransmitter and neuromodulator levels. An early study examined cerebral and cerebellar neurochemical changes accompanying behavioural manifestations of neurotoxicity (involuntary vertical jumping) in rats exposed to marijuana smoke for up to 87 days (Luthra, Rosenkrantz and Braude, 1976).

Sex differences emerged in the neurochemical consequences of chronic exposure: in females, AChE showed a cyclic increase and cerebellar enzyme activity declined. For both sexes, cerebellar RNA increased, but at different times for each sex, and at 87 days remained elevated only in females. Some of these neurochemical changes persisted during a 20 day recovery period, but the authors predicted the return to normality after a much longer recovery period. Cannabinoids administered prenatally not only impaired developmental processes in rats but produced significant decrements in RNA, DNA and protein concentrations and reductions in amine concentrations (dopamine, norepinephrine) in mice, which could be important in the role of protein and nucleic acids in learning and memory (see Fehr and Kalant, 1983). Bloom (1984) reported that chronic exposure to cannabinoids has been shown to lead to increased activity of tyrosine in rat brain.

However, recent evidence suggests that there are few, if any, irreversible effects of THC on known brain chemistry. Ali and colleagues (1989) administered various doses of THC to rats for 90 days and then assessed several brain neurotransmitter systems 24 hours or 2 months after the last drug dose. Examination of dopamine, serotonin, acetylcholine, GABA, benzodiazepine and opioid neurotransmitter systems revealed that no significant changes occurred. A larger study with both rats and monkeys examined receptor binding of the above neurotransmitters and the tissue levels of monoamines and their metabolites (Ali et al, 1991). No significant irreversible changes were demonstrated in the rats chronically treated with THC. Monkeys exposed to a chronic treatment of marijuana smoke for one year and then sacrificed after a 7 month recovery period were found to have no changes in neurotransmitter concentration in caudate, frontal cortex, hypothalamus, or brainstem regions. The authors concluded that there are no significant irreversible alterations in major neuromodulator pathways in the rat and monkey brain following long-term exposure to the active compounds in marijuana.

Slikker et al (1992), reporting on the same series of studies, noted that there were virtually no differences between placebo, low dose or high dose groups of monkeys in blood chemistry values. The general health of the monkeys was unaffected but the exposure served as a chronic physiological stressor evidenced by increases in urinary cortisol levels which were not subject to tolerance (although plasma cortisol levels did not differ). Urinary cortisol elevation has not been demonstrated in other studies with monkeys. Slikker et al reported a 50% reduction in circulating testosterone levels in the high dosed group with a nonsignificant rebound 1-4 weeks post cessation of treatment. It is worthy to note that these monkeys were 3 years of age at the commencement of the study and would have experienced hormonal changes over the course of entering adolescence during the study.

A recent pilot study compared monoamine levels in cerebrospinal fluid (CSF) in a small sample of human cannabis users and age and sex-matched normal controls (Musselman et al, 1993). The justification for the study was that THC administered to animals has been shown to produce increases in serotonin and decreases in dopamine activity. No differences were found between the user and nonuser groups in the CSF concentration of HVA, 5HIAA, MHPG, ACTH and CRH. The authors proposed a number of explanations for these results: 1) cannabis use has no chronic effect on levels of brain monoamines; 2) those who use cannabis have abnormal levels of brain monoamines which are normalised over long periods of time by cannabis use; or 3) those who use cannabis have normal levels of brain monoamines which are transiently altered with cannabis use and then return to normal. However, there is insufficient data in this study to permit a choice between these hypotheses to be made. The frequency and duration of cannabis use, and the time since last use in the user group could not be determined. All users had denied using cannabis, having been drawn from a larger normative sample and identified as cannabis users by the detection of substantial levels of cannabinoids in urine screens. Furthermore, the "normal" controls were assumed to

be nonusers on the basis of their drug free urines, a far from adequate source of evidence for or against cannabis use. Thus, the small sample size and faulty methodology preclude any conclusions to be drawn from this study about possible alterations in monoamine levels in cannabis users.

4.3 Electrophysiological effects

Cannabis is clearly capable of causing marked changes in brain electrophysiology as determined by electroencephalographic (EEG) recordings. Long-term residual abnormalities in EEG tracings from cortex and hippocampus have been shown in cats (Barratt & Adams, 1972; 1973; Domino, 1981; Hockman et al, 1971), rats (see Fehr and Kalant, 1983b) and monkeys (Adams and Barratt, 1975; Harper, Myers and Heath, 1977; Heath et al, 1980) exposed to cannabinoids. Some sleep EEG abnormalities, such as a decrease in slow wave sleep, were also observed. Stadnicki et al (1974) demonstrated increased EEG synchrony and high voltage slow wave activity in the occipital cortex, amygdala, septum and hippocampus of implanted rhesus monkeys following several days administration of oral THC, but tolerance developed to these EEG effects. Withdrawal effects are sometimes apparent in the EEG (Fehr and Kalant, 1983b) with epileptiform and spike-like activity seen most often.

Shannon and Fried (1972) related EEG changes in rat to the distribution of bound and unbound radioactive THC. Disposition of the tracer was primarily in the extra-pyramidal motor system and some limbic structures and 0.8% of the total injected drug which was weakly bound in the brain accounted for the EEG changes. In monkeys, serious subcortical EEG anomalies were observed in monkeys exposed to marijuana smoke for 6 months (Heath et al, 1980). The septal region, hippocampus and amygdala were most profoundly affected, showing bursts of high amplitude spindles and slow

wave activity. Such early studies often lacked critical quantitative analysis. The definition of abnormal spike-like waveforms in EEG were not made to rigorous criteria and EEG frequency was not assessed quantitatively.

More recent studies have examined the effects of THC on extracellular action potentials recorded from the dentate gyrus of the rat hippocampus (Campbell et al, 1986a; 1986b). THC produced a suppression of cell firing patterns and a decrease in the amplitude of sensory-evoked potentials, also impairing performance on a tone discrimination task. The evoked-potential changes recovered rapidly (within 4 hours), but the spontaneous and tone-evoked cellular activity remained significantly depressed, indicating an abnormal state of hippocampal/limbic system operation. The authors proposed that such changes accounted for decreased learning, memory function and general cognitive performance following exposure to cannabis. The long-lasting effects of prolonged cannabis administration on animal electrophysiology has not been investigated to any degree of specificity.

The waking or sleep EEG is increasingly recognised as a particularly sensitive tool for evaluating the effects of drugs in humans, especially drugs that affect the CNS, since EEG signals are sensitive to variables affecting the brain's neurophysiological substrate. The recording of the EEG is one of the few reasonably direct, nonintrusive methods of monitoring CNS activity in man. However, alterations in EEG activity are difficult to interpret in a functional sense. Struve and Straumanis (1990) provide a review of the human research dating from 1945 on the EEG and evoked potential studies of acute and chronic effects of cannabis use. While the data have often been contradictory, the most typical human alterations in EEG patterns include an increase in alpha activity and a slowing of alpha waves with decreased peak frequency of the alpha rhythm, and a decrease in beta activity (Fink, 1976a; Fink et al, 1976; Heath, 1972; Rodin, et al, 1970; Volavka et al, 1977). In general, this is consistent with a state of drowsiness.

Desynchronization, variable changes in theta activity, abnormal sleep EEG profiles and abnormal evoked responses have also been reported (Fehr and Kalant, 1983). Cannabis has been reported to reduce the duration of REM sleep (Feinberg et al, 1976; Jones, 1980), although this may only occur early in administration studies, followed by a resolution and then an increase in REM sleep above baseline levels as smoking continues (Kales et al, 1972).

Campbell (1971) compared EEG abnormalities observed in chronic cannabis users who had developed psychotic reactions, to the EEG patterns of schizophrenics, neurological patients and nonproblematic cannabis users, and claimed that the incidence of EEG abnormalities was higher in the two groups of cannabis users than in either patient sample. These included excess sharp and theta activity, severe dysrhythmia, and epileptiform spikes in frontal and temporal regions. In contrast, Dornbush et al (1972) reported increased EEG alpha activity in the intoxicated state, but no persistent changes following 21 day administration of cannabis to human volunteers. Koukkou and Lehman (1976; 1977) examined EEG frequency spectra during self reported THC induced hallucinations and found slower alpha and more theta. Subjects with a high tendency toward cannabis induced experiences exhibited resting spectra both before and after THC injection with higher modal alpha frequencies, reminiscent of subjects with high neuroticism scores, than subjects with a low tendency. Fink and colleagues suggested that the acute effects of cannabis on EEG are similar to those of anticholinergics, but differ to those of opiates and hallucinogens. Jones (1975) reviews the data on EEG characteristics of over 200 marijuana users from a number of studies, mostly during acute intoxication and reports very few EEG abnormalities being detected in those studies that were well controlled.

Clinical reports have associated cannabis with triggering seizures in epileptics (Feeney, 1979) and experimental studies have shown THC to trigger abnormal spike

waveforms in the hippocampus, whereas cannabidiol has an opposite effect. Yet there is suggestive evidence that cannabis may be useful in the treatment of convulsions. Feeney (1979) discusses these paradoxical effects.

A number of studies have investigated EEG in chronic cannabis users. The early cross-cultural studies were flawed in many respects (see Chapter 5) and also failed to used quantitative techniques in analysing EEG spectra. No EEG abnormalities were found in the resting EEG of chronic users from Greek, Jamaican or Costa Rican populations compared to controls (Karacan et al, 1976; Rubin and Comitas, 1975; Stefanis, 1976). In all of these studies, only subjects who were in good health and who were functioning adequately in the community were selected, thereby systematically eliminating subjects who may have been adversely affected by cannabis use and who may therefore have shown residual EEG changes.

The evidence from many studies has been contradictory: users have been found to show either higher or lower percentages of alpha-components than nonusers, and to have higher or lower visual evoked response amplitudes (Cohen, 1976; Deliyannakis, Panagopoulos and Huott, 1970; Richmon et al, 1974). Subjects in a 94 day cannabis administration study (Cohen, 1976) showed lasting EEG changes. The abnormalities were more marked in subjects who had taken heavier doses, but it was observed that even in abstinence, cannabis users had more EEG irregularities than nonusing controls. It was not determined for how long after cessation of use the EEG changes persisted. In general, most EEG studies produced equivocal results which may have been more consistent had quantitative methods been employed (many early studies relied on visual inspection, but by the mid 1970s power spectral analyses were sometimes being performed).

It has also been reported that chronic users develop tolerance to some of the acute

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EEG changes caused by cannabis (Feinberg et al, 1976). Fried (1977) reviewed the literature pertinent to the development of tolerance to EEG effects in animals and humans, which again produced many inconsistent effects. The question as to why chronic cannabis users can continue to display changes in EEG when tolerance is known to develop to such alterations remains unanswered.

In a series of well controlled ongoing studies, Struve and colleagues (1991, 1993) have been using quantitative techniques to investigate persistent EEG changes in long-term cannabis users, characterised by a "hyperfrontality of alpha". Significant increases in absolute power, relative power and interhemispheric coherence of EEG alpha activity over the bilateral frontal-central cortex in daily THC users compared to nonusers was demonstrated and replicated several times. The quantitative EEGs of subjects with very long cumulative THC exposures (> 15 years) appear to be characterised by increases in frontal-central theta activity in addition to the hyperfrontality of alpha found in THC users in general (or those with much shorter durations of use). These very long term users have shown significant elevations of theta absolute power over frontal-central cortex compared to short term users and controls, and significant elevations in relative power of frontal-central theta in comparison to short term users. Over most cortical regions, ultra-long term users had significantly higher levels of theta interhemispheric coherence than short term users or controls. Thus, excessively long duration of THC exposure (15-30 years) appears to be associated with additional topographic quantitative EEG features not seen with subjects using THC for short to moderately long time periods.

These findings have led to the suspicion that there may be a gradient of quantitative EEG change associated with progressive increases in the total cumulative exposure (duration in years) of daily THC use. Infrequent, sporadic or occasional THC use does

not seem to be associated with persistent quantitative EEG change. As daily THC use begins and continues, the topographic quantitative EEG becomes characterised by the hyperfrontality of alpha. While it is not known at what point during cumulative exposure it occurs, at some stage substantial durations of daily THC use become associated with a downward shift in maximal EEG spectral power from the mid alpha range to the upper theta/low alpha range. Excessively long duration cumulative exposure of 15-30 years may be associated with increases of absolute power, relative power and coherence of theta activity over frontal-central cortex. One conjecture is that the EEG shift toward theta frequencies, if confirmed, may suggest organic change. These data are supplemented by neuropsychological test performance features separating long-term users from moderate users and nonusers (see Chapter 5), however the relationship between neuropsychological test performance and EEG changes has not yet been investigated (Struve, personal communication).

While the EEG provides little interpretable information about brain function, brain event-related potential measures are direct electrophysiological markers of cognitive processes. Relatively few studies have utilised event-related potential measures in research into the chronic effects of cannabis. Studies by Herning and colleagues (1979) demonstrated that THC administered orally to volunteers alters event-related potentials according to dose, duration of administration, and the complexity of the task. Event-related potential studies are reviewed in Chapter 6.

4.4 Cerebral blood flow studies

Brain cerebral blood flow (CBF) is closely related to brain function. The use of CBF may help to identify brain regions responsible for the behavioural changes associated with drug intoxication. However, since psychoactive drugs may induce CBF

changes through mechanisms other than alteration in brain function (e.g. by increasing carbon monoxide levels, changing blood gases or vasoactive properties, affecting blood viscosity, autonomic activation or inhibition of intraparenchymal innervation, acting on vasoactive neuropeptides), any conclusions drawn from drug-induced CBF changes must be treated with caution.

Mathew and Wilson (1992) report several studies of the effects of cannabis on cerebral blood flow. Acute cannabis intoxication in inexperienced users produced a global CBF decrease, whereas in experienced users CBF increased in both hemispheres but primarily at frontal and left temporal regions. There was an inverse relationship between anxiety and CBF. The authors attributed the decrease in CBF in naive subjects to their increased anxiety after cannabis administration, while the increased CBF in experienced users was attributed to the behavioural effects of cannabis. A further study showed that the largest increases in CBF occurred 30 minutes after smoking. The authors concluded that cannabis causes a dose related increase in global CBF, but also appears to have regional effects, with a greater increase in the frontal region and in particular in the right hemisphere. CBF increases were correlated with the "high", plasma THC levels and pulse rate, loss of time sense, depersonalisation, anxiety and somatization scores (positively with frontal flow and inversely with parietal flow).

The authors claimed their results suggested that altered brain function was mainly, if not exclusively, responsible for the CBF changes. Carbon monoxide increased after both cannabis and placebo but did not correlate with CBF. Cannabis induced "red eye" lasted for several hours, but the CBF increases declined significantly within 2 hours of smoking. Nevertheless, the possibility remains that the CBF changes reflected drug-induced vascular (cerebral) change. Continued reduction in cerebral blood velocity was demonstrated following cannabis administration, and reports of dizziness but with normal blood pressure suggested that cannabis may impair cerebral autoregulation.

The time course of CBF changes resembled that of mood changes more closely than plasma THC levels. Global CBF was closely related to levels of arousal mediated by the reticular activating system. High arousal states generally show CBF increases while low arousal states show CBF decreases. Of all cortical regions, the frontal lobe has the most intimate connections with the thalamus which mediates arousal, and CBF increases after cannabis use were most pronounced in frontal lobe regions. The right hemisphere is generally associated with the mediation of emotions and the most marked changes after cannabis were seen there. Time sense and depersonalisation which are associated with the temporal lobe were severely affected but there were no significant correlations between these scores and temporal flow. CBF techniques are probably not sensitive enough in terms of spatial resolution to detect such effects and may well be limited to superficial layers of cortex. The parietal lobes are associated with perception and cognition. Cannabis reduces perceptual acuity, but during intoxication subjects report increased awareness of tactile, visual and auditory stimuli. It is possible that their altered time sense and depersonalisation is related to such altered awareness.

There have been a few investigations of chronic effects of cannabis on CBF. Tunving et al, (1986) demonstrated globally reduced resting levels of CBF in chronic heavy users of 10 years compared to nonuser controls, but no regional flow differences were observed. CBF increased by 12% between 9 and 60 days later, indicating reduced CBF in heavy users immediately after cessation of cannabis use with a return to normal levels with abstinence. This study was flawed in that some subjects were given benzodiazepines, which are known to lower CBF, prior to the first measurement. Mathew and colleagues (1986) assessed chronic users of at least 6 months (mean 83 months) after two weeks of abstinence. No differences in CBF levels were found between users and non-user controls. The number of studies available on the effects of cannabis on CBF are relatively small. Use of techniques with better spatial resolution

and the ability to quantify subcortical flow, such as positron emission tomography (PET), would yield more useful findings.

4.5 Positron emission tomography (PET) studies

Positron emission tomography (PET) is a nuclear imaging technique which allows the concentration of a positron-labelled tracer to be imaged in the human brain. PET can measure the regional distribution of positron-labelled compounds in the living human brain, and to some extent their time course. Some PET studies have labelled oxygen and measured blood flow, while many others have utilised an analog of glucose to measure regional brain glucose metabolism; nervous tissue uses glucose as its main source of energy. Measurement of glucose metabolism reflects brain function since activation of a given brain area is indicated by an increase in glucose consumption. PET may be used to assess the effects of acute drug administration by using regional brain glucose metabolism to determine the areas of the brain which are activated by a given drug. Assessment of brain glucose metabolism has been useful in identifying patterns of brain dysfunction in patients with psychiatric and neurological diseases. It is a direct and sensitive technique for identifying brain pathology since it can detect abnormalities in the functioning of brain regions in the absence of structural changes, such as is likely to occur with the neurotoxic effects of chronic drug use. It is accordingly more sensitive than either computer-assisted tomography (CAT) scans or magnetic resonance imaging (MRI) in detecting early pathological changes in the brain.

Only one study to date has used the PET technique to investigate the effects of cannabis use. Volkow et al (1991) reported preliminary data from an investigation comparing the acute effects of cannabis in 3 control subjects (who had used cannabis no more than once or twice per year) and in 3 chronic users (who had used at least twice a

week for at least ten years). The regions of interest were the prefrontal cortex, the left and right dorsolateral, temporal, and somatosensory parietal cortices, the occipital cortex, basal ganglia, thalamus and cerebellum. A measure of global brain metabolism was obtained using the average for the 5 central brain slices, and relative measures for each region were obtained using the ratios of region/global brain metabolism. Due to the small number of subjects, descriptive rather than inferential statistical procedures were used for comparison. The relation between changes in metabolism due to cannabis and the subjective sense of intoxication was tested with a regression analysis.

In the control subjects, administration of cannabis led to an increase in metabolic activity in the prefrontal cortex and cerebellum; the largest relative increase was in the cerebellum and the largest relative decrease was in the occipital cortex. The degree of increase in metabolism in the cerebellar cortex was highly correlated with the subjective sense of intoxication. The cannabis users reported less subjective effects than the controls and showed less changes in regional brain metabolism, reflecting tolerance to the actions of cannabis. However, the authors did not report comparisons of baseline levels of activity in the users and controls, perhaps due to the limitations of the small sample size. In a larger sample, such a comparison would enable an evaluation of the consequences of long term cannabis use on resting levels of glucose metabolism. The increases in regional metabolism in Volkow et al's study are in accord with the increases in cerebral blood flow reported by Mathew and Wilson (1992). The regional pattern of response to cannabis in this study is consistent with the localisation of cannabinoid receptors in brain. A further application of PET would be to label cannabinoids themselves: labelling of cannabis with a positron emitter has been achieved and preliminary biodistribution studies have been carried out in mice and in the baboon (Charalambous et al, 1991; Marciniak et al, 1991). The use of PET in future human studies is promising.

4.6 Brain morphology

4.6.1 Animal studies

Early attempts to investigate the effects of chronic cannabinoid exposure on brain morphology in animals failed to demonstrate any effect on brain weight or histology under the light microscope. Electron microscopic examination, however, has revealed alterations in septal, hippocampal and amygdaloid morphology in monkeys after chronic treatment with THC or cannabis. A series of studies from the same laboratory (Harper et al, 1977; Myers and Heath, 1979; Heath et al, 1980 discussed below) reported widening of the synaptic cleft, clumping of synaptic vesicles in axon terminals, and an increase in intranuclear inclusions in the septum, hippocampus and amygdala. These findings incited a great deal of controversy and the studies were criticised for possible technical flaws (Institute of Medicine, 1982) with claims that such alterations are not easily quantifiable.

Harper et al (1977) examined the brains of three rhesus monkeys 6 months after exposure to marijuana, THC or placebo, and two nonexposed control monkeys. In the treated group, one monkey was exposed to marijuana smoke 3 times each day, 5 days per week, another was injected with THC once each day, and the third was exposed to placebo smoke conditions. The latter two had electrode implants for EEG recording and had shown persistent EEG abnormalities following their exposure to cannabis. Morphological differences were not observed by light microscopy, but electron microscopy revealed a widening of the synaptic cleft in the marijuana and THC treated animals with no abnormalities detected in the placebo or control monkeys. Further, "clumping" of synaptic vesicles was observed in pre- and post-synaptic regions in the

cannabinoid treated monkeys, and opaque granular material was present within the synaptic cleft. The authors concluded that chronic heavy use of cannabis alters the ultrastructure of the synapse and proposed that the observed EEG abnormalities may have been related to these changes.

Myers and Heath (1979) examined the septal region of the same two cannabinoid treated monkeys and found the volume density of the organised rough endoplasmic reticulum to be significantly lower than that of the controls, and fragmentation and disorganisation of the rough endoplasmic reticulum patterns, free ribosomal clusters in the cytoplasm, and swelling of the cisternal membranes was observed. The authors noted that similar lesions have been observed following administration of various toxins or after axonal damage, reflecting disruptions in protein synthesis.

Heath et al (1980) extended the above findings by examining a larger sample of rhesus monkeys (N = 21) to determine the effects of marijuana on brain function and ultrastructure. Some animals were exposed to smoke of active marijuana, some were injected with THC and some were exposed to inactive marijuana smoke. After 2 to 3 months of exposure, those monkeys that were given moderate or heavy exposure to marijuana smoke developed chronic EEG changes at deep brain sites, which were most marked in the septal, hippocampal and amygdaloid regions. These changes persisted throughout the 6 to 8 month exposure period as well as the postexposure observation period of between 1 and 8 months. Brain ultrastructural alterations were characterised by changes at the synapse, destruction of rough endoplasmic reticulum and development of nuclear inclusion bodies. The brains of the placebo and control monkeys showed no ultrastructural changes. The authors claimed that at the doses used, which were comparable to human usage, permanent alterations in brain function and ultrastructure were observed in these monkeys.

Brain atrophy is a major nonspecific organic alteration which must be preceded by more subtle cellular and molecular changes. Rumbaugh et al (1980) observed six human cases of cerebral atrophy in young male substance abusers of primarily alcohol and amphetamines. They then conducted an experimental study of six rhesus monkeys treated chronically with various doses of cannabis extracts orally for 8 months and compared them to groups that were treated with barbiturates or amphetamines or untreated. No signs of cerebral atrophy were demonstrated in the cannabis exposed group and light microscopy revealed no histological abnormalities in four of the animals, but "equivocal" results for the other two. Brains were not examined under the electron microscope. The amphetamine treated group showed the greatest histological, cerebrovascular and atrophic changes.

More recently, McGahan et al (1984) used high resolution computerised tomography scans in three groups of four rhesus monkeys. One was a control group, a second was given 2.4 mg/kg of oral THC per day for 2-10 months and a third group received a similar daily dose over a five year period. The dosage was considered the equivalent of smoking one joint a day. The groups receiving THC were studied one year after discontinuing the drug. There was a statistically significant enlargement of the frontal horns and the bicaudate distance in the brains of the five-year treated monkeys as compared to the control and short-term THC groups. This finding suggests that the head of the caudate nucleus and the frontal areas of the brain can atrophy after long-term administration of THC in doses relevant to human exposure.

A number of rat studies have found similar results to those in rhesus monkeys described above. Investigators have reported that after high dose cannabinoid administration there is a decrease in the mean volume of rat hippocampal neurons and their nuclei, and after low dose administration there is a shortening of hippocampal dendritic spines. Scallett and coworkers (1987) used quantitative neuropathological

techniques to examine the brains of rats 7 to 8 months after 90 day oral administration of THC. The anatomical integrity of the CA3 area of rat hippocampus was examined using light and electron microscopy. High doses of THC resulted in striking ultrastructural alterations, with a significant reduction in hippocampal neuronal and cytoplasmic volume, detached axodendritic elements, disrupted membranes, increased extracellular space and a reduction in the number of synapses per unit volume (i.e. decreased synaptic density). These structural changes were present up to seven months following treatment. Lower doses of THC produced a reduction in the dendritic length of hippocampal pyramidal neurons two months after the last dose, and a reduction in GABA receptor binding in the hippocampus although the ultrastructural appearance and synaptic density appeared normal. The authors suggested that such hippocampal changes may constitute a morphological basis for the persistent behavioural effects demonstrated following chronic exposure to THC in rats, effects which resemble those of hippocampal brain lesions. These findings are in accord with those of Heath et al (1980) with rhesus monkeys and the doses administered correspond to daily use of approximately 6 joints in humans.

A study by Landfield et al (1988) showed that chronic exposure to THC reduced the number of nucleoli per unit length of the CA1 pyramidal cell somal layer in the rat hippocampus. The brains of rats treated 5 times per week for 4 or 8 months with 4-10 mg/kg injected subcutaneously were examined by light and electron microscopy. Significant THC-induced changes were found in hippocampal structure: pyramidal neuronal cell density decreased, and there was an increase in glial reactivity reflected by cytoplasmic inclusions similar to that seen during normal aging or following experimentally induced brain lesions. However, no effects were observed on ultrastructural variables such as synaptic density. Adrenal-pituitary activity increased resulting in elevations of ACTH and corticosterone during acute stress. The authors claimed that the observed hippocampal morphometric changes produced by THC

exposure were similar to glucocorticoid-dependent changes that develop in rat hippocampus during normal aging. They proposed that, given the chemical structural similarity between cannabinoids and steroids, chronic exposure to THC may alter hippocampal anatomical structure by interacting with adrenal steroid activity. More recently, Eldridge et al (1992) reported that delta-8-THC bound with the glucocorticoid receptors in the rat hippocampus and was displaced by corticosterone or delta-9-THC. A glucocorticoid agonist action of delta-9-THC injections was demonstrated. Injection of corticosterone increased hippocampal cannabinoid receptor binding. These interactions suggest that cannabinoids may accelerate brain aging.

It should be noted that where THC has been administered to monkeys for 6 months, this represents only 2% of their life span and may not have been long enough to detect the gradual effects that could arise from interactions with steroid systems (and affect the aging process). In contrast, 8 months administration to rats represents approximately 30% of their life span. The differences in the ultrastructural findings of Landfield's and Scallett's studies may be due to the largely different doses administered; the 8 mg/kg of Landfield's study was not sufficient to produce any marked behavioural effects. Further, the two studies examined slightly different hippocampal areas (CA1 or CA3).

Most recently, Slikker and colleagues (1992) reported the results of their neurohistochemical and electronmicroscopic evaluation of the rhesus monkeys whose dosing regime, behavioural and histochemical data were reported above. They failed to replicate earlier findings: no effects of drug exposure were found on the total area of hippocampus, or any of its subfields; there were no differences in hippocampal volume, neuronal size, number, length or degree of branching of CA3 pyramidal cell dendrites. Nor were there effects on synaptic length or width, but there were trends toward increased synaptic density (the number of synapses per cubic mm), increased soma size,

and decreased basilar dendrite number in the CA3 region with marijuana treatment. Slikker et al were able to demonstrate an effect of enriched environments upon neuroanatomy: daily performance of operant tasks increased the total area of hippocampus and particularly the CA3 stratum oriens, producing longer, more highly branched dendrites and less synaptic density, while the reverse occurred in the animals deprived of the daily operant tasks. The extent of drug interaction with these changes was not clear and may explain some of the inconsistencies between this study and those described above. Clearly, the question of whether prolonged exposure to cannabis results in structural brain damage has not been fully resolved.

The development of tolerance following chronic administration of psychoactive compounds is often mediated by a down-regulation of receptors. Thus, chronic exposure to THC could result in a decreased number of cannabinoid receptors in the brain. Such receptor down- regulation and reduced binding has recently been demonstrated in rats (Oviedo, Glowa and Herkenham, 1993). However, Westlake et al (1991) reported that cannabinoid receptor properties were not irreversibly altered in rat brain 60 days following 90 day administration of THC, nor in monkey brain 7 months after 1 year of exposure to marijuana smoke. It was argued that these recovery periods were sufficient to allow the full recovery of any receptors that would have been lost during treatment. Nevertheless, studies have not yet confirmed the parameters of any alterations in cannabinoid receptor number and function that may result from chronic exposure to cannabinoids, and the extent of reversibility following longer exposures has not been determined.

4.6.2 Human studies

There is very little evidence from human studies of structural brain damage. In their controversial paper Campbell et al (1971) were the first to present evidence

suggestive of structural/morphological brain damage associated with cannabis use in humans. They used air encephalography to measure cerebral ventricular size, and claimed to have demonstrated evidence of cerebral atrophy in ten young males who had used cannabis for 3 to 11 years, and who complained of neurological symptoms, including headaches, memory dysfunction and other cognitive impairment. Compared to controls, the cannabis users showed significantly enlarged lateral and third ventricular areas. Although this study was widely publicised in the media because of its serious implications, it was heavily criticised on methodological grounds. Most subjects had also used significant quantities of LSD and amphetamines, and the measurement technique was claimed to be inaccurate, particularly since there were great difficulties in assessing ventricular size and volume to any degree of accuracy (eg. Bull, 1971; Susser, 1972; Brewer, 1972). Moreover, the findings could not be replicated. Stefanis (1976) reported that echoencephalographic measurements of the third ventricle in 14 chronic hashish users and 21 nonusers did not support Campbell et al's pneumoencephalographic findings of ventricular dilation.

The introduction of more accurate and noninvasive techniques, in the form of computerised tomographic (CT) scans, (also known as computer-assisted tomographic (CAT) scans), permitted better studies of possible cerebral atrophy in chronic cannabis users (Co et al, 1977; Kuehnle et al, 1977). Co et al (1977), for example, compared 12 cannabis users recruited from the general community, with 34 non-drug using controls, all within the ages of 20 to 30. The cannabis users had used cannabis for at least five years at the level of at least 5 joints per day, and most had also consumed significant quantities of a variety of other drugs, particularly LSD. Kuehnle et al's (1977) subjects were 19 heavy users aged 21 to 27 years, also recruited from the general community who had used on average between 25 and 62 joints per month in the preceding year, although their duration of use was not reported. CT scans were obtained presumably at

the end of a 31 day study, which included 21 days of ad libitum smoking of marijuana (generally 5 joints per day), and were compared against a separate normative sample. No evidence for cerebral atrophy in terms of ventricular size and subarachnoid space was found in either study. Although these studies could also be criticised for their research design (e.g. inappropriate control groups, and the fact that cannabis users had used other drugs), these flaws would only have biased the studies in the direction of detecting significant differences between groups, yet none were found. The results were interpreted as a refutation of Campbell's findings, and supporting the absence of cortical atrophy demonstrated by Rumbaugh et al's (1980) CAT scans of monkeys. A further study (Hannerz and Hindmarsh, 1983) investigated 12 subjects who had smoked on average 1 gram of cannabis daily for between 6 and 20 years by thorough clinical neurological examination and CT scans. As in the studies above, no cannabis related abnormalities were found on any assessment measure.

4.7 Conclusions

Surprisingly few studies of neurotoxicity have been published and the results have been equivocal. There is convincing evidence that chronic administration of large doses of THC leads to residual changes in rodent behaviours which are believed to depend upon hippocampal function. There is evidence for long term changes in hippocampal ultrastructure and morphology in rodents and monkeys. Animal neurobehavioural toxicity is characterised by residual impairment in learning, EEG and biochemical alterations, impaired motivation and impaired ability to exhibit appropriate adaptive behaviour. Although extrapolation to man is not possible, the results of these experimental studies have demonstrated cannabinoid toxicity at doses comparable to those consumed by humans using cannabis several times a day. There is sufficient

evidence from human research to suggest that the cannabinoids act on the hippocampal region, producing behavioural changes similar to those caused by traumatic injury to that region.

The cognitive, behavioural and functional responses to long-term cannabis consumption in animals and man appear to be the most consistent manifestation of its potential neurotoxicity. The extent of damage appears to be more pronounced at two critical stages of central nervous system development: in neonates when exposed to cannabis during intrauterine life; and in adolescence, during puberty when neuroendocrine, cognitive and affective functions and structures of the brain are in the process of integration. As discussed in Chapter 5 with regard to cognitive functioning, research needs to investigate the possibility that more severe consequences may occur in adolescents exposed to cannabinoids. Human research has defined a pattern of acute CNS changes following cannabis administration. There is convincing evidence for long-lasting changes in brain function after long-term heavy use. Whether or not these changes are permanent has not been established.

Human studies of brain morphology have yielded generally negative results, failing to find gross signs of "brain damage" after chronic exposure to cannabis. Nevertheless, the results of many human studies are indicative of more subtle brain dysfunction. It may be that existing methods of brain imaging are not sensitive enough to establish subcellular alterations produced in the CNS. Many psychoactive substances exert their action through molecular biochemical mechanisms which do not distort gross cell architecture. The most convincing evidence on brain damage would come from postmortem studies but this type of information has not been available.

In 1983, Fehr and Kalant concluded that "The state of the evidence at the present time does not permit one either to conclude that cannabis produces structural brain

damage or to rule it out" (p. 602). In 1984, Nahas wrote "The brain is the organ of the mind. Can one repetitively disturb the mental function without impairing brain mechanisms? The brain, like all other organs of the human body, has very large functional reserves which allow it to resist and adapt to stressful abnormal demands. It seems that chronic use of cannabis derivatives slowly erodes these reserves" (p. 299). In 1986, Wert and Raulin (1986) proposed, that on the available evidence "there are no gross structural or neurological deficits in marijuana-using subjects, although subtle neurological features may be present. However, the type of deficit most likely to occur would be a subtle, functional deficit which could be assessed more easily with either psychological or neuropsychological assessment techniques." (p. 624). In 1993, little further evidence has emerged to challenge or refute these earlier conclusions. This conclusion was anticipated as early as 1845 by the Parisien physician Moreau when he wrote of his observations of chronic hashish smokers (see Frontispiece).

CHAPTER 5

CHRONIC EFFECTS OF CANNABIS ON COGNITIVE FUNCTIONING

One of the well-known acute effects of cannabis is to impair cognitive processes, so it has long been suspected that cognitive dysfunction may persist well beyond the period of acute intoxication, and that chronic cannabis use may cause lasting cognitive impairments. Although considerable research has been conducted into the acute cognitive effects of cannabis there is a paucity of well controlled studies of the chronic effects of cannabis use on cognitive function. This chapter reviews the literature from each of several methodological approaches that have been used to investigate the chronic effects of cannabis on human cognitive functioning. Clinical observations will only be covered very briefly, with discussion restricted to either key papers or recent research. The priority in this chapter will be given to those human studies which made some attempts to scientifically control for extraneous variables.

A number of terms which have been used interchangeably throughout the literature require definition and clarification at the outset. The term "residual", is defined by the Concise Oxford Dictionary as "remaining, left over, left as residue or residuum, still unaccounted for or not eliminated"; the term "chronic", is defined as "lingering, lasting, constant". While the difference between residual and chronic effects may appear subtle it is an important distinction.

Residual effects are those due to cannabinoid residues which are still present within the body, and causing the effect. Thus, residual effects may also be classified as

subacute effects, (defined by the Oxford Dictionary as "between acute and chronic"), which encompass "hangover" effects. The implication is that once the residue has been eliminated from the body, the effects should disappear.

Chronic effects, on the other hand, while not necessarily permanent, persist beyond the phase of elimination of cannabinoids from the body, and hence are not attributable to a direct action of cannabinoids. Chronic effects are the result of secondary changes induced by cumulative exposure to cannabinoids. Chronic effects, therefore, may be relatively enduring deficits in behaviour which presumably reflect changes in brain function. Actual structural changes may or may not be observed (see Chapter 4). This chapter will focus largely on neuropsychological assessments of brain function in chronic cannabis users.

A caveat must be born in mind whilst critically assessing the literature; it is difficult to assess the long-term consequences of the use of any psychoactive drug. Many factors other than drug use must be controlled in order to confidently attribute any effects to the drug in question. In the case of assessing the effects of drugs on cognitive function, these difficulties include: differentiating cognitive impairment that preceded drug use from that which may have been drug-induced; accurately determining the duration and frequency of past drug use; and taking account of the cognitive effects of multiple drug use. All these issues contribute to uncertainty in the attribution of any observed impairment to the use of a particular drug (Carlin, 1986).

5.1   Clinical observations

Concerns about the possibility that chronic cannabis use affected mental processes that were prompted by the acute effects of cannabis were reinforced by early clinical

reports of mental deterioration in long term cannabis users. Fehr and Kalant (1983b) provide a historical review of early clinical observations. In general, the clinical literature suggests that cognitive dysfunction is most often observed in persons who have used heavily (at least daily) for more than one year (Fehr and Kalant, 1983b, p. 506).

The most widely cited evidence for clinically significant impairment due to cannabis is the work of Kolansky and Moore (1971, 1972). These authors initially reported 38 cases of psychiatric symptomatology ranging from mild apathy through personality disturbance to psychosis which was observed in adolescents and young adults (aged 13 to 24) who had used marijuana at least twice per week. They later presented 13 case reports of adult psychiatric patients (aged 20 to 41) who had used marijuana or hashish 3-10 times per week or more for between 16 months and 6 years.

The clinical picture was one of "very poor social judgement, poor attention span, poor concentration, confusion, anxiety, depression, apathy, passivity, indifference and often slowed and slurred speech" (Kolansky and Moore, 1971). Various cognitive symptoms begun with cannabis use and disappeared within 3-24 months after cessation of drug use. These included: apathetic and sluggish mental and physical responses, emotional lethargy, mental confusion, difficulties with recent memory, incapability of completing thoughts during verbal communication, loss of interest in life, and goalessness.

The course and remission of symptoms appeared to be correlated with past frequency and duration of cannabis smoking. Those with a history of less intensive use showed complete remission of symptoms within 6 months; those with more intensive use took between 6 and 9 months to recover, while those with chronic intensive use were still symptomatic 9 months after discontinuation of drug use. Symptoms were also more

marked in users of hashish than in marijuana smokers.

Tennant and Groesbeck (1972) monitored the medical and psychiatric consultations of 720 hashish smoking US soldiers in West Germany. Just over half of the sample were occasional users who consumed between 0 to 12 g hashish per month. This group only complained of respiratory ailments. The heavy using group (N=110) who consumed between 50 and 600 g hashish per month, were described as "chronically intoxicated", generally apathetic and displaying impaired memory, judgement and concentration. Tennant and Groesbeck followed up nine heavily using patients after periods of abstinence, providing one of the few prospective studies to date. Six of the nine reported improvement in memory, alertness and concentration following discontinuation of use, while the other three complained of confusion and impaired memory for many months after ceasing use of the drug.

Both Kolansky and Moore, and Tennant and Groesbeck, emphasised the similarity between the symptoms they observed in long term heavy cannabis users and those of organic brain damage. Kolansky and Moore hypothesised that the use of cannabis:

"adversely affects cerebral functioning on a biochemical basis. In the mildest cases there appears to be a temporary toxic reaction when small amounts of cannabis are consumed over a short period of time. However, in those individuals who demonstrate stereotyped symptomatology after prolonged and intensive cannabis use, the possibility of structural changes in the cerebral cortex must be raised" (1972, p.41).

They called for investigation to assess structural and functional alterations in the brains of chronic cannabis users.

These clinical reports, together with a report of cerebral atrophy in young cannabis

users which appeared around the same time (Campbell, 1971), incited substantial controversy. Critics were quick to fault the experimental designs and to raise objections to the conclusions and extrapolations based on the evidence. Among these were the lack of objective measures of impairment and the biased sampling from psychiatric patient populations. The clinical observations, however, have been largely unchallenged, and the consistency of symptoms across reports and cultures is particularly striking. For example, the clinical descriptions of chronic users in India have matched those from the West (Chopra, 1971; 1973; Chopra and Smith, 1974; Chopra and Jandu, 1976).

While clinical observations may raise concerns, they do not provide definitive evidence of causality because they are unable to rule out alternative explanations of an apparent association between drug use and symptoms. Altman and Evenson (Altman, 1973), for example, examined 158 psychiatric patients and found 38 cases in which cannabis use had preceded such symptoms as confusion, depression, poor judgement, anxiety and apathy. In an exploration of possible relationships between other factors and psychiatric problems, they found ten other events (such as use of tobacco and beer, sexual intercourse, etc) which preceded the onset of psychiatric symptoms more frequently than did cannabis use. The authors criticised Kolansky and Moore's failure to include from their sample individuals who had used cannabis and did not develop psychiatric symptoms. They warned of the scientifically unsound practice of using the case history technique to test hypotheses about causal relationships.

The clinical observations in the early 1970s above were not new. Reports of adverse mental effects of cannabis use have appeared throughout history (see Fehr and Kalant, 1983a; Nahas, 1984). While the frequency of clinical reports of cognitive dysfunction has diminished in the past decade, this may reflect a decline in their novelty and noteworthiness rather than any reduction in the incidence of clinical disorders resulting from the chronic use of cannabis. In recent years, clinicians have sought to

characterise the specific deficits they observe with chronic cannabis users by integrating these into cognitive theory and evidence from empirical research (e.g. Lundqvist, 1991; Lundqvist and Ericsson, unpublished manuscript).

Treatment programs for chronic cannabis users have been established which focus upon specific areas of cognitive dysfunction, such as verbal and logical-analytic abilities, abstraction, psychomotility and memory (Lundqvist and Ericsson, unpublished manuscript). There is also converging evidence that the symptom pattern observed is very similar to the prefrontal syndrome, which is difficult to measure due to its complex effects on human behaviour (Stuss, 1986). The clinical reports which appeared in the early 1970s served to alert the community at large to the possible risks involved in using cannabis at a time when the substance was becoming increasingly popular among the young in Western countries, and prompted field studies and better controlled empirical research.

5.2 Cross-cultural studies

A logical starting point for the investigation of cognitive function in chronic cannabis users is to assess populations of users in countries where the chronic daily cannabis use has been an integral part of the culture for many decades, if not centuries. This kind of research was pioneered by Soueif (1971) in the largest scale study to date of 850 Egyptian hashish smokers and 839 controls. In response to public anxiety about the epidemic increase in marijuana use in the late 1960s, the National Institute on Drug Abuse (NIDA) commissioned three cross-cultural studies in countries with longer histories of cannabis use than the West, namely, Jamaica, Greece and Costa Rica. These studies are the most widely quoted and often considered to be definitive and comprehensive. This is not so much due to their sample sizes, which were quite small,

and therefore limit the conclusions that can be drawn, but mainly because each study was multidisciplinary, investigating not only cognitive function, but also medical-physiological status. These studies will each be reviewed in depth, together with other studies of non-Western cultures.

5.2.1 Egypt

Soueif's Egyptian sample was from a male prison population which was poorly educated, largely illiterate and of lower socio-economic status and hence unrepresentative of the general cannabis using populations in the West. Nonetheless, the study provided some evidence pertaining to possible long-term changes in brain function. Significant differences were found between users and controls on ten out of sixteen measures of perceptual speed and accuracy, distance and time estimation, immediate memory (digit span backwards), reaction time and visual-motor abilities, including the Trail Making Test (Part A) and the Bender Gestalt test (Soueif, 1971; 1975; 1976a; 1976b). These differences in performance were more marked in the youngest (< 25 years) and best educated urban users than the older, illiterate and rural subjects.

Soueif concluded that prolonged cannabis use produces subtle deficits in the cortical level of arousal (Soueif, 1976a). He argued that high cortical levels of arousal are associated with high levels of proficiency, and "the lower the non-drug level of proficiency on tests of cognitive and psychomotor performance the smaller the size of function deficit associated with drug taking" (Soueif, 1976b). Soueif called for cross-validation studies, examining women as well as men and cannabis smokers from other cultures (e.g. North American). He proposed that the arousal hypothesis reconciled various apparently contradictory observations of cannabis-induced effects in the literature (Soueif, 1976a). Soueif (1976b) later used the arousal hypothesis to explain the

apparently contradictory research findings of the acute effects of cannabis (e.g. Melges
et al, 1970a and Tinklenberg et al, 1972).

Soueif's Egyptian study was subsequently criticised for methodological reasons
(Fletcher and Satz, 1977). A major criticism was that the groups differed on a number
of variables that were relevant to cognitive performance, namely, education (with literate
nonusers being better educated than literate users) and higher rates of opiate and alcohol
use among the cannabis users. The apparent decrease in differences between users and
nonuser groups with increasing age was questioned since the oldest subjects had been
consuming cannabis for the longest period. Additional criticisms were that: the
experimenter was not blind to the cannabis use history of the subjects; that the large
sample size biased the results towards rejection of the null hypothesis making very small
group differences appear to be "significant". The question was also raised whether a
"floor effect" had masked potential differences between user and nonusers groups with
low ability. Fletcher and Satz (1977) also observed that Soueif's results were not
replicated in the Jamaican, Greek or Costa Rican studies (which are described below).

Soueif (1977) replied to these criticisms. He attributed the apparent failure to
replicate to the use of different measures of performance in the Greek, Jamaican and
Costa Rican studies. He reported that differences between users and nonusers were not
related to education, that polydrug use did not worsen test scores, and that floor effects
and experimenter bias were not relevant to measures of speed of performance. In a re-
analysis of the data, the distribution and variance of scores indicated that a floor effect
did not occur, and levels of significance far greater than 0.01 suggested that it was
unlikely that the results were artefacts of the large sample size (Soueif, 1977). The main
findings of Soueif's study were that long term use of cannabis may lead to deficits in
speed of psychomotor performance, distance and time estimation, immediate memory
and visuomotor coordination, particularly in young, educated and urban users.

However, the validity of these findings remain under doubt because some of the tests used by Soueif do not have established neuropsychological validity (Carlin, 1986).

5.2.2 Jamaica

Bowman and Pihl (1973) conducted two field studies of chronic cannabis use in Jamaica, one with a small sample of 16 users and 10 controls from rural and semi-rural areas, and the other with a small urban slum sample of 14 users and controls. Users had been very heavy daily consumers of cannabis for a minimum of 10 years (current use of about 23 high potency joints/day), while controls had no previous experience with cannabis. Tests were selected on the basis of having previously been shown to be sensitive to impairment following chronic heavy alcohol use (or other chemical insult). They were generally described as "measures of the efficiency of concept formation and memory" (Bowman and Pihl, 1973). The groups were matched for age, sex, social class, alcohol use, education and "intelligence", but most subjects were illiterate or semi-literate, with an average age of 30. No differences were found between the users and nonusers of either study, nor when the rural and urban samples were combined.

Soueif (1976b) later argued that such a null result would be expected from his hypothesis cannabis-induced impairments were a function of age, urbanism and literacy. Bowman and Pihl replied that the controls were sufficiently advantaged in terms of literacy to enable any impairment in the users to manifest. Moreover, their study required only a minimum of 4 hours abstinence prior to testing, which meant that some subjects were still intoxicated at the time of testing. This possibility would only have further biased the test results in favour of finding lower performance among the users. Bowman and Pihl's conclusion was not that long term heavy use does not result in cognitive impairment, but that cultural expectations and test specificity may be important

intervening variables.

A more extensive study of 60 lower working class males in Jamaica (Rubin and Comitas, 1975) came to be regarded as the main Jamaican project (NIDA funded). It was hailed as a major breakthrough in cross-cultural drug research because it used a combination of field-based social-scientific evaluation and hospital-based clinical evaluation (Rubin and Comitas, 1975). The neuropsychological and personality assessments were much more extensive than those conducted in Egypt or Greece. It compared 30 users and 30 nonusers matched on age, socioeconomic status and residence. The user group which was aged between 23 and 53 years with a mean age of 34 years, had used cannabis for an average of 17.5 years (range 7 - 37 years) at around 7 joints per day (range 1 - 24), estimated to contain 60 mg of THC. They had not used any substances other than alcohol and tobacco. While it was stated that no control had used cannabis heavily in recent years, it is not known whether there had been heavy use in the past. At least nine of the controls were current "occasional" users of cannabis and all but 12 of the controls had some experience with cannabis.

The aim of the study was to determine the long-term effects of cannabis use on higher brain function from neurological, neuropsychological, psychiatric and personality assessments. A battery of 19 psychological tests were administered, generally after 3 days of abstinence, as part of a 6 day inpatient drug-free hospitalisation period during which many other clinical and physiological examinations were performed. No significant physical abnormalities were found that could be linked to the use of cannabis. Significantly more users than nonusers (8 vs 2 respectively) had positive family histories of mental illness, but only one subject in each group had a personal history of schizophreniform psychosis. Further psychiatric assessment found no significant differences between groups in disturbances of mood, thought processes or behaviour, on extraversion or neuroticism, criminality or in the incidence of alcoholism. The resting

EEG pattern and number of EEG abnormalities did not differ between groups (see also Beaubrun and Knight, 1973).

The psychological battery of tests employed in this Jamaican study, included one personality test (Lowenfeld Mosaic Test), three tests of intellectual and verbal abilities (WAIS, Ammons Full-Range Picture Vocabulary Test and the Reitan Modification of the Aphasia Screening Test), and 15 neuropsychological tests measuring abilities previously shown to be affected by acute cannabis intoxication, such as motor strength, speed and coordination, short-term memory, and the ability to maintain attention. Simple and complex motor functions were tested by dynamometer, finger tapping, maze steadiness, graduated holes and pegboard. Sensory perception was assessed by tests of tactile and auditory stimulation, and tactile form and finger-tip writing recognition. Memory and attention were measured by the Tactual Performance Test (child's version), the Time-Sense-Memory Test and the Seashore Rhythm Test. The Indiana-Reitan Category Test (child's version) assessed concept formation. Portions of the WAIS, such as the Information, Vocabulary and Picture Arrangement subtests, were omitted as they were judged to be culturally inappropriate.

Comparisons of the users and nonusers on 47 subtest variables failed to reveal any consistently significant differences. There were three statistically significant results which were not easily interpreted and were considered chance findings. There was no strong suggestion of differences that failed to be detected because of a small sample size since the user group scored better than the nonuser group on 29 variables, albeit nonsignificantly. The authors considered their results to be consistent with Bowman and Pihl's Jamaican study, and concluded that "in a wide variety of human abilities, there is no evidence that long-term use of cannabis is related to chronic impairment" (Rubin and Comitas, 1975, p.119).

The interpretation of these null results as evidence of an absence of effect of cannabis on cognitive functioning is complicated by a number of factors that may have attenuated differences between users and nonusers. First, the tests used were not standardised for use in Jamaica. The authors' justification of this was that any cultural bias would be the same for both users and controls and therefore would not obscure any group differences (Rubin and Comitas, 1975, p.111). However, their attempts to cope with cross-cultural differences within the protocol of the study, such as the omission of subtests of the WAIS due to subjects' unfamiliarity with the required knowledge and skills, serves to weaken the interpretation of their results. The authors acknowledged the questionable relevance of other subtests but included them in an effort to have some metric of comparison of users and nonusers.

Second, there are problems with the interpretation of test scores. The lack of significance on WAIS subtests, for example, may be due to a floor effect, reflecting the inappropriate nature of test items, which meant that groups had little room to differ. Conversely, the use of the children's version of two of the most sensitive tests of higher level cognitive functioning (Category and Tactual Performance Test) might have created an artificial ceiling that obscured any drug effects. That is, if tests were either too easy or too difficult for both groups, group differences may have been masked by these artefacts. These hypotheses are difficult to evaluate since test score means were not published.

Third, the inclusion of cannabis users in the control group may have further contributed to the lack of significant group differences. Any such effect may have been detected had multivariate statistical methods been employed to assess the effect of duration and intensity of cannabis use on cognitive performance. However, no attempt was made to evaluate the long-term neuropsychological effects within the user group as a function of frequency or duration of use.

Fourth, a number of other cultural differences may have confounded the results of this study. Jamaican society at the time had a tradition of cannabis use within which many viewed the drug as medicinal, benign or even as a work enhancer. This is in marked contrast to the Western held beliefs of cannabis users as amotivated "drop outs" from society because heavy cannabis use precluded work. The cannabis users of this Jamaican sample were mainly farmers, fishermen and artisans from rural areas or casual urban labourers, who claimed to increase their work output by using cannabis to relieve the monotony of dull, repetitive, and laborious work. If only the higher cognitive functions are affected by cannabis, the work performance of rural or manual labourers would not necessarily be affected. However, this does not exclude the possibility that the long term use of cannabis may impair the performance of workers who have more complex tasks or those who come from higher socio-economic groups, for whom mental operations may predominate (Fink, 1976b). This sample was poorly educated, with a mean of 4.5 years of schooling (equivalent to third grade) so that if Soueif (1976a) is correct, there would only be small functional deficits associated with cannabis use.

5.2.3 Greece

The Greek NIDA study (Stefanis et al 1977) examined a sample of 47 chronic hashish users and 40 controls matched for age, sex, education, demographic region, socioeconomic status and alcohol consumption. The subjects were mostly refugees from Asia Minor, residing in a low income, working class area of Athens. The average duration of use was 23 years of an estimated daily use of 200 mg per day, and most users had smoked hashish on the day before testing, and some had smoked several hours before the test session. Controls were slightly better educated than users.

Noting that where adverse effects have been reported it has been on those tasks requiring concentration and manual dexterity, these researchers administered the WAIS and Raven's Progressive Matrices to assess general intelligence and mental functioning (Kokkevi and Dornbush, 1977). Subtests of the WAIS were used to evaluate the possibility of impairment in specific cognitive and perceptual functions. While the WAIS was not standardised on a Greek population it had been used by the authors in a translated form for many years. The Raven's test was considered to be a more culture-free assessment of intelligence and was used for reliability and validity purposes. The groups did not differ in global IQ score on either the WAIS or Raven's Progressive Matrices, but nonusers obtained a higher verbal IQ score than users. The users' performance was worse than controls on all but one of the subtests of the WAIS (Digit Span), even if not significantly so. Significant differences in performance between the two groups were obtained in three subtests of the WAIS: Comprehension, Similarities, and Digit Symbol Substitution. Impaired performance in the Comprehension and Similarities subtests indicates a possible defect in verbal comprehension and expression, verbal memory, abstraction and associative thinking. A low score on Digit Symbol Substitution (consistently shown to be affected by cannabis acutely) indicates a possible defect in visual-motor coordination and memorising capacity. A trend toward inferior performance in the Picture Arrangement test may indicate a dysfunction in logical sequential thought.

The interpretation of these results was complicated by the lack of a requirement that subjects abstain from hashish prior to testing. Consequently, it was not clear whether the impairment found on these subtests was related to long-term use of hashish, or whether it was due to the persistence of an acute drug effect at the time of testing. The poorer performance by users was assumed to "reflect their recent use of hashish, as the test was given within two hours of smoking hashish by some users" (Kokkevi and

Dornbush, 1977), an interval that coincided with increased pulse rates, a reliable sign of acute intoxication.

Because the differences between verbal and performance IQ were similar in both groups the authors argued that there was no evidence of deterioration in mental abilities in the hashish users. The impaired functioning on tests of judgement and abstract thinking (Comprehension and Similarities) were interpreted as signs of psychopathology, even though a comparison of subgroups of "mentally ill" and "normal" within the user group revealed no difference in performance in these subtests. The authors attributed the poorer performance by users to "acculturational and adaptational processes" rather than to "logical reasoning abilities". The authors concede that "it is possible that the detection of subtle intellectual dysfunctions in groups with initially low levels of mental functioning are less easily observed" (Kokkevi and Dornbush, 1977), as occurred in the Jamaican sample and portions of the Egyptian sample.

A subsample of 20 of the Greek chronic users were administered a brief psychometric battery after smoking a given dose of cannabis (Dornbush and Kokkevi, 1976). These subjects had smoked for over 25 years and were assessed on simple tests of perceptual-motor ability. This study demonstrated the acute response of chronic users to be similar to that of short term users in the United States: psychological test performances were adversely affected by cannabis in a way similar to that observed in naive subjects or short term users under acute intoxication. The adverse effects on mental functioning were short lived, persisting for approximately 70 minutes after commencing smoking. Thus, no evidence was provided for tolerance or withdrawal effects. The only effect to be inferred was that practice effects, although not abolished by the consumption of marijuana, were less than those observed under placebo conditions.

The authors concluded that long-term use does not qualitatively change the general response pattern to acute cannabis administration. Further, no differences were found in the EEG changes produced by an acute dose of cannabis in this Greek sample and a group of American volunteers; nor were there differences between the two samples in resting EEG patterns.

5.2.4 Costa Rica

The NIDA study of chronic heavy cannabis users in Costa Rica was modelled upon the Jamaican project but with greater sensitivity to cross-cultural issues. It involved an intensive physiological, psychological, sociological and anthropological study of matched-pairs of users and nonusers (Carter, 1980). Satz, Fletcher and Sutker (1976) reported the results of comparing 41 male long-term heavy cannabis users (on average 9.6 joints per day for 17 years) with matched controls on an extensive test battery designed to assess the impact of chronic cannabis use on neuropsychological, intellectual and personality variables. The educational level of the Costa Rican sample was slightly higher than that of either the Greek or the Jamaican populations, although more than half of the user group had not completed primary school, and both users and nonusers had commenced employment at 12 years of age on average. The users were working class, mostly tradesmen with lower than average income, who reported that they often used cannabis augment their work performance in a similar fashion to the Jamaican sample.

The tests included Finger Localisation and Finger Oscillation (tapping) Tests, the Tactual Performance Test, the Rey-Davis test of nonverbal memory and learning and the Word Learning and Delayed Recall tests from the Williams Memory Battery, Logical

Memory from the Wechsler Memory Scale, the Milner Facial Recognition Memory Test, the Benton Visual Retention Test, and a short form of the WAIS. These tests were translated into Spanish and standardised on a separate sample of the Costa Rican population. They were found to be free of cultural bias, and no floor or ceiling effects were demonstrated. Personality was assessed by form E of the 16-PF Personality Factors Questionnaire and an Incomplete Sentence Test. All data were subjected to appropriate multivariate statistical analyses.

Despite their long duration and heavy use, the Costa Rican users did not differ significantly from controls on any test. Users scored consistently lower, if not significantly so, than nonusers on eleven of sixteen variables in the neuropsychological test battery. These included the Word Learning, Delayed Recall and the Rey-Davis subtests of the Williams Memory Battery, the Logical Memory test of the Wechsler Memory Scale and the Facial Recognition Memory Test. Although users' performance was poorer, particularly in the mean number of errors made, learning curves were similar for both groups. The authors concluded that there was insufficient evidence for significant impairment of memory function in the chronic cannabis users.

A multivariate analysis of the 14 variables comprising the WAIS also revealed no significant differences between groups. Users performed slightly better on 6 of the 11 subtests and had a slightly higher verbal and full-scale IQ. A multivariate analysis of the 16 personality factors and 8 second-order factors of the 16-PF test also revealed no significant intergroup differences. An attempt to correlate test results with level of marijuana use yielded no consistent findings. The authors concluded that there was no evidence for irreversible brain damage, personality disturbance or cognitive impairment due to the chronic use of cannabis.

A ten year follow-up of the Costa Rican sample was conducted by Page, Fletcher

and True (1988). By the time of follow-up, the users had an average 30 years experience with cannabis, but the sample size had dropped to 27 of the 41 original users and 30 of the 41 controls. The test protocol included some of the original tests as well as a number of additional tests which measured short-term memory and attention which were selected for their sensitivity in detecting subtle changes in cognitive functioning. The new tests included: the Rey-Osterrieth Complex-Figure Test, Buschke's Verbal Selective Reminding Test, the Self-Paced Continuous Performance and Underlining Tests, Mazes and Trail Making Test Part A, and the MMPI as a measure of personality.

No differences were detected on any of the original tests, but three tests from the new battery yielded significant differences between users and controls. In Buschke's Selective Reminding Test, the user group retrieved significantly fewer words from long-term storage than the nonuser group, although the groups did not differ on a measure of storage. Users performed more slowly than nonusers in the Underlining Test, with particularly poor performance in the most complex subtest. Differences between groups were not a function of practice or purely motor speed. The Continuous Performance Test also revealed users to be slower than controls on measures requiring sustained attention and effortful processing, although there were no differences in correct hits nor false alarm rates.

Page et al interpreted their results as providing evidence that long-term consumption of cannabis is associated with difficulties in sustained attention and short-term memory. They hypothesised that such tests require more mental effort than the tests used in the original study, and, as such, the results imply that long-term users of cannabis experience greater difficulties with effortful processing. They provided anthropological data to further support their hypotheses: users exhibited lower levels of mental effort at work job than nonusers, although this was confounded by the choice of job. Users tended to work as labourers, street vendors or in the service industry, while

nonusers tended to be craftsmen, store tenders or office managers. Page et al claimed that if users "found it difficult to concentrate, especially on tasks that require attention to detail", they might be expected to choose jobs that are less demanding in mental performance than the jobs chosen by nonusers.

This study differs from previous cross-cultural investigations which have failed to demonstrate consistent deficits in cognitive functioning of long-term users of cannabis in that it found consistent differences between users and nonusers in tests of information processing, sustained attention and short term memory. Nevertheless, Page et al emphasised that the differences they found were "quite subtle" and "subclinical". Only a small number of subjects were classified as clinically impaired. Because the differences are so small and subtle it is difficult to exclude several other alternative explanations before concluding that they reflect the longer duration of use by the sample, or the greater sensitivity and specificity of tests used. These alternative possibilities include: that the differences were due to the inclusion of the few clinically impaired subjects within the sample; and that some of the differences were due to acute intoxication or recent use, since 24 hour abstinence was requested, but was not verified.

5.2.5 India

Studies of long-term cannabis use in India commenced with Agarwal et al's (1975) examination of chronic bhang drinkers. Bhang is a tea-like infusion of cannabis leaves and stems which is drunk, sometimes for medicinal purposes. The forty subjects had used bhang daily for about 5 years, were less than 45 years of age, reasonably well educated with 65% having completed high school and none illiterate. There was no control group so scores were compared to normative data on the tests used. By comparison with these norms, 18% of the bhang users had memory impairment on the

Wechsler Memory Scale, 28% showed mild intellectual impairment on the Bhatia Battery of Intelligence (IQs less than 90), and 20% showed substantial cognitive disturbances on the Bender-Gestalt Visuo-Motor Test. The authors concluded that bhang may cause mild impairment in cognitive functions.

Wig and Varma (1977) administered a test battery to 23 long-term male users of cannabis (comprised of both daily charas smokers and bhang drinkers of at least 5 years). Eleven of these were matched to a nonusing control group with respect to sex, education, income, marital status and occupation. The entire sample was compared to the eleven controls on scores from Raven's Progressive Matrices, Malin's Intelligence Scale for Indian Children (adapted from the WAIS), PGI Memory Scale (adapted from the WMS), Bender-Gestalt, speed and 'H' marking tests from the General Aptitude Test Battery, a colour cancellation test and a time perception test. Users scored significantly lower on the tests of intelligence, memory, speed and accuracy, replicating Agarwal et al's findings, and pointing to problems in memory and concentration associated with long-term cannabis use.

The results of these studies are limited by either the absence of controls or the use of poorly matched controls, inadequate consideration of pre-morbid variables, unreliable measurement of the duration and severity of cannabis and other drug use, and the use of culturally inappropriate psychometric tests or tests that had not been adequately validated in the sample population. Nonetheless, many of the subjects in these studies were extremely heavy users, and the differences in cognitive performance could not always be explained by the uncontrolled confounding variables.

Mendhiratta, Wig and Verma (1978) compared 50 heavy cannabis users (half bhang drinkers, half charas smokers of at least 25 days per month for a mean of 10 years) with matched controls. The entire sample was of low socioeconomic status.

Tests were administered after 12 hours abstinence which was verified by overnight admission to a hospital ward. The tests included digit span, a recognition test, pencil tapping test, speed and accuracy tests, a time perception test, a reaction time test, a size estimation test (most of which were not standardised for the population studied), and the Bender-Gestalt and Maudsley Personality Inventory.

The cannabis users reacted more slowly, and performed more poorly in concentration and time estimation. The charas smokers were the poorest performers, showing impaired memory function, lowered psychomotor activity and poor size estimation. The fact that the smokers were most impaired may be indicative of the importance of metabolites formed in the production of cognitive impairment. Nine to ten years later, Mendhiratta et al (1988) followed up 11 of the original bhang drinkers, 19 charas smokers and 15 controls. Repeat administration of the original tests showed significant deterioration on digit span, speed and accuracy tests, reaction time and Bender-Gestalt.

Ray et al (1978) assessed the cognitive functioning of 30 chronic cannabis users (aged 25-46) who had used bhang, ganga or charas for a minimum of 11 times/month for at least 5 years, comparing their performance to that of 50 randomly selected nonuser controls of similar age, occupation, socioeconomic status and educational background. Few differences were found on tests of attention (e.g. digits backwards, serial addition/subtraction), visuo-motor coordination (e.g. the Minnesota Perceptuo-Diagnostic Test) or memory (the PGI Memory Scale). Cannabis users performance was impaired on one of the subtests of the memory scale. However, the matching of subjects was not rigorous and the fact that all subjects were illiterate may have produced a floor effect masking differences between groups. As Fehr and Kalant (1983) noted, the raw PGI memory scale scores for both users and controls in this study were as poor as those of the cannabis user group in the study of Wig and Varma (1977).

Varma et al (1988) administered thirteen psychological tests selected to assess intelligence, memory and other cognitive functions, to 26 heavy marijuana smokers and 26 controls matched on age, education and occupation. The average daily intake of the cannabis users was estimated as 150 mg THC, with a frequency of at least 20 times per month, and a mean duration of use 6.8 years (minimum 5 yrs). Twelve hours abstinence was ensured by overnight hospitalisation. The tests included a pencil tapping, time perception, reaction time, size estimation, Trail Making (Form A), Bender-Gestalt, Nahor and Benson visuo-spatial reproduction, Standard Progressive Matrices, WAIS-R Verbal Scale, Bhatia's Short Scale (measure of IQ), PGI Memory Scale, Hindi Psychoticism, Extraversion and Neuroticism Scale, and a disability assessment schedule. Varma et al reported that the PGI Memory Scale was a locally developed and validated adaptation of the Wechsler Memory Scale which assessed memory function in 10 different domains.

Cannabis users were found to react more slowly on perceptuomotor tasks such as the pencil tapping and reaction time tests, but did not differ from controls on the tests of intelligence. When the scores of all the memory tests were combined, there was no difference between the total scores of cannabis users and controls, although cannabis users scored significantly more poorly on a subtest of recent memory. There were trends toward poorer performance on subtests of remote memory, immediate and delayed recall, retention and recognition. Users suffered disability in personal, social and vocational areas and indicated somewhat higher psychoticism and neuroticism scores. The authors concluded that impairment of cognitive functions associated with long-term heavy use of cannabis was more apparent in perceptuomotor tasks than in tests of intelligence or memory. Nevertheless, the perceptuo-motor tests employed in this study were of questionable validity, with particularly poor measures of reaction time and speed of responding, while the measures of memory function may have reached

significance had a larger sample been tested. This suggests that any cognitive deficits due to cannabis may be specific to particular aspects of short-term memory.

5.2.6 Summary

The results of the cross-cultural studies of long-term heavy cannabis users served to allay concerns about the consequences of cannabis use since overt signs of "brain damage" as measured by psychological tests were not found among heavy long-term cannabis users. There was equivocal evidence for an association between cannabis use and more subtle long term cognitive impairments.

Given that cognitive impairments are most likely to be found in subjects with a long history of heavy use, it is reassuring that most such studies have found few and small differences. It is unlikely that the negative results of these studies can be attributed to an insufficient duration or intensity of cannabis use within the samples studied. For example, the duration of cannabis use averaged 17.5 years and the daily THC level consumed ranged from an estimated 20-90 mg daily in Rubin and Comitas's Jamaican study; 23 years and 120-200 mg daily in the Greek sample; and 16.9 years and 20-160 mg daily in the initial Costa Rican study.

The absence of differences is all the more unexpected since a number of factors may have biased these studies toward finding poorer performance among cannabis users. These include: higher rates of polydrug use, poor nutrition, poor medical care, illiteracy among users; and the failure in many studies to ensure that subjects were not intoxicated at the time of testing, which would have increased the likelihood of detecting impairment. The use of a laboratory test to detect recent marijuana ingestion in studies with positive results would have been helpful in ruling out acute effects as the cause of

the apparent impaired performance among users. Given the generally positive biases in these studies it has been argued that if cannabis use did produce cognitive impairment, a larger number of these studies should have shown positive results (Wert and Raulin, 1986b).

The force of this argument is weakened, however, by the fact that most of these studies suffered from numerous other methodological difficulties which may have operated against finding a difference. First, the instruments most often used for assessment have been developed and standardised on Western populations. Second, many of these studies were based on small samples of questionable representativeness and subject to sampling bias, since only subjects who could be reached and were willing to participate were included in the studies while others possibly not equally resistant to drug-induced impairments might have been missed. Third, a number of studies failed to include a control group while others used inappropriate controls. Fourth, generalisation of the results of these studies to users in the West or other cultures is difficult in given the predominance of illiterate, rural, older and less intelligent or less educated subjects in these studies. Fifth, the studies were limited by their investigative instrumentation which may only be capable of detecting gross deficits at a group level. Sixth, few attempts were made to examine relationships between neuropsychological test performance and frequency and duration of cannabis use. Such an evaluation would rule out possible within-group differences in chronic users.

In terms of the specific deficits reported, slower psychomotor performance, poorer perceptual motor coordination, and memory dysfunction were the most consistently reported deficits. Of the studies that specifically included tests of memory function, four detected persistent short-term memory and attentional deficits in chronic cannabis users (Page, 1988; Soueif, 1976a; Varma, 1988; Wig, 1977), while three detected no such deficits (Bowman, 1973; Satz, 1976; Mendhiratta, 1978). Impairments were most

frequently found on such tests as the Wechsler Memory Scale, the Bender-Gestalt test, Buschke's Selective Reminding Test and the Continuous Performance Test of Buchsbaum and Sostek. The measures of short-term memory were often inadequate, failing to determine which processes may be impaired (eg. acquisition, storage, encoding, retrieval) and often with an exclusion of higher mental loads and conditions of distraction. A proper evaluation of the complexity of effects of long term cannabis use on higher cognitive functions requires greater specificity in the selection of assessment methods as well as the use of more sensitive tests.

5.3 Studies of Young Western Users

A number of empirical studies have been conducted on the cognitive performance of American or Canadian cannabis users. Most of the subjects in these studies have been young and well educated college students with relatively short-term exposure to cannabis in comparison to the long use history among chronic users in the cross-cultural studies. In 1970 Hochman and Brill (1973) surveyed a large sample of college students (N=1400). The sample comprised nonusers (65.5%), occasional users (26%), and chronic users (8.5%) defined as those who had used three times/week for three years or had used daily for two years. They found no evidence of an "amotivational syndrome" in terms of lethargy or social and personal deterioration, but did demonstrate significant psychosocial differences between users and nonusers. Marijuana users were more rebellious, reckless, questioning and anti-authoritarian. Chronic users were less certain of long-term life plans than nonusers, although there was no relationship between either frequency or duration of use and academic achievement. About 1% of marijuana users were estimated to suffer from impaired ability to function due to their use, but such loss

of ability was subject to large individual differences and variability.

In a follow-up of the original sample over two consecutive years (1971: N=1133; 1972: N=901), Brill and Christie (1974) assessed nonusers, occasional users (< 2 / week), frequent (2-4 / week), and regular users (≥ 5 / week) by a self-report questionnaire. The majority of users perceived no effect of cannabis use on most areas of psychosocial adjustment. A small proportion (12.3%) reported that their academic performance had declined and they were more likely to reduce their frequency of use or to quit. There were no significant differences found between users, nonusers or former users in grade point average. Cannabis users were more likely to drop out of college and had greater difficulty formulating life and career goals; fewer users planned to seek advanced academic degrees and more considered themselves to have poorer academic adjustment. Whether these attributes preceded cannabis use or were caused by it, is impossible to determine. It may be argued that such differences do not necessarily reflect impairment nor are they harmful. Indeed, the authors concluded that in a "functioning, intelligent undergraduate university population", few deleterious effects could be attributed to the use of the drug.

Entin and Goldzung (1973) conducted two studies of the residual impact of cannabis use on memory processes. In the first study, verbal memory was assessed by the use of paired-associate nonsense syllable (CVC) learning lists. Twenty six cannabis users (defined as daily for at least 6 months, but the range of use not reported) were compared to 37 nonusers drawn from a student population. Cannabis users scored significantly more poorly on both free recall (the number of words recalled after a delay) and on acquisition, measured as improvement in recall over repeated trials.

In the second study, verbal and numerical memory were tested by the presentation of word lists, interspersed with Wendt three step arithmetic problems prior to recall.

Cannabis users (N=37) recalled significantly fewer words than nonusers (N=37), but did not differ from controls on arithmetic test scores. The lack of an effect on the arithmetic tests was interpreted as a function of the short length of time during which numeric information must be stored for further manipulation, rather than being due to any numerical memory functions per se. That is, the verbal memory tasks required longer-term storage of information prior to retrieval.

These findings were interpreted as residual impairment of both the acquisition and recall phases of long-term memory processes. The authors attributed the impairments to either an enduring residual pharmacological effect on the nervous system, or to an altered learning or attention pattern due to repeated exposure to cannabis. No details were provided with regard to the length of abstinence prior to testing, however. The authors stated that subjects were assumed "not to be under the influence of marihuana or any other drug during the testing situation. Any who were suspected were asked to return at another time for testing" (p.171).

Grant et al (1973) studied the effects of cannabis use on test performance on 8 measures from the Halstead-Reitan Battery among medical students. They found no differences between 29 cannabis users (of median 4 year duration and frequency 3/month) and 29 age and intelligence matched nonusers on 7 of the 8 measures. Users performed more poorly on the localisation subtest of the Tactual Performance Test. These subjects were very select in that they were only light users, and as medical students were obviously functioning well. The failure to find any difference in sensory-motor integration or immediate sensory memory was later replicated by Rochford, Grant and LaVigne (1977) in a comparison of 25 users (of at least 50 times over a mean 3.7 years) and 26 controls matched on sex, age and scholastic aptitude scores. By limiting their samples to populations of successful students, these studies are flawed in the reverse direction to the reports of Kolansky and Moore (1971; 1972).

Weckowicz and Janssen (1973) compared eleven male college students who smoked cannabis 3-5 times/week for at least 3 years with nonusers who were matched on age, education and socioeconomic and cultural backgrounds. They were assessed on a variety of tasks designed to measure field dependence, personality traits, social attitudes and values, as well as cognitive function. Users performed better than controls on 8 of the 11 cognitive tests but performed more poorly on the Guilford Number Facility, suggesting that chronic use may affect sequential information processing. Otherwise, there was no evidence of organic brain damage or gross impairment of cognitive functioning. Weckowicz and Janssen followed Stefanis's group by interpreting their findings in terms of social deviance, lack of conformity, rebelliousness and alienation.

In a cross-validation of their previous findings, Weckowicz, Collier and Spreng (1977) compared 24 heavy smokers (at least daily for three years) belonging to the "hippie subculture" with nonuser controls matched for age (mean 22.5), education (mean 13.5 years), and social background. Cognitive functioning, personality traits and social values were assessed using the same test battery as used previously, with addition of the selective listening task (Treisman, 1964b), Wechsler Memory Scale, Miller Analogies Test, Utility Test, Word Association Test and Association Test. Cannabis users once again performed better on tests of "originality and cognitive ability", and scored significantly better on the selective listening task, leading the authors to interpret this as users having "better control of attention processes" and showing no signs of cognitive impairment. The measures analysed in the selective listening task were not reported. The cannabis users were also more likely to be current polydrug users, and to have used LSD, psilocybin, cocaine, amphetamines and heroin.

Culver and King (1974) used the Halstead-Reitan Battery, the WAIS, the Trail

Making Test, the Laterality Discrimination Test, 3 tests of spatial-perceptual abilities and
the MMPI, to examine the neuropsychological performance of three groups of
undergraduates (N=14) from classes in two successive years. These were: marijuana
users (of at least twice/month for 12 months), marijuana plus LSD users (LSD use of at
least once/month for 12 months), and non-drug users. Significant differences appeared,
disappeared and reappeared among the groups and classes in different years. The only
consistent difference was on the Trail Making Test, on which the cannabis group
performed significantly better than the cannabis plus LSD group, who also used more
cannabis, but cannabis users did not differ from nonusers.

Gianutsos and Litwack (1976) compared the verbal memory performance of 25
cannabis smokers who had used for 2-6 years and at least twice/week for the last 3
months, with 25 nonsmokers who had never smoked cannabis. Subjects were drawn
from an undergraduate university student population and were matched on age, sex, year
at university, major and grade average. Cannabis users were "asked not to smoke before
the experiment" and gave verbal report that they had not "smoked recently" prior to the
time of testing, although the length of abstinence was not reported.

The task was a modification of the Peterson-Peterson paradigm which allows
examination of short- versus long-term storage of verbal information. In the original
version of the task, arithmetic manipulations intervened between word presentation and
recall. The modified task substituted further word reading for the arithmetic, arguing
that such an interference task would prevent rehearsal of words and displace the to-be-
recalled words from short- to long-term storage. In interference tasks of this kind, the
number of words recalled is a function of the number of postlist interference task words.
Subjects were required to recall the first three words from a list of 5, 9 or 13 words read
aloud, and the forced reading of 2, 6 or 10 words constituted the postlist reading task.

Cannabis users recalled significantly fewer words overall than nonusers, and the difference in performance increased as a function of the number of postlist words. Users also generated significantly more intrusion errors than nonusers. The authors concluded that the chronic use of cannabis interfered with the transfer of information from short- to long-term storage.

Carlin and Trupin (1977) assessed ten normal subjects who smoked marijuana daily for at least 2 years (range 2.5 - 8, mean 5; mean age 24; mean years education 14.6) and who denied other drug use. They administered the Halstead Neuropsychological Test Battery after 24 hours abstinence. No significant impairment was found by comparison with nonsmoking subjects matched for age, education and full scale IQ. Cannabis users performed faster on the Trailmaking Test Part B, a test sensitive to frontal damage. Carlin and Trupin concluded that "relatively long-term chronic marijuana use does not impair an individual's ability to solve complex cognitive tasks requiring recurrent observations of subtle stimulus characteristics, to manipulate complex visual motor problems, to answer questions dependent on prior learning, and to be accurate in identifying sensory stimulations, both unilateral and bilateral" (p. 622). They acknowledged, however, that their sample was small and that perhaps less bright individuals may be at greater risk of developing impairments.

In 1981, Schaeffer et al (1981) reported no impairment of cognitive function in one of the first studies of a prolonged heavy cannabis using population in the United States. They assessed ten long-term heavy users of ganga, aged between 25 and 36 years, all of whom were Caucasian, and had been born, raised and educated in the USA (mean years of education 13.5). All had smoked between 30 and 60 gms of cannabis (> 8% THC) per day for a mean of 7.4 years for religious reasons and were active members of a religious sect. They had not consumed alcohol or other psychoactive substances. While this sample contained cannabis users who had not used any other substances, it is not

known what other confounding variables may have been introduced as a result of the peculiarities of belonging to a religious sect. Such a sample may not be representative of the general cannabis using population of Western cultures.

This study was also one of the first to use a laboratory test to assess levels of bodily cannabinoids. Schaeffer et al reported that at the time of testing, all subjects had at least 50 ng/ml cannabinoids in their urines but they also stated that subjects smoked continuously, even during the testing session. Clearly, heavy users such as these would have developed tolerance to many of the effects of cannabis. The tests which were selected to assess intellectual function included the WAIS, the Benton Visual Retention Test, the Rey Auditory-Verbal Learning Test, Symbol-Digits Modalities Test, Hooper Visual Organization Test, Raven's Progressive Matrices and Trail Making (Parts A and B). Since there was no control group, the data was compared with the standardised-normative information available for each test. An attempt was also made to obtain a measure of premorbid intellectual functioning. The authors obtained IQ measures from school assessments for two of the subjects, which were virtually identical to those measured in the study. Overall, WAIS IQ scores were in the superior to very superior range, and the scores of all other tests were within normal limits for age.

Despite the heavy and prolonged use of cannabis, there was no evidence of impairment in the cognitive functions assessed, namely, language function, non-language function, auditory and visual remote, recent and immediate memory, or complex multimodal learning. The authors suggested that tolerance may develop to one or more of the constituents of cannabis, explaining the lack of impairment. Further, it is possible that the superior to very superior intellect of these subjects may have allowed them to compensate for the effects of cannabis, and perhaps they would have performed not only within normal limits, but at a superior level had they not smoked cannabis.

5.3.1 Summary

The results of these empirical studies served to allay fears that cannabis smoking caused gross impairment of cognition and cerebral function. The lack of consistent findings failed to support Kolansky and Moore's (1971, 1972) clinical reports of an organic-like impairment. However, some critics (e.g. Cohen, 1982) have argued that the lack of evidence for impairment in these studies may be a function of their small sample sizes and potentially biased sampling techniques. By focussing on college students, it is suggested, these studies have sampled from a population unlikely to contain many impaired persons. The samples of younger, brighter and "successful" users may reflect the survivors whereas Kolansky and Moore reported on the casualties.

However, such hypotheses conflict with the explanations provided for the lack of evidence of impairment in the cross cultural studies. Soueif's proposition, for example, was that the lower the nondrug level of proficiency, the smaller the size of functional deficit associated with drug usage. This would imply maximal differences at the high end of cognitive ability. Perhaps the argument could be rephrased in terms of maximising the possibility of detecting impairment by sampling from a broader range of ability, minimising the possibility of sampling bias and floor and ceiling effects. In any case, Soueif's claim that the greatest drug-induced impairment would occur in users with the highest levels of arousal, i.e. those for whom mental operations predominate (Fink, 1976b), was not supported by these studies of college students.

A more pertinent explanation for the lack of impairment is that the duration of cannabis use in these samples was quite brief, generally less than 5 years. It has been argued that at the time, cannabis smoking in Western countries had not existed long

enough for impairments to emerge. Further, when psychometric testing was used as a metric of cognitive function as opposed to self-report questionnaires, sample sizes were often too small to permit the detection of any but very large differences between groups.

However, not all studies found negative results. A small number of studies did find significant impairments in their cannabis using populations. What distinguished those studies that found differences between users and nonusers from those that did not? The answer may lie in the specificity of assessment methods. Rather than administering a standard psychometric test battery or tests of general intelligence, the studies that found differences selected tests to assess a specific cognitive function (memory), and attempted to determine the specific stages of processing where dysfunction occurred. Entin and Goldzung (1973), for example, found that users were impaired on both verbal recall and acquisition of long-term storage memory tasks, but not on arithmetic manipulations which require short term storage of information. Gianutsos and Litwack (1976) used an interference condition in the verbal recall memory paradigm, thereby increasing the complexity of the task. Impairments became more apparent in the users as the interference increased, suggesting that cannabis use may affect the transfer of information from short to long term storage.

Given the lack of self-awareness of such deficits, self-report questionnaires would not be able to detect such an impairment. In the other studies, the only assessment of memory function was the inherent components of memory, alertness and concentration throughout all tests of the Halstead-Reitan Battery. Reitan himself acknowledged that their test battery "is probably not as specifically represented in terms of the memory factor as it might be" and that "it might be of value to include supplementary tests of memory" for proper evaluation (1986, p. 10).

5.4 Controlled laboratory studies

A different approach to the investigation of the cognitive consequences of chronic cannabis use is taken in laboratory studies of the effects daily cannabis use over periods of weeks to months. These studies have attempted to control for variation in quantity, frequency and duration of use, as well as other confounding factors such as nutrition and other drug use, by having select samples of subjects reside in a hospital ward while receiving known quantities of cannabis. All of these studies employed pre- and post-drug observation periods, and could be thought of as a short form of longitudinal research. Because of the expense of such studies, sample sizes have generally been were small and the duration of cannabis administration has ranged from 21 to 64 consecutive days.

Dornbush et al (1972) administered 1 g of marijuana containing 14 mg THC to 5 regular smokers (all healthy young students) for 21 consecutive days. The subjects were tested immediately before and 60 minutes after drug administration. Data were collected on subjective ratings of mood, clinical observations, short-term memory and digit symbol substitution tests, and physiological signal recordings. Four subjects demonstrated partial tolerance to the euphoric effects of cannabis after the first week.

Performance on the short-term memory test decreased on the first day of drug administration but gradually improved until by the last day of the study performance had returned to baseline levels. On the post-experimental day baseline performance was surpassed. Performance on the digit symbol substitution test was unaffected by drug administration and also improved with time, suggesting a practice effect. There was evidence of a cumulative effect of THC on behaviour and no withdrawal symptoms were observed after the end of administration. The authors interpreted their results as showing "the apparent safety of smoking 14 mg/day THC for 3 weeks".

Mendelson, Rossi and Meyer (1974) reported a 31 day cannabis administration study in which 20 healthy, young male subjects (10 casual and 10 heavy users, mean age 23) were confined in a research ward and allowed 21 days of ad libitum marijuana smoking. A multidisciplinary battery of tests (psychiatric, psychological, physiological, biochemical and sociological) were administered during: a 5 day drug-free baseline phase, the 21 day smoking period, and a 5 day drug free recovery phase. Acute and repeat dose effects of marijuana on cognitive function were studied with a battery of psychological tests known to be sensitive to organic brain dysfunction (WAIS, Halstead Category Test, Tactual Performance Test, Seashore Rhythm Test, Finger Tapping Test, Trail Making Test).

Overall, there was no overt impairment of performance prior to or following cannabis smoking nor was there any difference between the performance of the heavy and the casual users. Short term memory function, as assessed by digit span forwards and backwards, was impaired whilst intoxicated and there was a relationship between performance and time elapsed since smoking. An interesting finding was that subjects performed better when they were aware that the effects of cannabis smoking on memory were being assessed, than when they were not. This was interpreted as evidence that the:

"acute deleterious effect of marihuana on ability to perform on a memory task may not be a reflection of direct impairment of neuronal systems subserving memory, but rather a reflection of what a person chooses to attend to while under the influence of the drug" (p. 180).

Reed (1974) reported that two of the subjects in each group showed "unequivocal evidence of impairment" in some aspect of cognitive or motor functioning. Two of the heavy users performed quite poorly on the Trail Making Test, and they and two casual

users showed no consistent patterns of improvement on other tests. Their scores were lower than would have been predicted on the basis of their IQ scores and educational background. The probability of detecting such impairment in the normal population of healthy young adults would be low but it was not possible to find any relationship to prior history of cannabis use. The authors claimed that tolerance did not develop to the impairing effect of cannabis over the 21 day period, and that there were no indications that cannabis interfered with the ability of subjects to improve their performance with practice, which could be interpreted as a result of the development of tolerance.

Rossi and O'Brien (1974) assessed memory and time estimation in the same sample of subjects. They wanted to explore the possible mechanisms of the observation that marijuana produces a subjective impression that time is passing slowly. One hypothesis is that of a direct pharmacological action on neuronal systems serving as a "biological clock". Another possibility is that altered time perception is incidental to the effects of cannabis on perception, memory and organization of thought, with a loosening of associations and the rapid flow of ideas speeding up the subjective sense of time. A further possibility is that short-term memory impairment may interfere with a sense of temporal continuity which is an essential element in time perception.

The results of the study suggested that the effect on time perception was mediated directly through the action of THC on the central nervous system. They found a short term acute effect on time perception (speeding up of the internal clock), and a longer-lasting compensatory effect (slowing of the internal clock) which parallelled the stimulatory and depressant effects of the drug. Tolerance to the acute effect on time perception developed during the 21 day period.

Similar failures to detect cognitive effects have been reported by three other groups of investigators. Frank et al (1976) assessed short term memory and goal directed serial

alternation and computation in healthy young males over 28 days of cannabis administration. Harshman et al (1976) and Cohen (1976) conducted a 94 day cannabis study in which thirty healthy moderate to heavy male cannabis users, aged 21-35, were administered on average 5.2 joints per day (mean 103 mg THC, range 35-198 mg) for 64 days and were assessed on brain hemisphere dominance before, during and after cannabis administration. Psychometric testing was not employed, but subjects were given two work assignments with financial incentive; a "psychomotor" task involving the addition of two columns of figures on a calculator, and a "cognitive task" of learning a foreign language. No long term impairments were detected with these somewhat inadequate assessment materials.

5.4.1 Summmary

The experimental studies of daily cannabis usage for periods of up to 3 months in young adult male volunteers have consistently failed to demonstrate a relationship between marijuana use and neuropsychological dysfunction. This is not surprising given the short periods of exposure to the drug in these studies. Furthermore, since subjects served as their own controls, and had all used cannabis for at least one year prior to the study, it would be surprising if an additional few months of cannabis produced any significant decrements in performance. It may take many years for subtle impairments to be detected.

5.5   Recent research

The equivocal results of the early investigations into long term effects of cannabis on cognitive function, together with the problem of relatively short exposure in Western cultures, led to something of a hiatus in research on the cognitive effects of cannabis in the 1980s. Although the accumulated evidence indicated that cannabis did not severely affect intellectual functioning, uncertainty remained about more subtle impairments. Their study required advances in methodology and assessment techniques. Reports of mental deterioration and impaired cognitive functioning in cannabis users continued to be reported in the clinical literature (eg. NIDA, 1982) and anecdotally.

In the meantime, considerable advances were made in the field of cognitive psychology and neuropsychology. There were substantial theoretical developments in the fields of cognition, memory function and information processing, and more sensitive measures of cognitive processes were developed. Moreover, by the late 1980s, it was no longer the case that the use of cannabis was a relatively recent occurrence in Western societies. Indeed, cannabis use had become so widespread, and was being used at a progressively younger age, to revive interest in the issue.

Research from the late 1980s through the 1990s improved upon the design and methodology of previous studies in a number of ways. It ensured the use of adequate control groups, attempted to verify abstinence from cannabis prior to testing, and attempted to precisely quantify the levels of cannabis use. In addition, there has to some extent been a narrowing of focus on the cognitive functions assessed, with greater attention to investigating specific cognitive processes and relating impairments in them to the quantity, frequency and duration of cannabis use.

The greater specificity in focus has been made possible by accumulating evidence from previous research, and advances in pharmacology and biochemistry, which suggests that cannabis primarily exerts its effect upon those areas of the brain responsible for attentional and memory functioning. Miller and Branconnier (1983), for example, reviewed the literature and concluded that the effects of cannabis on human memory is the single most consistently reported psychological deficit produced by cannabinoids acutely, and the most consistently detected impairment in studies of long-term cannabis use. They proposed that the observed deficits in attention, memory consolidation and sequential-integration behaviours were mediated by the cholinergic limbic system, particularly in the septal-hippocampal pathway.

This proposal was supported by an earlier study which reported the similarity between cannabis-induced impairments of memory and those due to hippocampal damage (Drew et al, 1980). Performance of hippocampally lesioned patients on a battery of psychometric tests thought to assess various aspects of auditory and visual recent memory and mental set shifting, were compared to retrospective data from cannabis intoxicated subjects. Tests for comparison included the Babcock Story Recall, digit span, paired-associate learning, and the Benton Visual Retention Test (for patients) or the similar Army Designs task (for marijuana intoxicated subjects). When compared to controls, the two groups exhibited similar impairments of memory function, although the cannabis intoxicated subjects produced significantly more intrusion errors.

Intrusion errors are one of the most robust phenomena of cannabis-induced memory deficits in tasks of both recall and recognition (Miller and Branconnier, 1983). Such errors involve the introduction of extraneous items, word associations or new material during free recall of words, or the identification of false or previously unseen items in recognition. Miller and Branconnier conjectured that the mechanism causing intrusion errors was the failure to exclude irrelevant associations or extraneous stimuli

during concentration of attention, a process in which the hippocampus plays a major role. The finding of high densities of the cannabinoid receptor in the cerebral cortex and hippocampus (Herkenham et al, 1990) supports the hypothesis that cannabinoids are involved in attentional and memory processes. Past studies of long-term effects of cannabis have not used sufficiently specific nor sensitive measures of such processes.

It is also important to note that most past studies have been conducted on adults, while the effects of long-term cannabis use on the young have not been adequately addressed. With an increase in the prevalence of cannabis use among adolescents and young adults in Western society, there has been a growing concern about its possible impact on the psychological development of young people. This is important because of the possibly deleterious effects of such a psychoactive substance upon psychosocial adaptation and maturation during their formative years, and the effects on cognition, learning and scholastic achievement.

In the first study of its kind with adolescents, Schwartz et al (1989) reported the results of a small but carefully controlled pilot study of persistent short-term memory impairment in 10 cannabis-dependent adolescents (aged 14-16 years). Schwartz's clinical observations of adolescents in a drug-abuse treatment program suggested that memory deficits were a major problem, which according to the adolescents persisted for at least 3 to 4 weeks after cessation of cannabis use. His sample was middle-class, North American, matched for age, IQ and absence of any previous learning disabilities with 17 controls, 8 of whom were drug abusers who had not been long-term users of cannabis, and another 9 had never abused any drug. The cannabis users consumed approximately 18 g per week, smoking at a frequency of at least 4 days per week (mean 5.9) for at least 4 consecutive months (mean 7.6 months but the range was not reported). Subjects with a history of excessive alcohol or phencyclidine use were excluded from the study. Cannabinoids were detected in the urines of 8 of the 10 users over 2 to 9 days.

Users were initially tested between 2 and 5 days after entry to the treatment program, this length of time allowing for dissipation of any obvious short-term effects of cannabis intoxication on cognition and memory. Subjects were assessed by a neuropsychological battery which included the Wechsler Intelligence Scale for Children, and six tests "to measure auditory/verbal and visual/spatial immediate and short term (delayed) memory and praxis (construction ability)" (p. 1215). These were the Peterson-Peterson Short-Term Memory Paradigm, Buschke's Selective Remembering Test, the Benton Visual Retention Test, Wechsler Memory Scale Prose Passages, Rey-Osterrieth or Taylor's Complex Figure Drawing, and a Paired Associate Learning Test. After six weeks of supervised abstinence with bi-weekly urine screens for drugs of abuse, they were administered a parallel test battery.

On the initial testing, there were statistically significant differences between groups on two tests: cannabis users were selectively impaired on the Benton Visual Retention Test and the Wechsler Memory Scale Prose Passages. The differences were smaller but were still detectable 6 weeks later. Analysis of test measures showed cannabis users to commit significantly more errors than controls initially on the Benton Visual Retention Test for both immediate and delayed conditions, but differences in the 6-week post-test were not significant. Users scored lower than controls on both immediate and delayed recall in the Wechsler Memory Prose Passages Test in both test sessions. The authors concluded that "cannabis-dependent adolescents have selective short-term memory deficits that continue for at least 6 weeks after the last use of marijuana". Further testing beyond 6 weeks, while not possible in this study, would have provided useful information on the recovery of function. The fact that there was a trend toward improvement in the scores of cannabis users suggests that the deficits observed were related to their past cannabis use and that functioning may return to normal following a longer period of abstinence.

The authors discussed the clinical implications of their results in terms of the need to develop treatment strategies which address the possible long-lasting cognitive deficits which affect both performance of complex tasks and the ability to learn. They referred to investigations which suggest that adolescents with learning disabilities are at high risk of cannabis abuse. Their own results heighten concerns about the effects of long-term cannabis use on learning-impaired adolescents. For such individuals, regular use of cannabis, even to a lesser degree than that used by Schwartz's sample, may significantly contribute to worsening school performance. Further, they suggest that individuals with learning disabilities and those who have a borderline or low IQ might be even more susceptible to cannabis-induced deficits of short-term or recent memory.

Schwartz's study was the first well controlled study to demonstrate cognitive dysfunction in cannabis using adolescents with a brief mean duration of use. The implications of these results are that young people may be more vulnerable to any impairments resulting from cannabis use. Unfortunately, like many of its predecessors, Schwartz's team made little effort to interpret the significance of the selectivity of their results. There was nothing to suggest which specific elements of memory formation or retrieval were disrupted. The two tasks represented two different types of information processing. The Benton requires the retention of visual information in iconic or unprocessed form over very brief periods, whereas the Wechsler task requires the extraction of abstractions from stories, encoding these abstractions, retrieving information and complex responding. The authors acknowledged that their "data provide little guidance on which to formulate hypotheses concerning the neurologic substrates of the observed results" and suggested that the "isolation of the location and types of disruptions that account for the current results should therefore be one goal of future research in this area".

One crucial requirement for evaluating the performance of chronic marijuana users is comparison with an appropriately matched group of nonusing subjects. Although the studies described have made substantial progress in this regard, one concern remains that some of these impairments may have been present in the cannabis users prior to their cannabis use. Short of an expensive longitudinal study that follows children over many years, the most desirable procedure is to match groups of users and nonusers on some measure of intellectual functioning obtained before the onset of drug use.

Block et al (1990) have conducted a study in which they used scores on the Iowa Tests of Basic Skills collected in the fourth grade of grammar school. These are standardised ability tests that have been administered to almost all grammar school children in Iowa for several decades. Block et al used these scores to establish that their user and nonuser samples were comparable in intellectual functioning before they began using marijuana. The study's aim was to determine whether chronic marijuana use produced specific cognitive impairments, and if so, whether these impairments depend on the frequency of use. Block and colleagues assessed: 144 cannabis users, 64 of whom were light users (1-4/week for 5.5 years) and 80 heavy users ($\geq$ 5/week for 6.0 years) (range 2-10+ years use), and compared them with 72 controls. Subjects were aged 18-42, but mean age was not reported and subjects did not appear to be matched on sex. Twenty-four hours of abstinence was required prior to testing.

Subjects participated in two sessions. In the first session they completed the 12th grade version of the Iowa Tests of Educational Development, which emphasise basic, general intellectual abilities and academic skills and effective utilisation of previously acquired information in verbal and mathematical areas (subtests include Vocabulary, Correctness and Appropriateness of Expression, Ability to do Quantitative Thinking and Ability to Interpret Literary Materials plus a Short Test of Educational Ability). In the second session subjects were administered computerised tests that emphasise learning

and remembering new information, associative processes and semantic memory retrieval (eg.free and constrained associations, paired-associate learning, text learning, Buschke's Selective Reminding Task), concept formation and psychomotor performance (eg. discriminant reaction time and critical flicker fusion). The tasks selected had been previously shown to be sensitive to the acute effects of cannabis, or (from the limited data available) the effects of chronic use. They were also relevant to the skills required in school and work performance.

The results showed that while users and nonusers were matched on 4th grade Iowa scores, heavy users showed impairment on two tests of verbal expression and mathematical skills when tested on the 12th grade Iowa test. The results of the computerised tests, reported several years later (Block and Ghoneim, in press) showed that heavy, chronic marijuana use of at least 7 times/week did not produce overall impairments in Buschke's Test but selectively impaired the retrieval of words that were easy to visualise. Only two tests showed overall impairment (Correctness and Appropriateness of Expression, and Ability to Do Quantitative Thinking), while one showed superior performance in a particular test condition (Concept Formation, fuzzy concepts) in users of moderate frequency (5-6/week). The authors were also able to show reasonable, albeit imperfect, agreement between acute and chronic effects of marijuana on cognition by comparison with the results of another study examining the acute effects of cannabis in the same battery of tests (Block, Farinpour and Braverman, 1992). The impairments associated with heavy, chronic use were much less pervasive than the immediate effects of marijuana smoking. Two tests showing a large degree of impairment acutely (Ability to Interpret Literary Materials, and Text Learning) showed no long term adverse effect. This research has been among the first to directly compare the acute and chronic effects of cannabis upon the same test battery, and the authors point out that while acute and chronic effects of drugs are sometimes similar, they can also be markedly different.

Leon-Carrion (1990) compared a group of 23 male chronic cannabis users (aged 18-27, 2.5 joints/per day for 4.5 years) to a matched control group on the subscales of the WAIS. The cannabis users had significantly lower scores than controls on six of the eleven subscales: Comprehension, Similarities, Vocabulary, Block Design, Picture Arrangement and Object Assembly. Overall, the cannabis users scores were lower than would be expected for their age. Their Full Scale IQ, and both Verbal and Performance IQ, were lower than controls. These results suggest that the cannabis users may well have differed in ability from controls prior to their having commenced using cannabis, even though the author argues against this on the basis of socioeconomic, cultural and educational status. A vocabulary score alone is perhaps the single best indicator of original intellectual endowment, being the the most resilient to insult. Nevertheless, the author's interpretation of the results is in accord with many other observations: users were most impaired in their ability to learn from experience, their capacity for compromise, elaboration of adequate judgements and situational adaptation, and organizational, verbal and communication skills. Many of these abilities are thought to be under the control of the frontal lobes.

It appears that the same group of subjects were assessed on an 8 hour long version of the Trail Making Test to investigate cognitive styles and relations between both cerebral hemispheres (Leon-Carrion and Vela-Bueno, 1991). Cannabis users exhibited great fluctuation between cognitive styles and weaker dominance-subdominance hemispheric alternation which was clearly maintained over time in controls. The authors interpreted these findings to suggest that chronic consumption of cannabis "can affect cognitive styles and the brain, altering the Basic Rest Activity Cycle between the hemispheres" (p. 948). The significance of these findings is open to interpretation, although the tests may be tapping some aspect of frontal lobe function.

A very different approach to assessing the long-term consequences of exposure to cannabis has been taken in an exceptionally well controlled longitudinal study of children who had been prenatally exposed to cannabis in utero (the Ottawa Prenatal Prospective Study (OPPS)). A summary of the results to date is presented by Fried (1993). For the purposes of this paper, only assessments of the cognitive and central nervous system development of the children, and only those effects which remained statistically significant after controlling for many potentially confounding variables, such as birth weight, other drug use, socioeconomic status and nutrition, will be discussed.

The levels of exposure to cannabis in the sample were approximately as follows: 60% of the mothers used cannabis irregularly, 10% reported smoking 2-5 joints per week, and 30% smoked a greater amount during each trimester of pregnancy. Prenatal exposure to cannabis was associated with high pitched cries, disturbed sleep cycles, increased tremors and exaggerated startles in response to minimal stimulation in newborn to 30 day old babies. The babies showed poorer habituation to visual stimuli, consistent with the sensitivity of the visual system to the teratogenic effects of cannabis demonstrated in rhesus monkeys and rats. Fried's interpretation of these findings was that exposure to cannabis may affect the rate of development of the central nervous system, with particularly slow rate of maturation of the visual system. This hypothesis was supported by visual evoked potential studies of the children at 4 years of age. Children who had been exposed to cannabis in utero showed greater variability and longer latency of the evoked potential components, indicating immaturity in the system.

From 1 to 3 years of age, no adverse effects of prenatal exposure were found. At 2 years it appeared that the children were impaired on tests of language comprehension, but this effect did not persist after controlling for other factors such as ratings of home environment. At 4 years of age, however, the children of cannabis using mothers were significantly inferior to controls on tests of verbal ability and memory. The explanation

for the gap in detecting impairments in the preceding age range, was that the degree and types of deficits observed may only be identifiable when cognitive development has proceeded to a certain level of maturity. It has been suggested that it is around this age that the frontal lobes begin to function.

At 5 and 6 years of age, the children were not impaired on global tests of cognition and language. By age 6, however, there was a deficit in sustained attention on a task that differentiated between impulsivity and vigilance. Fried proposed that "instruments that provide a general description of cognitive abilities may be incapable of identifying nuances in neurobehavior that may discriminate between the marijuana-exposed and non-marijuana exposed children" (p. 332). He suggested the need for tests which examine specific cognitive characteristics and strategies, such as the test of sustained attention. Fried warned that his sample came from a middle class, low risk population and that his findings should therefore be interpreted as somewhat conservative estimates of the potential risk. In accordance with the results of many of the studies reviewed here, he concludes that cannabis "may affect a number of neonatal behaviours and facets of cognitive behavior under conditions in which complex demands are placed on nervous system functions".

Converging evidence for frontal lobe dysfunction is also available from the results of an ongoing NIDA funded project (principal investigator F. Struve) to investigate persistent central nervous system sequelae of chronic cannabis exposure. This research which has focussed upon quantitative EEG techniques, has found significant increases in absolute power, relative power and interhemispheric coherence of EEG alpha and theta activity, primarily in frontal-central cortex, in daily cannabis users of up to 30 years duration compared to short term users and nonusers (eg. Struve et al, 1993). The results suggest that there may be a gradient of quantitative EEG change associated with progressive increases in the total cumulative exposure (duration in years) of daily

cannabis use which may indicate organic change. One major limitation of this research, however, is that changes in frequency of EEG spectra have not been related to cognitive operations, unlike event-related potentials (ERPs) which as their name implies have identified components reflecting specific cognitive events. Therefore, the EEG results, interpreted as a basic measure of brain function and discussed in Chapter 4, will not be discussed any further here. One study from this group did use cognitive event-related potential measures (Straumanis et al, 1992) and is discussed in Chapter 6. The remainder of the discussion of research from this group concentrates on the assessment of cognitive functioning by neuropsychological tests.

Complete results of these investigations have not yet been published, but preliminary analyses of the neuropsychological test data have been presented at conferences (eg. Leavitt et al, 1991; 1992; 1993). These investigations have been exceptionally well controlled. Subjects were extensively screened for current or past psychiatric or medical disease or CNS injury, and underwent extensive drug history assessments with 8 weeks of twice weekly drug screens. Groups were matched for age and sex. Daily cannabis users who had at least 3 years to 6 years of use were compared to a group who had used for 6-14 years, a special interest group who had used on a daily basis for 15 years or more, and a nonuser control group. Sample sizes varied from study to study, but averaged approximately 15 per group.

An extensive battery of psychological tests included measures of simple and complex reaction time (using Sternberg's procedure), attention and memory span (eg. digits forward and backward, continuous performance task, Trail Making, serial addition/subtraction, divided attention (paced auditory serial addition test), Stroop interference task), language and comprehension tasks, construction (complex Rey figure), verbal and visual learning/memory (Wechsler Memory Scale and California Verbal Learning Test (CVLT)) and "higher" mental abilities/concept formation/logical

reasoning (WAIS-R, Category Test and Conceptual Level Analogies Test (CLAT)). The effects of age and education were addressed through a multiple regression procedure which removed expected values computed using only age and education from all outcome variables. Only nonusers were used to estimate regression weights and these were "jackknifed".

Preliminary analyses have shown test scores in general to show a gradation, with the best performance characterising nonuser controls, followed by the daily cannabis users and the worst mean scores occurring for the ultra long-term special interest group (Leavitt et al, 1991; 1992; 1993; Leavitt, personal communication). Neuropsychological measures which would not be expected to be affected by cannabis use (eg. Information and Vocabulary subtests of the WAIS-R) were not significantly different between groups. Selected WAIS-R subtests did show significant differences between groups, with, in each case, the daily cannabis users performing more poorly than controls and the greatest level of impairment being found in the ultra long-term group. Select subscales of the Revised Wechsler Memory Scale showed similar trends. Long duration users performed more poorly than short term users and controls, and there were few differences between the latter two groups, on complex reaction time, verbal learning/recall (CVLT), complex reasoning/conceptual abilities (Category, CLAT) and short term memory (verbal, visual, delayed Wechsler Memory Scale subtests). There was a trend toward poorer performance on the complex mental tracking task (paced serial addition test). The authors claimed that duration of use was related to impaired performance, but did not report any correlations. Tests sensitive to mild cortical dysfunction were those most affected in the long-term user groups. The results attest to the importance of taking cumulative duration of exposure to cannabis into account when studying the cognitive functioning of chronic cannabis users.

One of the robust sequelae of acute intoxication is altered time sense and the underproduction of time estimations has been demonstrated and replicated in many studies. A further study from this group has investigated time production in chronic users after 24 hours abstinence (Webb et al, 1992; 1993). In one study (Webb et al, 1992), 28 daily users ($\geq$ 7 joints/week for $\geq$ 3 years) displayed greater time underproduction than 32 controls, suggesting that time distortion may persist beyond the acute phase of intoxication. Additional analyses suggested that time distortions were greater for long-term than short-term users. A further study verified these observations with 21 long duration users of more than 15 years who were compared with 13 moderate users of 3-7 years, who in turn did not differ from 44 controls (Webb et al, 1993). The major differences occurred in a condition which involved incorporating feedback, and the authors concluded that the ability to benefit from feedback was compromised by long duration exposure to cannabis.

This series of studies made an important advance in terms of its rigorous methodology, extensive range of neuropsychological assessment tests, and the analyses and interpretations of the results. The authors acknowledge that small sample sizes dictate caution and that there were no data available to assess the premorbid cognitive capacity of these subjects. Nevertheless, the results allowed the following conclusions to be drawn (Leavitt, personal communication):

1) while basic attentional processes appear to be intact, long-term cannabis users are less efficient when performing complex cognitive tasks or attempting to resist distraction;

2) long-term users' ability to efficiently process information declines more rapidly under a moderate cognitive load when compared with controls or short duration users;

3) while remote memory appears unaffected, long-term users are inefficient at learning and recalling information over the short-term, especially when the task is unfamiliar or complex; they show increased susceptibility to retroactive interference, whereby new information interferes with the retrieval of old information (which is consistent with difficulty in resisting distraction);

4) long-term users are inefficient at performing complex tasks that require cognitive flexibility, recognition of unproductive planning strategies, and learning from experience, functions that have been clinically associated with the frontal area;

5) because language and verbal intellectual abilities appear unaffected, long-term cannabis users may cope reasonably well with routine tasks of everyday life, but they may have difficulties with verbal tasks that are novel and/or which cannot be solved by automatic application of previous knowledge.

Overall, the results suggested that long duration users seem to process some kinds of information more slowly as compared to nonusers, and that the effects of long-term cannabis use are most likely to surface under conditions of moderately heavy cognitive load. The authors recommend further specific assessments to fully explore the scope and nature of deficits in long duration user populations (Leavitt et al, personal communication).

5.6 Conclusions

The weight of evidence suggests that the long term use of cannabis does not result in any severe or grossly debilitating impairment of cognitive function. However, there is

sufficient evidence from the studies reviewed above, that the long term use of cannabis leads to a more subtle and selective impairment of cognitive functioning. Impairments appear to be specific to higher cognitive functions, which include the organization and integration of complex information involving various mechanisms of attention and memory processes. The evidence suggests that prolonged heavy use may lead to progressively greater impairment. It is not known to what extent such impairment may recover with prolonged abstinence.

Our understanding of the long term cognitive effects of cannabis is far from complete. Researchers in the field have continued to recommend that these effects be examined with greater sensitivity and specificity. It is is the aim of this thesis to do precisely that. Selective attention was selected as a specific aspect of cognitive functioning for assessment, on the grounds that attentional mechanisms underly most of the functions where impairments have been detected. The particular susceptibility to distraction, the loosening of associations and the intrusion errors seen in memory tasks all point to a problem with distractibility, perhaps an inability to maintain a focus of attention. It is clear that any deficit will only manifest under a moderate cognitive load, in a complex task. Event-related potentials (ERPs) were selected as a sensitive measure of the processes of selective attention, an as yet under-utilised tool in the cannabis research arena. The combination of a complex task with a sound normative base, and careful experimental design provide the opportunity to explore with validity, reliability and greater specificity the long term cognitive effects of cannabis.

CHAPTER 6

SELECTIVE ATTENTION AND EVENT-RELATED POTENTIALS (ERPs)

6.1 Selective attention

Selective attention is one of a number of processes which collectively comprise the state of attending to the environment. William James described the essence of this process more than a century ago:

"Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously impossible objects or trains of thought. Focalization, concentration of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others" (James, 1890).

Thus, selective attention could simply be defined as those processes which allow some stimuli to be processed more rapidly and effectively than others, or "the predisposition of an organism to process selectively relevant, as compared to irrelevant, environmental information" (Harter and Aine, 1984). An adequate model of selective attention has not yet been formulated. Selective attention may be viewed as a facilitatory mechanism that enhances the processing of relevant stimuli, or it may be viewed as a filtering mechanism protecting a limited capacity central processor from overload by irrelevant sources of information.

Early behavioural research and theorising in the area was initiated by Broadbent (eg. 1958). The aim of continuing research has been to elucidate the processes involved in the selection of relevant from irrelevant information, to determine where how and when differential processing occurs, and to establish the fate of the irrelevant information or to what extent it is processed. The main models of selective attention have been based on "early" versus "late" selection theories. Early selection theories propose that the selection of the to-be-attended stimulus occurs at a very early stage of processing and is based on the physical feature differences between the to-be-attended and the to-be-ignored stimuli. Late selection theories propose that all incoming information is fully analysed before selection of the to-be-attended stimulus occurs, and selection is based on the representation of an appropriate stimulus in a short-term memory store. Each theory has variously been supported or discredited by experimental evidence.

Much of the discrepancy from behavioural data may have arisen from the fact that there were two types of dichotic listening tasks generally used in selective attention experiments which were assumed to invoke the same processes. In the first, subjects are required to shadow information presented in the relevant channel (eg. an attended ear) while ignoring competing prose or words in the irrelevant channel (eg. the other, unattended ear). The degree of interference and intrusions from the irrelevant channel provide a measure of the processing of the irrelevant stimuli and their distractibility value. In the second type of paradigm subjects are required to attend to a particular channel and respond to a predetermined stimulus or class of stimuli. Measures of reaction time were thought to indicate the amount of processing required for correct selection of targets in the presence of competing distractors. Kahneman and Treisman (1984) pointed out that these paradigms may not necessarily tap the same underlying processes.

Broadbent's (1958) "early selection" theory proposed that selection is achieved by a filter which screens irrelevant input based on differences between physical features of the to-be-attended and the to-be-ignored stimuli at a very early stage, before conscious perceptual analysis has even taken place. One problem with this model was that while it allowed for switching between channels, it did not allow for simultaneous processing of more than one channel, such as in divided attention tasks, yet various dichotic listening studies established that deeper processing of stimuli from the to-be-ignored channel did occur (eg. Treisman, 1964a; evidence also came the Stroop effect). Broadbent argued that irrelevant stimuli were completely eliminated from the information processing system, while Treisman proposed that unselected messages were merely attenuated.

According to "late selection" models (eg. Deutsch and Deutsch, 1963) all incoming information is processed in parallel and fully analysed before selection of the to-be-attended stimulus occurs. Selection is based on a comparison of incoming information with a representation of the physical characteristics of a stimulus in a short term memory store. The late selection models, however, were unable to explain why a semantic change, for example, would be more difficult to detect than a physical change. Johnston and Dark (1982) cited many examples of experimental evidence which did not fit either early or late selection theories. A number of intermediate models were developed to account for the seemingly discrepant findings of behavioural research.

Broadbent (1971), for example, modified his original all-or-none theory in proposing two different processes: "stimulus set" or filtering in which relevant stimuli are distinguished from irrelevant stimuli at an early stage on the basis of a simple physical feature (eg. colour); and "response set" when the difference between relevant and irrelevant stimuli is less discriminable (eg. semantic) and relevant stimuli are distinguished by a common set of responses. With further revision, these terms were dispensed with and replaced by a model of early filtering, which was passive, and

occurred in the pre-attentive stage, a later, active attentional phase of verification, termed "pigeonholing", and a third phase of "categorizing" complex stimulus configurations (Broadbent, 1977; 1982). All of these modifications nevertheless assumed discrete, limited capacity stages of information processing of limited speed. Early selection of a single channel achieved by a filter was a requirement in order to not overload the system. Neither early nor late selection theories were able to adequately explain the intrusion of irrelevant information at certain times and not others.

Kahneman (1973) proposed an allocation model of selective attention in which attentional processing resources from a limited capacity pool are flexibly distributed amongst competing tasks. The amount allocated depended on the nature of the task and may facilitate the processing of some stimuli at the expense of others; "spare" capacity resources may be allocated to the processing of irrelevant stimuli. Little spare resources are available for irrelevant stimuli in complex and demanding tasks. This model allowed for concurrent performance of a number of tasks, with flexible allocation of resources according to task demands, which may change (or the perception of which may change) momentarily. Only if the combined processing demands of the tasks exceeded the limited capacity available, was performance on one or the other or both tasks impaired.

The variation in cognitive processing requirements implied that some processes must occur automatically and can hence occur in parallel while others entail controlled, conscious and effortful processing, drawing upon the limited resources (eg. Schneider and Shiffrin, 1977; Shiffrin and Schneider, 1977). However, these distinctions could not adequately explain how attentional resources are selectively allocated nor the fate of irrelevant information. The extent of automaticity of information processing was contentious also between the early and late selection models: late models assumed far more automaticity. The issue of automaticity is central to the debate concerning the processes of selective attention, for the more that can be explained by automatic

processing, the less that needs to be attributed to attentional mechanisms (Näätänen, 1988).

A different school of thought described selective attention in terms of encoding, schema theory and priming effects (eg. Hochberg, 1978; Neisser, 1976). In this facilitatory conceptualisation, certain information is primed for processing whereas irrelevant stimuli are neither filtered, inhibited or attenuated, but are simply not analysed further because they fail to match the schema. Tipper and Cranston (1985) proposed that active inhibition of distractors, as opposed to passive decay, may be one mechanism of successful selective attention; initially targets and distractors are processed in parallel up to categorical levels of representation, from which point targets receive further processing but distractors are actively inhibited. Cowan (1988) proposed a habituation model of selective attention, whereby a physical representation of the irrelevant stimuli is formed in memory and following repeated presentations allows habituation to such stimuli. When a physical change occurs in the irrelevant channel, a mismatch with the representation causes orientation to that stimulus or channel. This mismatch is supported by psychophysiological evidence of "mismatch negativity" (MMN) (Näätänen, 1985; Näätänen and Picton, 1986) (see below). This model assumes that perceptual analysis takes place automatically, and that controlled activation by a central executive processor directing attention to relevant stimuli, prevents their habituation. *How* the central executive does so is not explained.

Aside from these traditional cognitive theories, selective attention has recently been explained in terms of connectionist models (eg. Grossberg and Stone, 1986; McClelland, 1988). However, these theories focus on parallel, distributed processing that occurs very quickly and cannot explain those processes that take longer and have a serial component. Broadbent (1985) has argued that connectionist models are inappropriate in cognitive psychology because they are on a different computational

explanatory level, intermediate between cognitive and neural models.

The argument over whether the processing of multiple attributes of stimuli proceeds in parallel or in a serial manner has been around for decades and also remains unresolved, with much experimental evidence to support or discredit either theory. The data suggests that processing begins in parallel, with some attributes processed independently and some simultaneously, some features extracted earlier than others (Posner, 1978). Some have argued that processing in a novel task is initially serial and that parallel processing only develops with practice (eg. Shiffrin and Schneider, 1977). Treisman and colleagues (eg. 1980) developed a feature integration theory in which it was proposed that the processing of complex multidimensional stimuli occurred in two stages; in the first, simple analysis of stimulus features (eg. colour, orientation) occurred rapidly, in parallel and automatically; the second stage involved the conjunction of these features into objects, which occurred slowly in a serial fashion and required focal attention. (Woods, Alho and Algazi (1994) recently reported brain event-related potential (ERP) evidence that feature conjunction in the auditory modality occurs very early, before the analysis of individual features is complete). Most of these theoretical developments, however, arose from research into visual selective attention.

In contrast, auditory attention research was dominated by dichotic listening type tasks which continued to be interpreted in terms of filtering models. While this research provided some information regarding the nature of selective attention, the debates about early versus late selection, the extent of automaticity, and the extent of processing of irrelevant stimuli were not resolved. This was due to the fact that theories could only be developed and tested by reliance on behavioural data obtained during performance of such tasks as dichotic listening, signal detection and priming tasks. Since overt responses are withheld for irrelevant stimuli, behavioural data cannot reveal the extent of automaticity, nor to what extent unattended information is processed. The advent of

sensitive new techniques of recording the electroencephalograph (EEG) while subjects were engaged in dichotic listening tasks, for example, provided a way of re-evaluating the nature of selective attention processes. Such techniques based on event-related potential interpretations, discussed below, have amassed a wealth of data over the past 15 years which has generally been interpreted as resolving the debate in favour of early selection theories (Hansen and Hillyard, 1983; Hansen, 1989).

Early selection models, generally implied serial dependency between the early and later stages of analysis. However, Hansen and Hillyard (1983) pointed out that equivalent economy of processing is possible under parallel or holistic models of feature analysis, "provided that analyses terminate as soon as sufficient evidence accrues that a stimulus is irrelevant". This interpretation implied contingent or hierarchical information processing, where "the level of one stimulus dimension influences the depth or extent of processing of other dimensions" (Hansen and Hillyard, 1983). Hierarchical models of information processing predict that those stimulus features that are easily discriminable are initially selected for allocation of attention, followed by more complex, less discriminable features. This process continues until all stimuli that do not share every attribute of the relevant attended stimulus are gradually filtered out and not accorded any further processing. Thus, only those stimuli selected on the basis of having one relevant attribute would receive further processing for the presence of other relevant attributes. This model was well supported by ERP data. Late selection models, on the other hand, predicted an exhaustive search of all stimulus attributes, which was found not to occur under analysis of ERP traces to relevant attended and irrelevant unattended stimuli.

The selective attention task of Hansen and Hillyard (1983) has become a most widely researched paradigm, producing results consistent with a hierarchical information processing model across various experimental manipulations. It is a complex multidimensional auditory selective attention task in which tone pip stimuli vary on the

dimensions of location, pitch and duration. In their 1983 paper, Hansen and Hillyard manipulated the physical dimensions of location and pitch such that one discrimination was more difficult than the other. For example, in the easy location/difficult pitch condition, tone pips were delivered randomly to the left or right ear, an easy discrimination, but within each ear, tone pips varied only slightly in pitch, either high or low, such that they were difficult to discriminate. In the difficult location/easy pitch condition, tone pips were delivered such that they were subjectively perceived to be occurring at some point towards the back of the head, making a decision as to whether they were occurring on the left or right quite difficult, but they were vastly different in pitch. In each case, the ERP pattern indicated that the rejection of the easy irrelevant dimension occurred early (eg. rejecting half the stimuli on the basis of location), and selection/rejection within the difficult dimension was contingent upon further processing of the selected stimuli (eg. after half of the stimuli were selected on the basis of coming from the relevant location, they were further processed before half were rejected again on the basis of being of the wrong pitch).

Anatomical concepts of cerebral organization lend support to both parallel and hierarchical mechanisms in stimulus processing, but no single anatomical model has been able to fully explain the anatomy of selective attention, in terms of how the nervous system selects relevant stimuli and suppresses irrelevant stimuli. One theory claims that selection occurs at the periphery, say at the level of the cochlea in auditory selective attention (eg. Hernández-Peón, Scherrer and Jouvet, 1956; Hernández-Peón, 1966). According to this theory, involuntary attention occurs as a result of the transmission of sensory information controlled by the reticular formation; voluntary attention occurs through modification by the descending fibres of cortical origin, the cortico-reticular-sensory pathway, which is also thought to inhibit irrelevant information. This theory, however, was developed from animal research and further substantiation and replication with human data has proved elusive (Hirschhorn and Michie, 1991).

Evidence for selection at the thalamic level has also come from animal research. This theory proposes that the thalamic reticular nucleus regulates the transmission of sensory information by acting as an inhibitory gating mechanism in inhibiting thalamocortical circuits carrying irrelevant information (Skinner and Yingling, 1977).

The most favoured anatomical model of selective attention is the cortical model, based upon a vast array of psychophysiological data from ERP studies, magnetoencephalography (MEG) and regional cerebral blood flow (rCBF) studies. Näätänen and Picton (1987) summarised the evidence for the auditory cortex as a possible selection site and Woods (1989) discussed the connections throughout the brain emphasising their activation through a progressively narrowing attentional spotlight, highlighting the hierarchical organization of information processing in the auditory system. While lower centres may be responsible for simple sensory feature detection, complex processing allowing the complete perception, integration and interpretation of complex stimuli occurs in the cortical regions of the brain. Woods (1989) also suggested that there may be separate selective attention mechanisms in different sensory modalities, and Woods, Alho and Algazi (1994) provided evidence that ERP components elicited by attention to different features of stimuli (eg. frequency, location) had different scalp distributions consistent with generation in different cortical fields.

The essence of the cortical model is that all auditory inputs undergo rapid, involuntary processing of their physical characteristics by a "permanent feature-detection system" (Näätänen, 1985; 1988, 1990). All physical features of stimuli, such as location, pitch, intensity and duration, are encoded in a passive neuronal trace. These passive neural representations may be responsible for involuntary attention switching which enables unattended stimuli to attain conscious processing momentarily, thus offering an explanation for the intrusion of irrelevant stimuli (as well as mismatch

negativity , discussed below). Voluntary, effortful focussing of attention leads to the formation of a more permanent "attentional trace", a voluntarily maintained representation of the relevant stimulus characteristics. All other inputs are actively compared against this representation, and the duration of this matching process reflects the degree of similarity between the input and the attentional trace. Only those stimuli with a perfect match are selected for further processing, for updating and maintaining the attentional trace. These concepts are discussed further below, as indexed by various ERP components.

The prefrontal cortex is also an area known to be involved in attentional functions. Damage to the prefrontal area of the frontal lobe appears to cause attention related problems with ready formation of irrelevant associations and disturbances in the selectivity of action (Luria, 1966). Patients with frontal lobe lesions are often unable to suppress irrelevant information, and have tendencies to perseverate, being unable to shift attention, but also having difficulties in focussing and sustaining attention (eg. Damasio, 1979; Fuster, 1980). Cerebral blood flow increases in the region of the frontal lobe during auditory attention (eg. Näätänen, 1987), consistent with evidence that the frontal lobes maintain and control the attentional trace. At least two ERP studies have reported dysfunction in selective attention and increased distractibility in patients with lesions of the dorsolateral prefrontal cortex (Knight et al, 1981; Woods and Knight, 1986). Further ERP evidence of frontal activation is discussed below. The involvement of the anterior cingulate cortex in attentional processes was discussed in Chapter 2. It is unlikely, however, that selective attention can be localised to any one area, but most likely occurs as a result of numerous connections or networks in the brain (Mesulam, 1990).

6.2 Event-related potential (ERP) indices of selective attention

Event-related potentials (ERPs) are scalp recorded electrical changes occurring in the brain in response to an event or stimulus. The procedure of recording ERPs is a sensitive technique which permits the simultaneous assessment of electrophysiology, cognition and behaviour and the detection of subtle dysfunction in specific stages of information processing.

The procedure for generating ERPs involves recording the electroencephalograph (EEG) while subjects are engaged in a cognitive task. Portions of the EEG, which are time-locked to specific stimuli are extracted and averaged (see Figure 6.1). These represent the brain's response to an event or stimulus and are hence referred to as event-related potentials. As such, they are distinguished from the spontaneous potentials that make up the ongoing EEG in the absence of stimulation, thought to reflect the global state of the subject (eg. the generalised psychological states of arousal or drowsiness). ERPs, on the other hand are evoked by, and hence time-locked to, specific discrete environmental events open to a vast array of experimental manipulation. By averaging the response to repeated presentations of stimuli of a certain type, the background noise of the ongoing EEG is diminished, while the constant ERP response to that stimulus type becomes increasingly distinct.

The typical ERP consists of a series of peaks and troughs, positive and negative deflections (see Figure 6.1), which reflect the synchronous activity of large neuronal populations, such as a localized area of cerebral cortex or thalamus, or specific auditory nuclei in the brainstem. What are referred to as ERP "components", can only be inferred from the results of experimental manipulation and measurement of the resultant ERP deflections (Näätänen and Picton, 1987). Thus an ERP component constitutes a cerebral

event reflecting a distinct cognitive process. While much research is being conducted into the neural generators of the various ERP components, the actual neural source of the component need not be the defining criterion for the differentiation of components, but rather the cognitive process itself (Donchin et al, 1978).
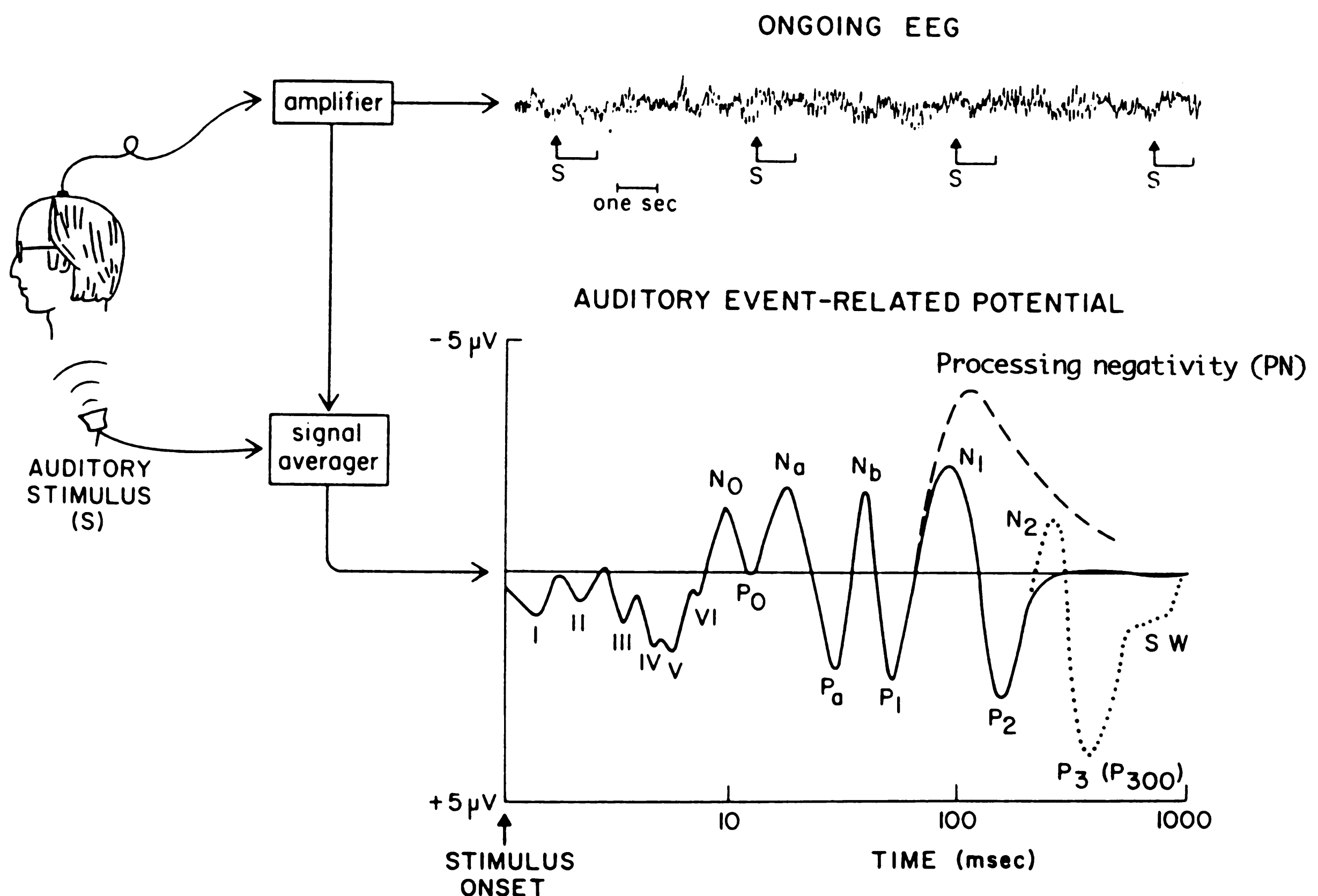
Figure 6.1   An idealized auditory ERP waveform depicting the process of recording the EEG and averaging around a stimulus, and the major early brainstem, middle latency and late "endogenous" components. (Adapted from Hillyard and Kutas, 1983).

The focus of current ERP and cognitive research has been to identify ERP components as markers of specific stages of information processing. The amplitude and latency of ERP components are thought to reflect the nature, timing and duration of various cognitive processes. These are indexed by the later "endogenous" components of the ERP waveform, as opposed to the earlier obligatory "exogenous" components.

Exogenous components

Exogenous components are responses evoked by factors extrinsic to the nervous system, being sensitive to variations in physical stimulus characteristics regardless of their processing demands or task relevance. They begin shortly after stimulus onset and last for up to the first 250 ms post-stimulus, varying in amplitude and latency according to the physical characteristics of stimuli, and varying across the scalp according to stimulus modality. They are comprised of early, middle and late components.

Early brainstem potentials occur within the first 10 ms post-stimulus and reflect the neural activity of auditory nuclei in the cochlea and brainstem. The middle latency thalamic potentials are evident between 10 - 50 ms post-stimulus and reflect the procession of auditory information through to the auditory cortex. Following the animal research of Hernández-Peón and colleagues (1956; 1966), much human research has been directed toward attempting to discover early signs of selective attention in both brainstem and thalamic potentials, and where evidence has been demonstrated, this has proved impossible to replicate (eg. Lukas, 1980;1981 vs Hirschhorn and Michie, 1991).

While early and middle latency components are of very low amplitude, they are closely followed by large amplitude waves named according to their polarity and sequence: the P1-N1-P2 complex refers respectively to the first large positive wave occurring around 50 ms post-stimulus (also known as P50), the first large negative wave occurring around 100 ms post-stimulus (also known as N100), and the second large positive wave occurring around 200 ms post-stimulus. It is important to point out that in a cognitive task, these exogenous waves are overlapped by the appearance of endogenous components signalling the beginnings of conscious effortful attentional processing.

P1 has been implicated in the gating or inflow control of sensory information. A number of psychiatric patient populations, including schizophrenics, have shown inreases in the amplitude of P1 in conditioning test paradigms, reflecting diminished gating, and the mechanism responsible for sensory gating has been suggested to interact with the catecholaminergic system (Adler et al, 1982).

The N1 component is viewed as a true onset response generated by cerebral systems responding specifically to stimulus onset (Näätänen and Picton, 1987). N1 is thought to be made up of several components, each with different generators within the brain, but all sensitive in amplitude and latency to the registration of various stimulus parameters. Its scalp distribution is modality specific and in the auditory modality N1 is larger in the hemisphere contralateral to the ear of stimulation. The P2 wave follows N1, and while it may have different neural generators, it appears to be similar to N1 in its sensitivity to various stimulus characteristics.

Endogenous components

There are a number of endogenous ERP components which are elicited in a variety of cognitive tasks, representing a wealth of cognitive operations. This discussion will be limited to those components of relevance to auditory selective attention.

N2: The N2 is the second major negative component peaking after stimulus onset. It is an endogenous component best seen when an occasional stimulus is either omitted from a train of stimuli delivered at a constant rate, or replaced by a physically

deviant stimulus (Näätänen, 1982; Squires, Squires and Hillyard, 1975). It is closely

coupled with the P300 and particularly with P3a (see below) (Picton and Stuss, 1980;

Squires, Squires and Hillyard, 1975), reflecting the operation of a cerebral "mismatch

detector" engaged by stimulus deviance (Snyder and Hillyard, 1976). However its

morphology and topography were found to differ as a function of experimental

manipulation, suggesting that the N2 is not a single entity, but rather, a number of

different components are active in the N2 range (Näätänen and Gaillard, 1983).

Näätänen and Picton (1986) were able to identify eight N2 subcomponents, however the

two most well recognised are the mismatch negativity (MMN) and the N2b.

The MMN is a negative component which can overlap the N1 and P2 components

and is observed when stimulus deviance is defined by changes in pitch, intensity,

duration, spatial location and phonemic change (Näätänen, 1990). The larger the

difference between the deviants and standards, the larger the MMN and the earlier it is

elicited. However MMN is best observed under nonattend conditions when subjects are

asked to ignore auditory stimuli and perform a distractor task. As such it is considered

to index an automatic process independent of attention, being generated by a cerebral

process sensitive to stimulus change, which compares the sensory input from a deviant

stimulus to a stored neuronal representation of the physical features of previous standard

stimuli (Alho et al, 1989; Näätänen, 1985). It is argued that it serves the biologically

vital function of causing attention to switch towards changes in unattended auditory input

(Näätänen, 1990). The MMN has a fronto-central distribution and is larger at temporal

than midline sites. There is continuing debate about whether the MMN is or is not

enhanced by overt attention (Alho, Woods and Näätänen, 1992; Woldorff, Hackley and

Hillyard, 1991).

The other component in the N2 range is the N2b which is elicited under conditions

of attention to deviants, being superimposed on the MMN. It has a longer latency than

the MMN (approximately 220 ms), a centro-parietal distribution, is modality nonspecific
and is closely coupled with P3a (Näätänen and Gaillard, 1983; Picton and Stuss, 1980;
Squires, Squires and Hillyard, 1975) reflecting the beginnings of cognitive stimulus
evaluation, target selection and decision making processes. Some have suggested that
the N2 may actually be a better index of decision processes than the later P300 wave
(discussed below) (Ritter et al, 1979).

Processing negativity (PN): This is the ERP component most specifically related
to selective attention. ERP studies of selective attention have primarily utilised the
"cocktail party" paradigm, a version of the dichotic listening task described above, in
which multiple channels of multidimensional auditory stimuli are presented to the subject
at rapid rates. While the subject's task is to attend to one channel only, ERPs elicited by
stimuli from every channel are recorded and differences between attended-channel ERPs
and unattended-channel ERPs constitute the attention effect. This effect of attention is
seen as a broad negativity in the ERP waveform, termed "processing negativity"
(Hansen and Hillyard, 1983; Näätänen, 1982).

The onset of processing negativity (PN) provides evidence for selection in the
auditory system to occur as early as 60 to 80 ms post-stimulus. Originally this negativity
was interpreted as an enhancement of N1 amplitude in attended as opposed to unattended
stimuli (Hillyard et al, 1973), but later studies isolated a separate endogenous negative
component, PN, superimposed upon the N1 wave (Näätänen and Michie, 1979). PN is
elicited by all stimuli sharing the more salient properties of the relevant stimulus,
generated when selective attention is directed toward the relevant sensory attributes of the
passive neuronal trace. PN is argued to be the best index of the more permanent
attentional trace (Näätänen, 1990).

PN may be clearly seen in the ERP waveform as a negativity in the trace to

attended stimuli compared to unattended stimuli, or it may be observed in difference waveforms (Nd) created by subtracting the unattended trace from the attended. This method has demonstrated two overlapping components: early PN (or Nd) which is maximal over fronto-central areas and reflects the selection of relevant from irrelevant sources of information by a matching process between the stimulus and the attentional trace, and a more prolonged negativity in the attended ERP, termed late PN (or Nd), which has a much more frontal distribution (Hansen and Hillyard, 1980; Näätänen, 1982; Woods, 1989). This late frontal component of processing negativity most likely reflects the maintenance and rehearsal of the attentional trace (Näätänen, 1982). PN may also be present in unattended ERPs if the discrimination is difficult, ie. a small physical separation between attended and unattended stimuli, although evidence is accumulating for a third component contributing to Nd: a positivity in the unattended ERP starting at about 170 ms (Alho et al, 1987; Michie et al, 1990; 1993). This positivity may reflect active inhibitory processing of the irrelevant stimuli; an active suppression of processing when the irrelevant stimulus has been found to be incompatible with the attentional trace (Alho et al, 1987; Michie et al, 1993).

P300: If a conscious decision about the significance of a stimulus has to be made, or a response to a particular stimulus in the attended channel is required, the ERP waveform to that stimulus will show a large positive component, generally referred to as the P300 complex. P300 is one of the most researched and largest of the endogenous ERP components, but many years of research have failed to determine precisely its functional role (Picton, 1992). P300 is elicited by task relevant, infrequently occurring target stimuli in the attended channel (Donchin, 1981; Pritchard, 1981). It occurs maximally at parietal scalp sites with a peak latency of 300-500 ms depending on task difficulty among other parameters. There is evidence that P300 amplitude reflects the allocation of attentional resources for stimulus evaluation processes, while its latency is a sensitive index of stimulus evaluation time (Isreal et al, 1980; Pritchard, 1981). This

component, now recognised as the P3b, is distinguished from the smaller, more fronto-central P3a which is elicited by unattended, task irrelevant and intermittent novel stimuli, reflecting the degree of contrast with frequently occurring stimuli and hence associated with the N2b component (Squires et al, 1975; 1977; Näätänen and Gaillard, 1983). Recent evidence suggests that there may be multiple neural generators of the P300 component distributed throughout the brain (Johnson, 1993).

Contingent negative variation: In paired stimulus paradigms where one stimulus acts as a warning signal that the other will soon follow, a slow negativity develops in the ERP during the interval between the two stimuli, reaching a maximal amplitude just prior to the presentation of the second stimulus. This anticipatory component is termed contingent negative variation or CNV (Walter, 1964). It has variously been interpreted as a sign of expectancy, intention to act, attention and arousal (eg. Tecce, 1972). Increased attention generally results in increased CNV amplitude, but general tonic arousal leads to CNV decrement. Tecce and Cole (1974) showed that reports of alertness following amphetamine administration correlated with larger CNV, while paradoxical drowsiness was associated with CNV reduction. A separate component nevertheless closely related to CNV is the post-imperative negative variation (PINV). This is a continuation of the CNV beyond the point of normal resolution, which has been observed in schizophrenics (Timsit-Berthier et al, 1984), but also in normal subjects only when the second stimulus in the pairing is uncontrollable by the subject (eg. when the subject is not able to terminate it by a motor response).

It is these endogenous ERP components discussed above, primarily processing negativity and P300, that are of particular interest for the purposes of this thesis. The Hansen and Hillyard (1983) multidimensional auditory selective attention paradigm was

selected for the study of selective attention processes in long term cannabis users. There exists a wealth of normative data on the ERP patterns elicited by this paradigm, and it has been used to investigate information processing among other groups suspected of deficient attentional mechanisms, for example, schizophrenics (Michie et al, 1990). The paradigm has proved useful in the study of hierarchical models of information processing by manipulating the difficulty of discrimination of each dimension.

For the series of studies to be described here, the version of the paradigm used was that where stimulus duration was the most difficult discrimination, followed by pitch and then location. In this paradigm, the subject's task is to selectively attend to a particular combination of these dimensions (eg. right ear, high pitch) and to detection infrequent long duration target tones. The most efficient strategy in performing this task, is one where the subject rapidly rejects half the stimuli from further analysis on the basis of location, continues to process those stimuli entering the relevant attended ear and rejects half of those on the basis of pitch, before finally deciding whether the stimulus is of long or short duration. This strategy enables the formation of the attentional trace to the frequent short duration tones of relevant pitch in the attended ear, evidenced by processing negativity (PN) in the ERP waveform to these tones. Hierarchical models predict that tones occurring in the unattended ear should be rejected rapidly, evidenced by a positive shift in the ERP following the N1 peak, whereas tones of irrelevant pitch in the attended ear would be processed for a little longer but rejected soon after with a later positive shift in the ERP waveform. Use of this paradigm will determine whether chronic cannabis users engage in a less efficient mode of information processing than do controls.

It was hypothesised that long term cannabis users may adopt a less efficient mode of information processing than controls and show evidence of intrusion of irrelevant information in their ERP waveforms. Particularly strong evidence of this would be a

lack of separation between relevant and irrelevant pitch ERPs to tones in the attended ear, with inappropriately large PN to the pitch irrelevant tones. Evidence of PN to tones in the unattended ear, with a large separation between relevant and irrelevant pitch ERPs, would suggest engagement in exhaustive analysis of independent stimulus dimensions. The use of ERPs as a tool in the study of the cognitive effects of cannabis has been virtually non-existent.

6.3 Cannabis and ERPs

Most of the studies investigating the electrophysiological effects of cannabis examined the electroencephalogram (EEG), producing equivocal results, and most of this research was done in the 1970s. These EEG studies have been reviewed in Chapter 4. Very few studies have investigated the effects of cannabis upon ERPs: most have been acute studies and none have investigated the processes of selective attention. The small literature on cannabis and ERPs will briefly be reviewed here.

A number of the early EEG studies included a cursory examination of evoked responses without adequate description of how these were evoked nor what components were measured. Generally, evoked responses are a reflection of exogenous components only, being passively elicited by the presentation of auditory or visual stimuli in the absence of any cognitive task demands. The effects of cannabis on evoked potentials has also been variable.

Rodin et al (1970) found no consistent changes in auditory (AEP),visual (VEP) or somatosensory evoked potentials (SEP) during an induced "social high" but reported no details. Low et al (1973) found no effect of low or high dose THC on VEP peak

amplitude or latency. Stefanis, Dornbush and Fink (1977) reported no latency changes but increased N150 peak amplitude after administering various doses of hashish to their Greek sample of chronic hashish smokers. Tinklenberg (1972) found an increase in amplitude of the N200 and P280 components of the VEP, and some prolongation of latency, following low dose THC, and Tassinari (1974) reported similar increases in amplitude of the late VEP components. Lewis et al (1973) reported significant latency prolongation of almost all VEP peaks with high dose THC, with a similar trend for low dose THC and a trend toward SEP peak latency prolongation. Additionally they reported a decrease in VEP N75-P100 peak amplitude at both high and low doses and a significant SEP N130-P200 amplitude reduction. These effects were evident in occasional and frequent cannabis users alike. Lewis et al (1973) interpreted the prominence of evoked potential latency prolongation being due to an increase in "the threshold of cortical and subcortical neurons or neural networks involved in producing the evoked response" and claimed that there was no evidence of an excitatory action of THC on the central nervous system.

Two studies used a passive attention task with frequent and infrequent tone bursts which subjects were instructed to ignore. Roth et al (1973) reported decreased P2 amplitude to frequent and infrequent stimuli following cannabis, but no effect on N1 amplitude and no latency differences. There was suggestive evidence for a reduction in P300 amplitude to the infrequent stimulus. Roth and colleagues interpreted their findings as indicating that subjects under the influence of cannabis may have an increased ability to "tune-out" the outside world, substantiated by users' claims of dreamlike states with reduced attention to the environment, but the authors cautioned that this should not be interpreted as enhanced ability to selectively ignore irrelevant stimuli. Kopell et al (1978) using a similar paradigm found neither amplitude nor latency changes.

Earlier, Kopell had reported an enhancement of CNV with the oral administration of low dose THC, but not high dose (Kopell et al, 1972). He interpreted this as an enhanced ability of mildly intoxicated subjects to selectively attend and suggested that this may be due to better exclusion of miscellaneous irrelevant stimuli while anticipating a relevant stimulus. Low et al (1973) replicated these findings of increased CNV amplitude with low dose smoked THC using a similar simple reaction time task to that used by Kopell, but they also employed a difficult discrimination task and found the high dose actually decreased CNV amplitude in this task. Both low and high doses increased PINV. Similarly, Braden et al (1974) demonstrated no overall effect of moderate dose smoked THC on CNV amplitude in the simple reaction time task, but found that subjects who reported experiencing a below-average "high" showed CNV amplitude increase, while those reporting above-average "high" showed CNV amplitude decrease. They proposed that the relationship between CNV amplitude and THC dose is probably in the form of an inverted U, suggesting possible enhancement of attentive mechanisms at low doses but impaired attentional functioning with high doses. They also proposed that since cannabis is often demonstrated to slow reaction time, the increase in CNV amplitude may "due to a compensatory effort to concentrate". However, at higher doses "with more complete impairment of task orientation, this compensatory effort might not be possible". Alternately, they proposed that low dose cannabis might serve to make a dull task more interesting, which is not incompatible with greater difficulty in concentration.

Heming, Jones and Peltzman (1979) studied 27 male regular users, aged 21-31, over a 3-4 week period as inpatients receiving various daily doses of THC. Auditory event-related potentials and contingent negative variation (CNV) were recorded during a series of behavioural tasks of varying complexity pre-drug treatment, early and late during the inpatient treatment, and post-treatment. The auditory N1 component was significantly depressed in the high dose group during the first few days of treatment but

resolved over time, remaining depressed only during the most demanding behavioural tasks. The CNV was depressed during all tasks for high and low dose groups early in treatment, but once again mostly resolved, remaining only in the high dose group during the most difficult task. These results suggest the development of tolerance to these effects. The authors suggested, however, that these changes may persist with high doses, and were more likely to manifest during complex stimulus processing tasks. The changes were hypothesised to be related to different aspects of a common attentional alteration during stimulus processing.

More recently, Howard and Menkes (in press) administered moderate to high dose THC to regular cannabis users and found reduced CNV in a noise avoidance task which required a response on some occasions and the inhibition of responding on others (go/no go). The CNV reduction was maximal at the same time that salivary THC levels and subjective intoxication were highest. Subjective arousal was reported to increase following cannabis smoking. P300 amplitude was significantly reduced in an auditory oddball task and reaction time was longer, but not significantly so. The change in reaction time from pre- to post-smoking in the oddball task, and the change in CNV in the noise avoidance task, correlated with salivary THC levels. The authors interpreted these results in terms of high impulsivity, which has previously been shown to reduce CNV amplitude.

In one of the few studies to directly compare the effects of cannabis and alcohol on event-related potentials, Roth et al (1977) incorporated a complex memory search task based on the Sternberg paradigm which presented 1 to 4 digits, and then a warning tone followed by a single digit probe. They found no drug effects on the amplitude or latency of auditory N1 or P2 to the warning tone, but P300 amplitude to the probe was reduced by both cannabis and alcohol. CNV amplitude between the warning tone and test digit showed no drug effects, but the latency of resolution of the CNV was longer under

cannabis than alcohol or placebo and reaction time was significantly increased by cannabis alone.

The overall effects of acute administration on human evoked potentials are difficult to summarise due to the lack of consistency in routes of administration, doses given, tasks employed and indeed their variable results. Nevertheless, it can be surmised that cannabis may affect either the latency or amplitude or both of the evoked potential in an adverse manner. There has been insufficient research into the effects of cannabis on ERPs in well designed studies employing sensitive tasks that tap quite specific cognitive functions.

Most recently, and perhaps in the only evoked potential study of chronic cannabis users, Straumanis et al (1992) found smaller auditory P2 and N2 amplitudes in long-term cannabis users (> 15 years) compared to moderate users (of 3-6 years). Cannabis users overall showed significantly smaller auditory and visual P300 amplitudes than controls, but no significant latency differences. Unfortunately, this study has only been reported in abstract form and results have not been examined as a function of frequency of cannabis use (Struve, personal communication). Struve and Straumanis (1990) briefly mention the results of their pilot study of chronic cannabis users, abstinent for 5-7 days prior to testing, which found decreased VEP P100 amplitude, increased SEP N18-P30 amplitude and smaller and later P300 in an auditory oddball task. No details were given.

Clearly, there is a need for further research into the long term effects, and indeed the acute effects, of cannabis on human event-related potentials, particularly now that their interpretation is enhanced by more modern cognitive theories. For the purposes of this thesis, it was considered of greater urgency to investigate long term cognitive effects than to contribute to the labyrinth of acute studies.

CHAPTER 7

AN EVENT-RELATED POTENTIAL STUDY OF ATTENTIONAL PROCESSES IN LONG TERM CANNABIS USERS

Previous studies provided little information as to the nature of any specific deficits associated with the long term use of cannabis, although attentional mechanisms were often implicated. As argued above, one reason for the equivocal nature of results from past studies may be that the tests used were insufficiently sensitive to detect subtle dysfunction of specific cognitive processes. There has been relatively little use of quantitative measures derived from experimental cognitive psychology in any studies of chronic drug-related deficits.

The advent of brain event-related potential (ERP) recording technology allowed for the simultaneous assessment of electrophysiology, cognition and behaviour and the detection of subtle dysfunction in specific stages of information processing. The interpretation of ERP components is based on modern theories of cognition and information processing. This study employed such techniques to address the question of the existence and nature of attentional deficits in long term cannabis users.

7.1   Experiment one: Effects of long term cannabis use on ERPs recorded during an auditory "oddball" paradigm

The auditory "oddball" paradigm was selected as an initial starting point in assessing the effects of long term cannabis use upon electrophysiological indices of attention. The oddball paradigm is a discrimination task in which a rare target must be detected from a background of frequently occurring stimuli. The subject is presented with a train of identical tone pips which are occasionally replaced by a single deviant tone, differing on some aspect of the parameters of the tone, most often pitch or intensity. The order of stimuli is randomized, as a Bernoulli sequence, to avoid expectancy, with the low-probability target stimuli embedded within the sequence. This simple auditory discrimination "oddball" paradigm has been used by many researchers of cognitive psychophysiology over the years, to reliably elicit the P300 component of the auditory event-related potential.

P300 is elicited by attended, task relevant, infrequent target stimuli and occurs maximally at centro-parietal scalp sites. Since P300 reflects various processes associated with evaluating a stimulus, including the allocation of attentional resources, it was hypothesised that P300 may be delayed or reduced in amplitude in the cannabis users compared to controls. P300 amplitude has consistently been found to be reduced in schizophrenics (Michie et al, 1990; Pfefferbaum et al, 1984; 1989; Pritchard, 1986; Ward et al, 1991) among other psychiatric groups (Pfefferbaum et al, 1984) and alcoholics (Porjesz and Begleiter, 1987; Williams, 1987). P300 amplitude has also been found to correlate with ratings of clinical symptoms of schizophrenia (Pfefferbaum et al, 1989; Shenton et al, 1989; Ward et al, 1991) and with performance on perceptual-motor tests in alcoholics and controls (Parsons, Sinha and Williams, 1990).

P300 latency reflects the time taken to evaluate a stimulus. If stimulus-encoding processes were impaired in cannabis users, P300 latency would be delayed by a constant amount regardless of task difficulty. If stimulus-encoding processes were normal but stimulus-evaluation was impaired, then any latency differences in P300 would increase as a function of task difficulty. These hypotheses were tested by presenting two tasks of increasing difficulty. The auditory oddball task also allowed examination of the earlier exogenous and endogenous components P1, N1, P2 and N2 described in Chapter 6.

7.1.1 Method

Subjects

Ten cannabis users were recruited from the general community by advertising in the newsletter of NORML (National Organization for the Reform of Marijuana Laws) and by word of mouth. Three were personally known by the experimenters. Control subjects were selected from the friends and associates of the experimenters (N = 7) and respondents to an advertisement at a student employment centre on a university campus (N = 3). All subjects were paid for their participation.

Subjects were initially screened in a telephone interview. The criterion for inclusion in the user group was a minimum of three years of regular use of cannabis. This was defined as using cannabis at least twice a week on average over the last three years. Subjects were asked specific questions relating to their general health (see Appendix B) and any respondents with a history of fits, febrile, neurological or psychiatric illnesses, multiple concussion or periods of unconsciousness were excluded from testing.

Subjects on any prescribed medication other than antibiotics were excluded from the sample. Subjects were screened for alcohol consumption with the following criteria for inclusion in the sample: less than 28 standard drinks per week on average for males and less than 14 for females, based on the National Health & Medical Research Council (1986) guidelines for levels of "safe" drinking. A standard drink in Australia contains 10 g of absolute ethanol. Further criteria for inclusion were no more than one month of continuous drinking above these levels in the last three years and no more than six months ever of drinking above these levels. Subjects were screened for other drug use and rejected on the basis of a history of any regular substance use (defined as greater than or equal to once a month) or any subject having used any other drug in the month prior to testing.

Technical malfunction of computer equipment resulted in lost oddball data for two cannabis users. Hence, the final sample in this experiment consisted of five male and three female cannabis users, aged 19-45 (mean 32.25 yrs, SD = 9.90). These were matched on age (to within three years), sex and years of education with eight of the non-user controls, aged 21-44 (mean 32.38 yrs, SD = 9.10). The average number of standard drinks per week consumed by the user group was 11.25, (SD = 10.54) and 4.50, (SD = 3.16), by the control group. Alcohol consumption did not differ between groups $(F_{(1,14)}= 3.01, p = 0.1047)$. All subjects had completed 13 years of school education and at least one year at tertiary level.

The National Adult Reading Test (NART) (Nelson, 1984) was used as a measure of premorbid IQ. Cannabis users and controls did not differ in this regard [Users: 39.88 (SD = 5.64) = Full Scale IQ 119.6; Controls: 39.63 (SD = 3.93) = Full Scale IQ 119.39; $F_{(1,14)} = 0.01; p > 0.90$]. All subjects were right handed, assessed on the Edinburgh Inventory (Oldfield, 1971).

The mean years of cannabis use in the user group was 11.6 yrs (SD = 6.25, range 3 - 20 yrs) and the average level of use was 5.13 days per week (SD = 1.64, range: three days per week to daily use). The mean weekly consumption was 727 mg THC (SD = 804, range 150 - 2400 mg/week), calculated as 15 mg THC per average cannabis cigarette. The longest period of abstinence from cannabis in the last three years ranged from none to three months, mean 32 days (SD = 30.48). Of the controls, two had never tried cannabis, three had tried it once or twice, and the remainder had used cannabis occasionally at parties between 3 and 7 years ago with the most experienced control having used 12 times in his entire life.

Following the telephone screen, an appointment was made for the test session (usually within the following week). Subjects were instructed to abstain from cannabis and alcohol for at least twelve hours prior to testing. The day before the test session subjects were telephoned and reminded of these instructions and requested to provide a urine sample prior to going to bed. All subjects complied with this request.

Stimuli

A series of tone pips was presented binaurally through TDH-49 headphones at 80 dB SPL with random stimulus onset asynchrony (SOA) of 1000 - 2100 ms (mean 1550 ms). Each run consisted of the presentation of 102 tones of 50 ms duration with a rise and fall time of 10 ms. The duration of the run was 160 seconds. Most of the tones were of low frequency (1000 Hz), while 25% were of a higher pitch, the designated targets. There were two conditions representing two levels of difficulty in discriminating the high from the low pitched tones: in the easy condition, high tones were set at 2000 Hz; in the difficult condition the high tones were 1100 Hz. Subjects were instructed to respond with a button press whenever they heard a high tone.

ERP recording

Seven channels of electrophysiological data, six EEG and one EOG, were recorded using an electrode cap (Electro-cap International) and tin electrodes respectively. The data were recorded using a Beckman Accutrace EEG machine with a time constant of 5 seconds and high frequency cut off of 30 Hz (3 dB down). Scalp electrodes were located over six lateral sites, F3, F4, C3, C4, P3 and P4. The EOG channel monitored vertical and horizontal eye movement via electrodes taped above and on the outer canthus of the left eye. All scalp electrodes were referred to linked earlobes. A light-emitting diode one metre away from the subject at eye level was used as a fixation point. The ground electrode was located on the forehead. EEG and EOG channels were continuously digitised at 5.76 ms/point (175 Hz) for the duration of a run and stored on disk with stimulus and response markers for later analysis. Stimulus presentation and data acquisition were controlled by a Data General NOVA 4-C computer.

Procedure

Upon arrival at the laboratory, subjects provided written informed consent (as per Appendix A) and deposited their urine sample from the previous evening in a freezer. They were requested to provide a second urine sample sometime during the test session. Urine samples were subsequently analysed to confirm that the subject was not in an acutely intoxicated state during testing. The criterion upon which this assertion was based was that the THC levels detected in the second sample were lower than those detected in the first.

Subjects participated in a single three hour test session. They were interviewed

about their general health and detailed drug history according to a structured questionnaire (see Appendix B) and completed a number of other questionnaires designed to assess various aspects of anxiety and other psychopathologies. The results of these assessments are discussed in Chapter 10.

Subjects were tested for normal hearing by standard audiometric assessment. They sat in an arm-chair in a darkened, sound-reduced room adjacent to the laboratory. The response button was mounted on the arm of the chair and they were instructed to use their index finger to depress the button. Subjects were given a short demonstration of each of the tone types to familiarise them with their sound. The electrodes were then attached and the recording session commenced. They completed two runs of each condition (easy and difficult), responding with alternate hands. The order of responding hand and condition was counterbalanced across subjects.

Data analysis

Button press responses were classified as correct detections or "hits" if they occurred within a 200 to 1200 ms response window after a target stimulus (a high tone). Reaction time was measured as the latency in ms of the button press from the onset of the tone. A target not followed by a response within the response window was regarded as an error of omission or "miss". All other button presses were regarded as errors of commission or "false alarms". The number of hits as a ratio of the total number of targets (high tones) provided an estimate of the hit rate, while the false alarm rate was calculated as a ratio of the total number of nontargets (low tones).

The digitised EEG data with stimulus and response markers were analysed on a VAX11/780 using a program which extracted overlapping epochs of 1050 ms including a 150 ms pre-stimulus baseline. All epochs containing EOG artefact greater than 64 μV

were rejected prior to averaging. Separate averages were created for hits and misses, and for nontarget stimuli, excluding those which were followed by a false alarm response. Averages to the same stimulus type were summed over runs with left and right hand responses. All amplitude measures were made relative to a 150 ms pre-stimulus baseline. Latency measures were relative to stimulus onset. The data were analysed using BMD-P2V analysis of variance. The Greenhouse-Geisser method of adjusting the degrees of freedom was used to determine the significance of main effects and interactions where appropriate (Vasey and Thayer, 1987) for all analyses reported in this thesis.

7.1.2   Results

Performance data

Performance measures from cannabis users and controls for both easy and difficult conditions of the auditory oddball task are presented in Table 7.1. Measures of reaction time in milliseconds, percent correct detections and percent errors of commission (false alarms) were subjected to an analysis of variance with a group factor and two levels of difficulty for condition. As to be expected from the experimental manipulation, reaction times were significantly longer [$F(1,14) = 31.55$, $p < 0.0001$] and the number of correct detections significantly fewer [$F(1,14) = 4.61$, $p < 0.0498$] in the difficult condition than in the easy condition. However there were no significant differences between groups and no interactions between group and condition.

While cannabis users appeared to have longer reactions times than controls, this difference failed to reach statistical significance [Group: $F(1,14) = 2.10$, $p > 0.16$; Condition x group: $F(1,14) = 0.15$, $p > 0.70$]. The number of correct detections dropped marginally for both cannabis users and controls in the difficult condition, with no significant difference between the two groups [Group: $F(1,14) = 0.00$, $p = 1.00$; Condition x group: $F(1,14) = 0.14$, $p > 0.71$]. The increased difficulty between

conditions was not reflected in a greater number of errors of commission [F(1,14) = 1.18, p > 0.29] and once again there were no group differences [Group: F(1,14) = 0.56, p > 0.46; Condition x group: F(1,14) = 1.84, p > 0.19].

Table 7.1 Mean performance measures of reaction time (RT), hit rate and false alarm rate (SD in parentheses) for cannabis users and controls in the auditory "oddball" paradigm.

	RT (ms)		HIT RATE %		FALSE ALARM RATE %	
	Easy	Diff	Easy	Diff	Easy	Diff
CANNABIS	385.11	454.62	98.13	94.75	0.63	0.68
USERS	(54.57)	(55.41)	(2.10)	(6.10)	(0.89)	(0.60)
CONTROLS	348.25	408.74	97.63	95.25	0.68	0.23
	(67.36)	(67.78)	(2.10)	(5.30)	(0.68)	(0.31)

Paradoxically it appeared that controls made more errors in the easy condition than the difficult, however, the actual numbers of errors were extremely low: a percentage of 0.68 reflects 0.51 false alarms per every 75 stimuli that are nontargets, that is, on average less than one false alarm per run. A large number of both users and controls made no errors whatsoever. Therefore, while the difficulty of discriminating the high from the low tone resulted in increased reaction times for the difficult condition, the task itself remains a relatively simple task of comparatively low cognitive load. Thus, the demand for cognitive resources would be low.

ERP data

Grand average ERPs to infrequent target stimuli recorded at frontal, central and parietal scalp sites from cannabis users and controls are depicted in Figure 7.1 for both easy and difficult conditions. Figure 7.2 shows ERPs to the frequent stimuli for which no response was required. Visual inspection of the waveforms indicated few differences between groups. Both groups showed large N1 components, followed by the P2-N2 complex and a well formed P300 component to the target stimuli. The analyses reported below were performed on target data.

N1, measured as the most negative peak between 50 and 200 ms at frontal and central sites, was found to occur slightly later in the left hemisphere [$F(1,14) = 8.51$, $p < 0.0113$], with a trend toward longer latency at frontal sites in the difficult condition [$F(1,14) = 4.29$, $p < 0.0572$], but there were no group effects or interactions, indicating that cannabis users and controls did not differ in the latency of this component. The amplitude of the N1 peak was larger at frontal than central sites [$F(1,14) = 6.25$, $p < 0.0255$], and there was a trend toward N1 being larger in the left hemisphere in the user group but larger in the right hemisphere in controls [$F(1,14) = 4.57$, $p < 0.0506$].

N2, the most negative peak between 180 and 400 ms at frontal and central sites, was larger in the difficult condition for both users and controls [Condition: $F(1,14) = 5.60$, $p < 0.0330$] but there was no significant group interaction [$F(1,14) = 2.59$, $p = 0.1302$]. However, analysis of N2 latency revealed a significant effect of group [$F(1,14) = 5.06$, $p < 0.0412$] and an interaction between condition and group [$F(1,14) = 7.81$, $p < 0.0143$]. Multiple comparisons of each group for each condition revealed N2 to peak significantly later in users than controls in the difficult condition [$F(1,14) = 11.11$, $p < 0.0049$].

EASY CONDITION

F3

F4

C3

C4

P3

P4

DIFFICULT CONDITION

F3

F4

C3

C4

P3

P4

——— CANNABIS USERS

———— CONTROLS

⌐4.0 μV

200 400 600 800

msec
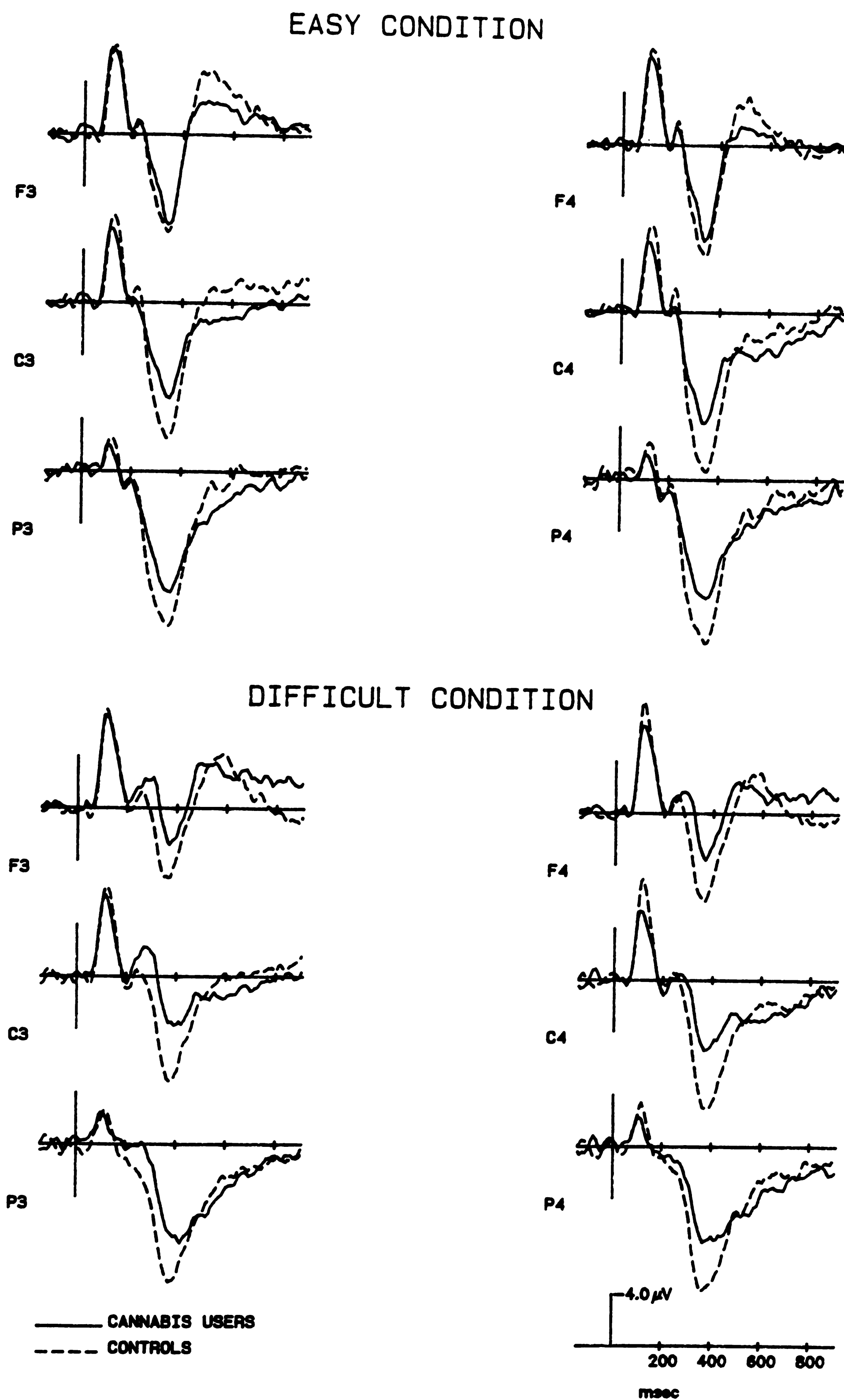
Figure 7.1 Grand average ERPs to infrequent target stimuli (high pitch tones) recorded during easy and difficult auditory "oddball" paradigms from cannabis users and controls.

EASY CONDITION

F3

F4

C3

C4

P3

P4

DIFFICULT CONDITION

F3

F4

C3

C4

P3

P4

——— CANNABIS USERS

– – – CONTROLS

–4.0 μV

200 400 600 800

msec
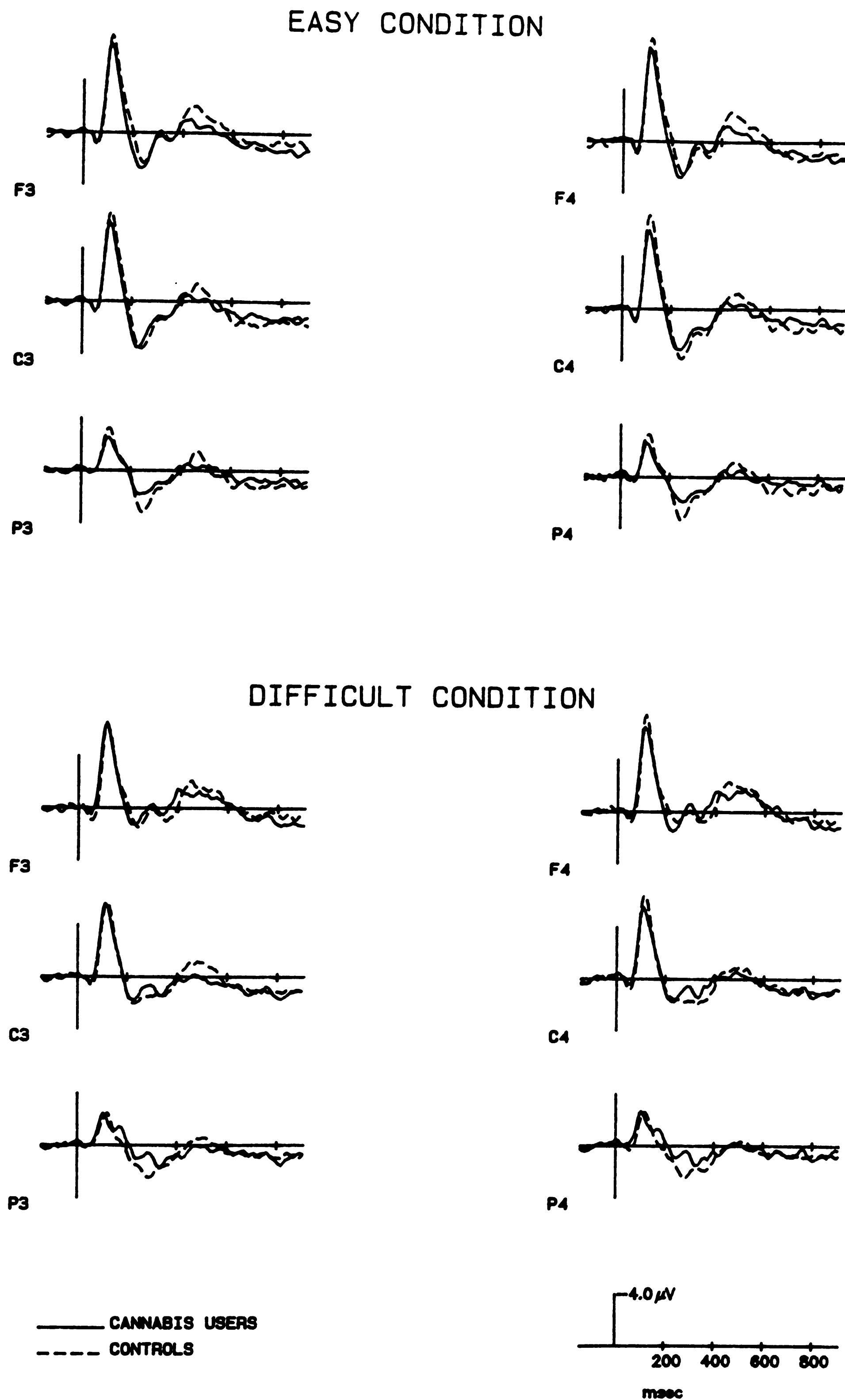
Figure 7.2   Grand average ERPs to frequent stimuli (low pitch tones) recorded during easy and difficult auditory "oddball" paradigms from cannabis users and controls

The P300 was measured as the most positive peak occurring between 200 and 600 ms at all scalp sites to examine possible differences between groups in the frontal P3a and parietal P3b components. P300 peaked significantly later in the difficult condition [$F(1,14) = 78.30$, $p < 0.0001$] and at parietal sites [$F(2,28) = 9.91$, $p < 0.0020$], however groups did not differ in P300 latency [$F(1,14) = 0.97$, $p > 0.34$] and there was no interaction between condition and group [$F(1,14) = 1.64$, $p > 0.22$].

Analysis of P300 peak amplitude revealed a significant interaction between condition, electrode and group [$F(2,28) = 8.66$, $p < 0.0024$). Multiple comparisons of each group at each site for each condition failed to reveal the nature of the significant interaction, but simple comparisons of easy and difficult conditions at each site for each group separately indicated that in cannabis users P300 peak amplitude was markedly reduced at frontal [$F(1,7) = 48.32$, $p < 0.0002$] and central [$F(1,7) = 20.42$, $p < 0.0027$] sites in the difficult condition compared to the easy condition. Controls showed no significant reduction in P300 amplitude in the difficult condition at any site. Overall, P300 was larger in the easy condition [$F(1,14) = 9.11$, $p < 0.0092$], largest at parietal scalp sites [$F(2,28) = 13.26$, $p < 0.0001$] and was smallest in amplitude at frontal sites in the difficult condition [$F(2,28) = 7.34$, $p < 0.0049$].

The nature of these effects on P300 peak amplitude and group differences is apparent in Figure 7.3: P300 appears reduced steadily across all sites in the difficult condition for controls (albeit nonsignificantly), whereas for users P300 is drastically reduced at frontal sites, although the scalp topography distribution of P300 appears quite different in the users in the easy condition compared to controls. Users showed an uncharacteristically large frontal P3 component in the easy condition.
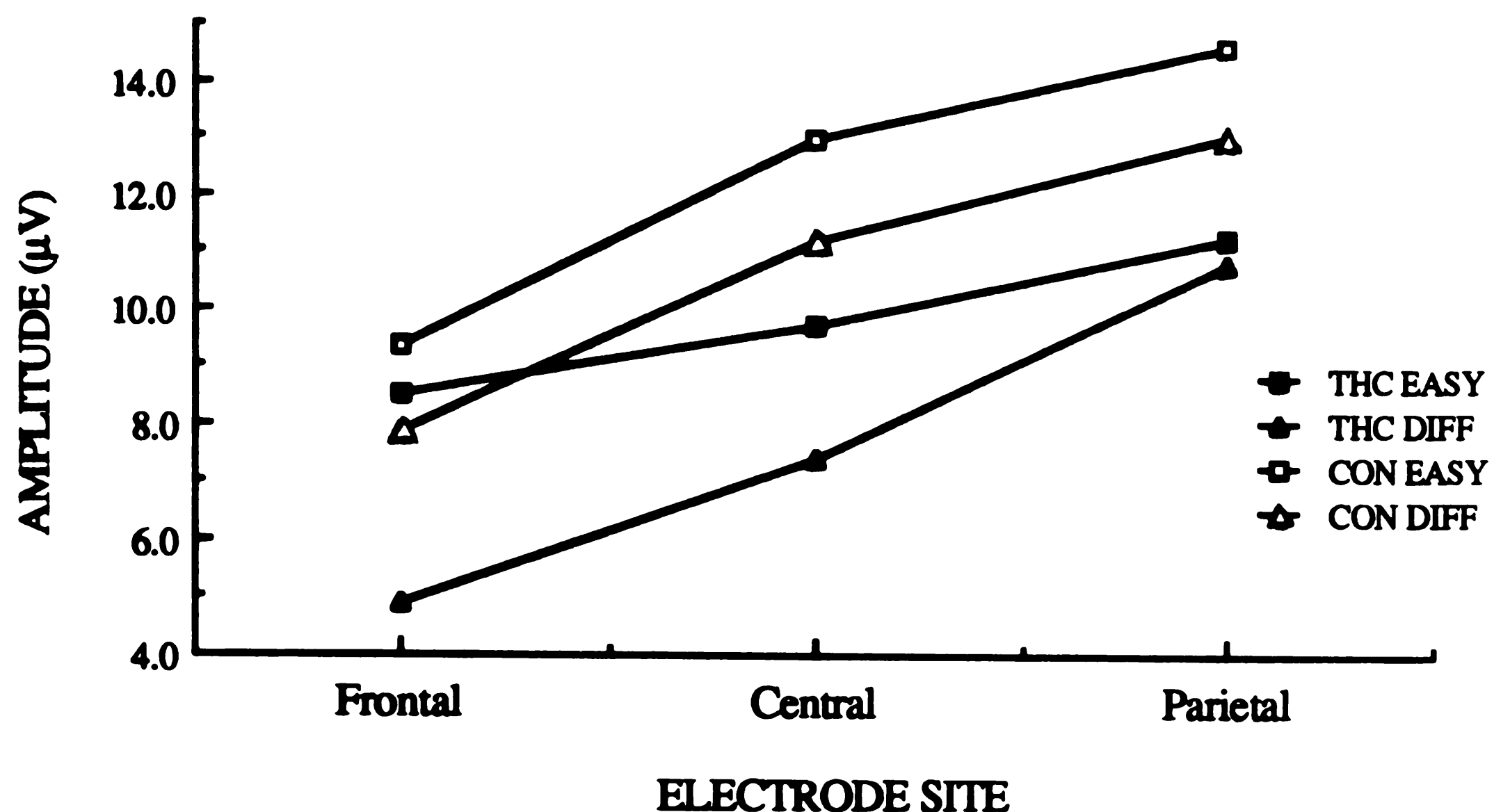
Figure 7.3 Easy versus difficult auditory "oddball" P300 amplitude data from cannabis users (THC) and controls (CON).

P300 was largest in the right hemisphere [F(1,14) = 7.70, p < 0.0149] and this hemispheric laterality was most apparent at central sites [F(2,28) = 3.55, p < 0.0422]. Analysis of the mean amplitude measured over 200 to 600 ms revealed no differences between groups. Although users appeared to show smaller late frontal negativity than controls in the easy condition, analysis of the mean amplitude between 400 and 800 ms revealed no group differences or interactions.

ERPs to frequent tones (Figure 7.2) appeared to be quite similar in both cannabis users and controls. The only component measured, N1, was larger in the easy than in the difficult condition [F(1,14) = 10.22, p < 0.0065] and was largest at frontal sites [F(1,14) = 8.39, p < 0.0117], but did not differ between groups.

7.1.3   Discussion

The results of this first experiment were suggestive of possible electro-
physiological and information processing differences between cannabis users and
controls. The experimental manipulation of task difficulty supported the hypothesis that
any differences between cannabis users and controls are more likely to be detected in
difficult and demanding tasks.

There were no significant differences between users and controls in the easy
oddball paradigm. The scalp topography of the P300 component appeared to be
different in the user group, with a much more frontal distribution in the easy condition.
This may reflect the elicitation of a P3a component which has a more fronto-central
distribution. P3a amplitude is related to the degree of physical contrast with background
stimuli (Squires, Squires and Hillyard, 1977; Squires et al, 1975), making it more likely
to be elicited in the easy condition. However, since it is generally elicited by infrequent,
unattended, task irrelevant stimuli, there is doubt as to whether the frontal component
observed in users is really a P3a. If anything, this result may be suggestive of some
functional differences between cannabis users and controls in frontal regions of the
brain.

The main differences between users and controls occurred in the difficult
condition. Cannabis users showed a delayed N2, which suggests a possible delay in
stimulus evaluation in cannabis users with more difficult stimulus discriminations.
N200 latency has been shown to correlate with reaction time (Ritter et al, 1979) and
cannabis users indeed had longer reaction times than controls, albeit nonsignificantly.
Interestingly, N2 latency has been reported to increase as a function of age (Iragui et al,
1993) and the same authors reported in their auditory oddball paradigm that aging is also

associated with greater anterior positivity, in terms of larger frontal P300 components. Zeef and Kok (1993) and Friedman, Simpson and Hamberger (1993) have also demonstrated that the scalp distribution of P300 changes with age to a more frontal orientation. The latter authors point out that the shift to a more anterior distribution of P300 is one of the most robust age-related findings in the ERP literature, and is consistent with a change in frontal lobe activity with increasing age. It is possible that the effects observed here on N2 latency and the large frontal P300 component in cannabis users may reflect accelerated aging in terms of cognitive decline. This hypothesis is in accord with the studies of Landfield (et al, 1988) and Eldridge (et al, 1992) which examined the interactions between cannabinoids and glucocorticoid system in the brain and suggested that cannabinoids may accelerate brain aging (see Chapter 4).

Despite the delay in N2, P300 was not significantly later in users than controls. The lack of overt P300 latency differences in the user group suggests that stimulus-encoding processes in users may be intact. However, it does not eliminate a deficit in stimulus evaluation. As discussed in Chapter 6, N2 has been suggested to be a better index of stimulus evaluation time than P300. Further, the amplitude of P300 was smaller in users than controls for both easy and difficult conditions, nonsignificantly overall, although the more difficult pitch discrimination significantly reduced the P300 in cannabis users at frontal and central sites. This is suggestive of some dysfunction in stimulus evaluation strategies and allocation of attentional resources, evident primarily in the region of the frontal cortex. It has recently been suggested that there may be multiple neural generators of the P300 component distributed throughout the brain (Johnson, 1993), and it is possible that cannabinoids may selectively disrupt neural sources in the frontal lobes. This hypothesis of frontal dysfunction is not entirely inconsistent with the aging related effects on P300 discussed above, as it may be that strategic or functional differences due to an increase in task difficulty camouflage the aging effect on P300. Nonetheless, these hypotheses are speculative and any interpretation of data from such a small sample must be treated with caution.

The auditory oddball paradigm provided a means to examine auditory ERPs reliably elicited by a simple task in cannabis users compared to controls. Although, differences between groups may have been more apparent had a larger sample been studied, the simple nature of this task may not permit the detection of any cognitive dysfunction. The results provide some clues as to possible deficits, but the nature of these has not been elucidated. The auditory oddball task does not draw heavily upon attentional resources (ie. was not attentionally demanding), requiring little more than simply responding to a deviant stimulus.

The next experiment was designed to engage attentional resources more fully in a substantially more demanding task, tapping specifically the ability to selectively attend to task-relevant stimuli while suppressing task-irrelevant information.

7.2 Experiment two: Effects of long term cannabis use on ERPs recorded during an auditory selective attention paradigm

In this experiment, ERPs were recorded during a complex multidimensional auditory selective attention task based on a paradigm developed by Hansen and Hillyard (1983). This task involved the presentation of a random series of tone pips which varied on the dimensions of location, pitch and duration. Subjects were required to attend to tones of a particular location and pitch and to respond to infrequent target tones of slightly longer duration than the short duration background standards. The task is difficult and cognitively demanding, but has been used successfully to investigate information processing among a number of other clinical groups suspected of deficient attentional mechanisms, for example, schizophrenics (Michie et al, 1990; Ward et al,

1991). There exists a wealth of normative data on the ERP patterns elicited by this paradigm, as discussed in Chapter 6.

The paradigm is useful for studying hierarchical modes of information processing by manipulating the difficulty of discrimination of each dimension. In this case, the duration discrimination was the most difficult, followed by pitch and then location. This enables the subject, whose task is to selectively attend to a particular combination of these dimensions, to rapidly reject half of the stimuli from further analysis on the basis of location. Use of this paradigm would determine whether chronic cannabis users engage in a less efficient mode of information processing than do controls, and whether their ability to selectively attend and ignore irrelevant information is compromised. Processing negativity (PN) and P300 were the two components of particular relevance in this study.

7.2.1   Method

Subjects

Subjects in this experiment consisted of the same sample as that initially recruited for experiment one (N=10 cannabis users). Subjects were tested immediately following the oddball paradigm of experiment one and were therefore abstinent from cannabis and alcohol for at least twelve hours prior to testing. One cannabis user was unable to do the selective attention task. Hence, the final sample in this experiment consisted of six male and three female cannabis users, aged 19-40 (mean 29.4 yrs, SD = 8.47). These were matched on age (to within two years), sex and years of education with nine non-user controls, aged 21-41 (mean 29.5 yrs, SD = 7.76). The average number of standard drinks per week consumed by the user group was 11.44 (SD = 9.41) and 5.67 (SD =

5.68) by the control group. Alcohol consumption in the two groups was not significantly different [F(1,16) = 2.49, p > 0.13].

Premorbid IQ, as assessed by the NART (Nelson, 1984) did not differ between groups [F(1,16) = 0.11, p > 0.74]. All subjects had completed 13 years of school education and at least one year at tertiary level. Within each group, eight subjects were right handed and one left handed, as determined by the Edinburgh Inventory (Oldfield, 1971).

The mean years of cannabis use in the user group was 11.2 yrs (SD = 6.98, range 3 - 20 yrs) and the average level of use was 4.77 days per week (SD = 1.85, range twice a week to daily use). The mean weekly consumption was 766 mg THC (SD = 859, range 30 - 2400 mg/wk). The longest period of abstinence from cannabis in the last three years ranged from 3-4 days to three months, mean 42 days (SD = 27.76). Controls had no more experience with cannabis than that described for experiment one.

Stimuli

Stimuli consisted of sequences of tone pips delivered randomly to the left or right ear via stereophonic headphones (TDH 49) at an intensity of 80 dB SPL. The tones varied in location (left ear/right ear), pitch (high/low) and duration (long/short). Half the tone pips presented to each ear were 1047 Hz and the remainder were of a higher pitch at 1319 Hz (representing C6 and E6 on the musical scale). Tones at each ear/pitch combination occurred with equal probability (p = 0.25). Within each ear/pitch combination, nineteen percent of the stimuli were 51 ms in duration (the standards) and six percent were 102 ms (the targets), both having a 10 ms rise and fall time. The stimuli were presented as a random sequence lasting 160 seconds per run with and SOA of 200 to 500 ms. All aspects of stimulus delivery and randomisation were under

computer control (Data General Nova 4-C), the only constraint placed on the randomisation procedure being that two target stimuli of the same type could not occur consecutively.

ERP recording

As subjects completed the selective attention task immediately following the auditory oddball paradigm of experiment one, all ERP recording parameters were identical to those described above.

Procedure

The procedure followed has been described above in experiment one. One additional procedural step prior to the commencement of this experiment was that subjects were given training on the selective attention task until they achieved the criterion level of performance of 50% hits and no more than 25% of responses being false alarms. This was generally achieved after two practice runs of two and half minutes each for both users and controls.

Subjects were instructed to attend to a particular location and pitch, and to respond as rapidly as possible to the long duration tones by pressing the response button mounted on the arm of the chair. There were four attention conditions: respond to left low long, left high long, right low long or right high long. Each subject completed two runs of each attention condition, one with a right hand response and one with a left hand response. The order of attention conditions and responding hand was randomised among subjects and counterbalanced across groups.

Data analysis

Button press responses were classified as correct detections or "hits" if they occurred within a 200 to 1200 ms response window after an attended target stimulus. Reaction time (RT) was measured as the latency in ms of the button press from the onset of the attended target. An attended target not followed by a response within the response window was regarded as an error of omission or "miss". Button presses at other times were regarded as errors of commission or "false alarms". The number of hits as a ratio of the number of attended targets provided an estimate of the hit rate, while the false alarm rate was calculated as a ratio of the total number of nontargets.

The EEG data was processed and analysed as described above for experiment one, and statistical analyses are described in more detail in the results section below. Hansen and Hillyard (1983) adopted a procedure for stimulus classification to denote whether the stimulus matched (+) or did not match (-) the target of each run, on each of the stimulus characteristics of location (L), pitch (P) and duration (D). Thus, the attended target requiring a response was denoted by L+P+D+, whereas a stimulus presented to the same location but of a different pitch and of short duration, was denoted by L+P-D-. For purposes of simplicity, and also to emphasise the differences between cannabis users and controls that will become apparent later, the labels adopted in this thesis for each stimulus type will use Hansen and Hillyard's abbreviation for attended and unattended location as L+ and L- respectively, but otherwise will denote the stimulus as being of relevant or irrelevant pitch. Thus, a stimulus notation of "L+ irrelevant pitch" denotes a stimulus presented to the ear to which the subject was to attend, but of a pitch the subject was to ignore. According to Hansen and Hillyard's classification system, such a stimulus would be denoted by L+P-D+ if it were of long duration, or by L+P-D- if it was a short duration tone. Here, short duration tones will be referred to as standards and long duration tones as targets. Averages to the same stimulus type across different

attention conditions were created, but collapsed across high and low pitched stimuli and runs with left and right hand responses, and sorted according to whether they were recorded from the hemisphere ipsilateral or contralateral to the stimulated ear.

7.2.2 Results

Performance data

Task performance measures of reaction time, percent correct hits and false alarms are depicted in Table 7.2. The mean reaction time of the user group was longer than that of the control group but this difference failed to reach statistical significance [$F(1,16)$ = 1.08, $p > 0.31$]. Cannabis users had a significantly lower correct hit rate than controls [$F(1,16) = 4.67$, $p < 0.0461$]. Users made significantly more false alarms than controls [$F(1,16) = 6.10$, $p < 0.0251$]. Thus, most of the performance measures indicated that the performance of cannabis users in this selective attention task was poorer than that of the controls.

ERP data

The processes of selective attention were assessed by comparing the amplitudes of the various ERP components elicited by the four standard and four target stimuli distinguished on the basis of their location and pitch characteristics. These measures were subjected to a repeated measures analysis of variance (BMD-P2V), with factors of group, stimulus, electrode site and hemisphere. Here, and for the remainder of this thesis, analyses of the early components (P1, N1, P2) will only be reported if significant

Table 7.2 Mean task performance measures of reaction time (RT), hit rate and false alarm rate of cannabis users and controls (with SD in parentheses).

	RT (ms)	Hit rate (%)	False alarm rate (%)
USERS	573.06	71.94	1.64
	(67.63)	(16.04)	(1.58)
CONTROLS	536.96	86.72	0.32
	(79.25)	(12.79)	(0.29)

group effects or interactions were found. Similarly, the results reported from analyses of all other ERP components will focus on group differences and not effects due to experimental manipulation.

Figure 7.4 depicts grand average ERPs to long duration target stimuli recorded from frontal, central and parietal scalp sites of cannabis users and controls. The L+ relevant pitch trace represents the brain's response to the attended target tones which the subjects had to identify and respond to with a button press. The large positive component evident in this trace is the P300, and the most noticeable difference between groups upon first inspection of the plots is the amplitude of this component. It appears greatly reduced in cannabis users compared to controls at all electrode sites.

The P300 component was measured as the mean amplitude between 300 and 900 ms. Analysis of variance confirmed that this component was smaller across all electrode sites in the user group compared to the control group [F(1,16) = 4.37, p < 0.0528]. When measured as the most positive peak occurring in the same range, there was a trend toward smaller peak P300 in users compared to controls [F(1,16) = 3.61, p < 0.0757], but the latency of the peak did not differ between groups [F(1,16) = 0.63, p > 0.43].

The other striking difference between groups was the large N200 also in the L+ relevant pitch trace in controls, which appeared greatly reduced in users. In the early part of the epoch, similar patterns of processing of the location dimension were evident in both groups, with early separation of the L+ and L- traces at frontal and central sites. By about 200 ms, the L+ relevant pitch trace separated sharply from the L+ irrelevant pitch trace in controls with a second negative peak, the N200. The L+ relevant pitch and L+ irrelevant pitch ERPs fail to separate well in the user group compared to controls.

The lack of separation between relevant and irrelevant pitch traces in users was due not only to the reduced N200 in the relevant pitch ERP, but also the appearance of an N200 in the irrelevant pitch trace in users, seen most clearly between 200 and 300 ms at frontal and central sites. There is no evidence of an N200 in the L+ irrelevant pitch trace in controls. Due to its close proximity to the N1 component and large intersubject variability in its latency, the N200 peak in the both L+ relevant and irrelevant pitch traces was not measurable. Inspection of the individual subject waveforms revealed eight of the nine users to show a clear N200, while only four of the controls tended to show small negative peaks to the irrelevant pitch stimulus. Attempts to verify this difference between groups resulted in a marginally significant interaction between stimulus and group when the mean amplitude between 250 and 275 ms was analysed [F(1,16) = 4.36, p < 0.0532], but multiple comparisons of each stimulus for each group failed to

CANNABIS USERS

Ipsi F

Contra F

Ipsi C

Contra C

Ipsi P

Contra P

CONTROLS

Ipsi F

Contra F

Ipsi C

Contra C

Ipsi P

Contra P

_____ L+ relevant pitch
_ _ _ _ L+ irrelevant pitch
. . . . L- relevant pitch
_ . _ L- irrelevant pitch

⎡2.0 μV

200 400 600 800
msec
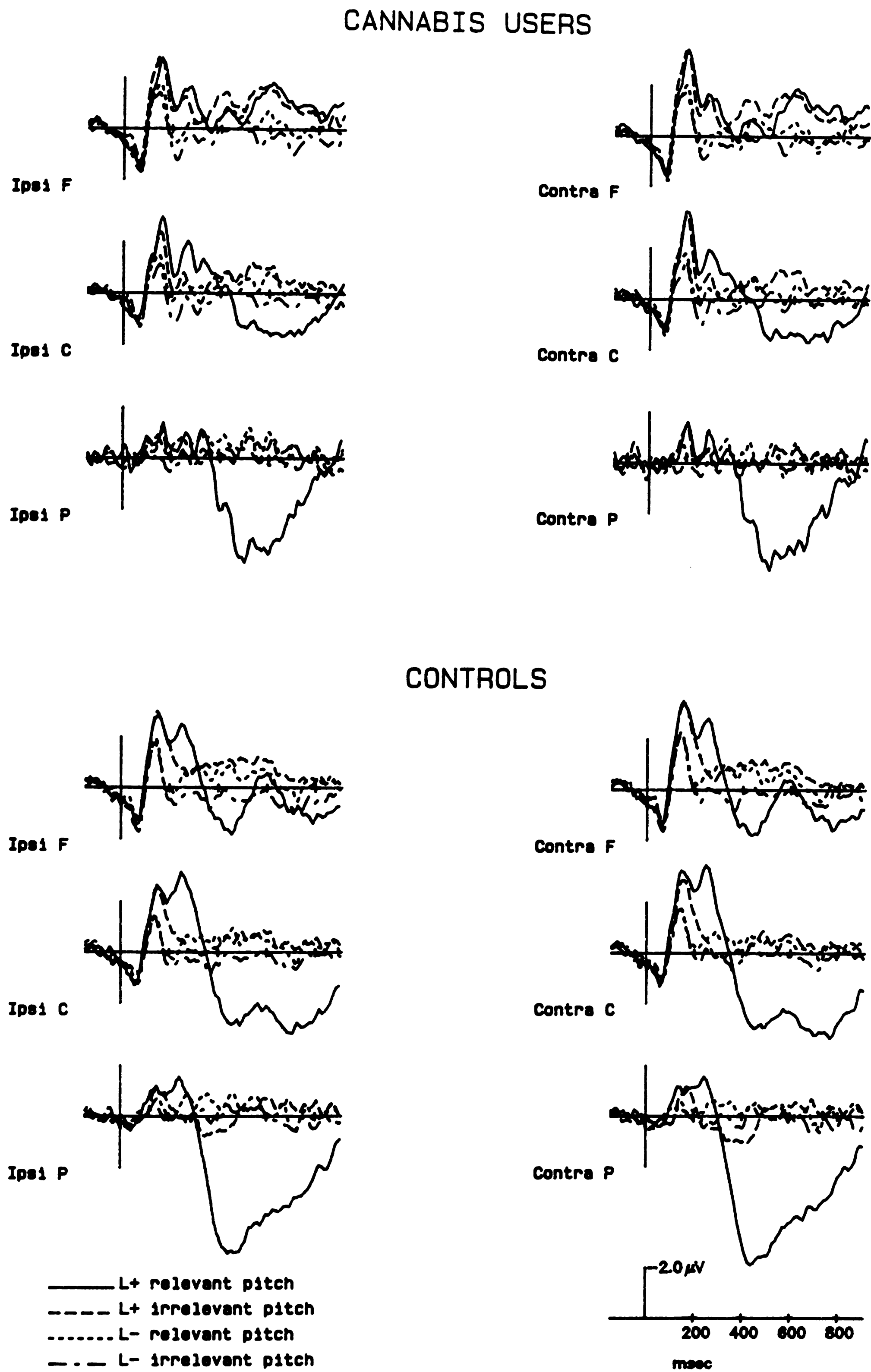
Figure 7.4 Grand average ERPs to target stimuli (long duration tones) recorded during an auditory selective attention task from cannabis users and controls.

reach significance. This pattern of results is indicative of poor selection of the relevant pitch target stimulus, and unnecessary processing of the irrelevant pitch stimuli in the user group, perhaps reflecting an inability to reject pitch irrelevant stimuli at an early stage of processing.

Figure 7.5 depicts grand average ERPs to short duration standard stimuli. The importance of examining ERPs to standard stimuli is that they provide a measure of the processes involved in selective attention, uncontaminated by target detection, response preparation and response execution processes. The ERPs of the two groups appeared to be similar in the early range of the epoch. The early components, P1, N1 and P2 were measured at frontal and central scalp sites as the most positive peak between 25 and 150 ms, the most negative peak between 50 and 250 ms and the most positive peak between 100 and 300 ms respectively. Analyses of peak amplitude and latency revealed some unexpected differences between groups. Cannabis users showed shorter latency P1 [Group: $F_{(1,16)} = 4.36$, $p < 0.0530$] and N1 [$F_{(1,16)} = 7.79$, $p < 0.0131$] components than controls. P2 latency did not differ between groups [$F_{(1,16)} = 1.10$, $p > 0.30$]. There were no group differences in the amplitude of P1 [$F_{(1,16)} = 0.16$, $p > 0.69$], N1 [$F_{(1,16)} = 0.07$, $p > 0.78$] or P2 [$F_{(1,16)} = 1.31$, $p > 0.26$]. A stimulus by group interaction was marginally significant for P1 amplitude [$F_{(3,48)} = 2.88$, $p < 0.0510$], but multiple comparisons of each group for stimulus failed to reveal the nature of the interaction. Means suggested that users had smaller amplitude P1 to all stimuli apart from the L+ relevant pitch stimulus. The latency differences between groups in these early components are difficult to interpret.

The processes of selective attention can be seen from Figure 7.5 to commence around the beginning of the N1 peak with the separation of the two L+ and two L-ERPs. Early processing negativity (PN) is evident around the N1 peak in both groups in the two L+ ERPs. This early enhancement of the L+ traces and positive going shift of

the two L- traces indicates that cannabis users had no difficulty selecting or rejecting stimuli on the basis of location. With the processing of the pitch dimension, the controls show a large PN to L+ relevant pitch stimuli, while the user group fails to sustain this negativity between 200 and 300 ms at frontal and central sites. Analysis of the mean amplitude of the L+ relevant pitch trace within this range determined a significant group difference [$F(1,16) = 5.05$, $p < 0.0391$]. This is indicative of difficulty in users in selecting relevant from irrelevant information when the selection is based on more complex stimulus attributes.

The most striking difference between the two groups apparent in Figure 7.5 is the large processing negativity (PN) shown by cannabis users to the irrelevant pitch stimuli in the attended ear. Relative to the L+ relevant pitch trace, the L+ irrelevant pitch ERP shows an enhanced negativity in the user group in comparison to controls. This difference between groups was evident as early as the N1 peak, where N1 appeared larger to irrelevant pitch stimuli than relevant pitch stimuli in users, but vice versa in controls. This observation was confirmed by a significant stimulus by group interaction for N1 peak amplitude measured from ERPs to the L+ stimuli [$F(1,16) = 9.79$, $p < 0.0065$].

Mean amplitude measures over 50 ms intervals at frontal and central sites were subjected to a four way analysis of variance with a group factor and repeated measures for stimulus type, electrode site and hemisphere. When all four stimuli were included in the analysis, the results suggestive of interactions between stimulus and group over the range from 50 to 400 ms, however, it was apparent that large variability in the measures of the two L- stimuli may have served to obscure any group differences in PN to L+ stimuli. As a result of this observation, analyses for L+ and L- stimuli were conducted separately. Although the two L- traces appeared to show larger separation in the control group than in users, the large variability in these measures resulted in no significant differences between groups in any range measured.

CANNABIS USERS

Ipsi F

Contra F

Ipsi C

Contra C

Ipsi P

Contra P

CONTROLS

Ipsi F

Contra F

Ipsi C

Contra C

Ipsi P

Contra P

```
————————— L+ relevant pitch
— — — — L+ irrelevant pitch
.........L- relevant pitch
— . — ..L- irrelevant pitch
```

┌ 2.0 μV

200 400 600 800

msec
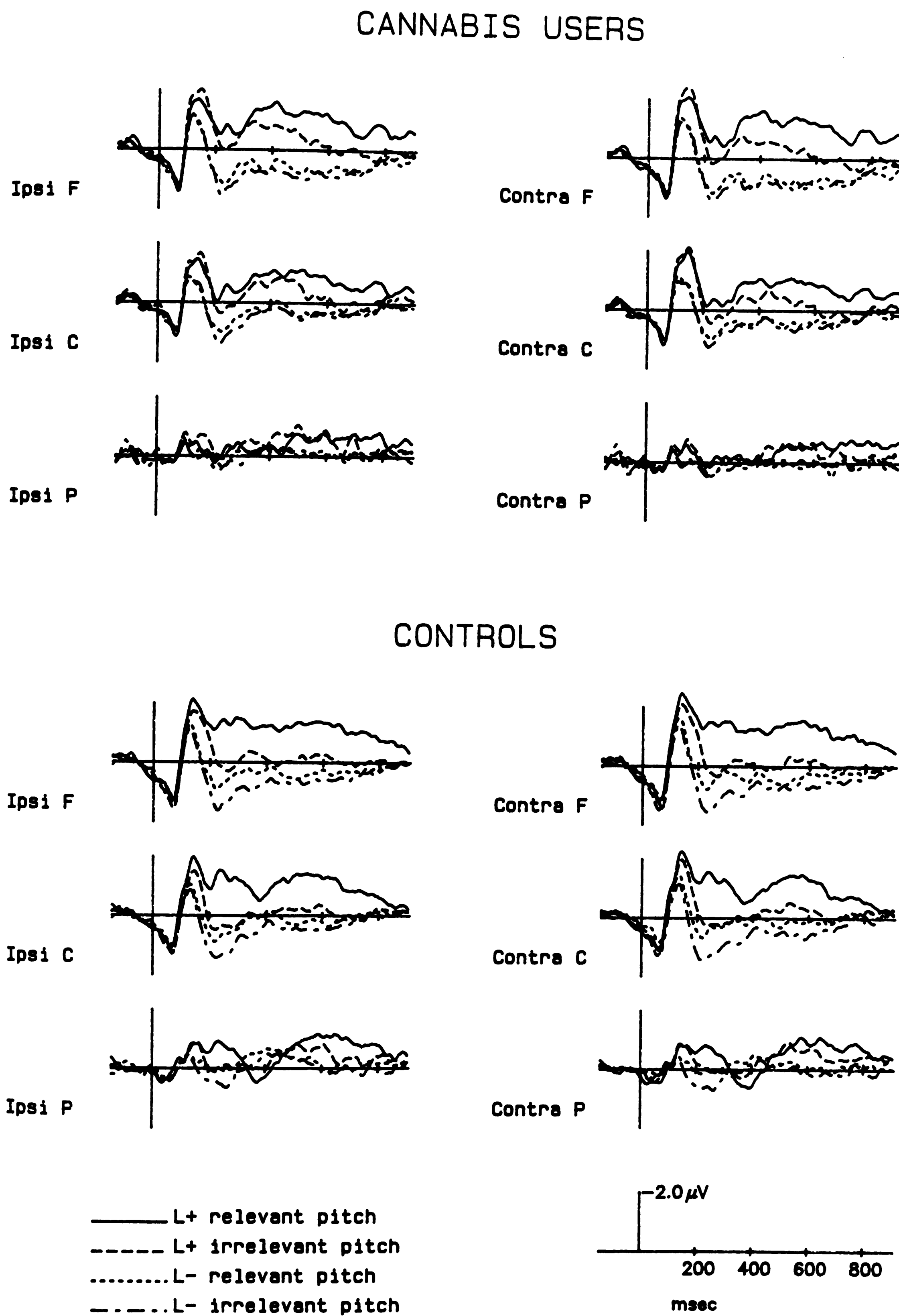
Figure 7.5 Grand average ERPs to standard stimuli (short duration tones) in an auditory selective attention task recorded from cannabis users and controls.

Analyses of mean amplitudes of the ERPs to L+ stimuli determined a significant interaction between stimulus and group for almost every range measured from 50 to 400 ms into the epoch: [50-100 ms $F(1,16) = 14.14$, $p < 0.0017$; 100-150 ms $F(1,16) = 11.98$, $p < 0.0032$; 150-200 ms $F(1,16) = 5.74$, $p < 0.0292$; 200-250 ms $F(1,16) = 3.27$, $p < 0.0893$; 250-300 ms $F(1,16) = 4.30$, $p < 0.0545$; 300-350 ms $F(1,16) = 6.60$, $p < 0.0256$; 350-400 ms $F(1,16) = 2.68$, $p < 0.0942$]. Low power due to the small sample size resulted in no significant effects upon multiple comparisons of the two groups for each stimulus. The trends were in the direction of larger negativity to irrelevant pitch stimuli in users over most of the range, but smaller mean amplitude in users to relevant pitch stimuli in the range from 200 to 300 ms. The mean amplitude from 50 to 400 ms was analysed and showed a significant stimulus by group interaction [$F(1,16) = 4.74$, $p < 0.0447$]; multiple comparisons suggested that this was primarily due to the large PN to irrelevant pitch stimuli in users [$F(1,16) = 3.25$, $p < 0.0901$]. There was also a tendency for PN to relevant pitch stimuli to be smaller in users [$F(1,16) = 2.36$, $p < 0.1439$].

Although this negativity in the irrelevant pitch ERP appeared to persist to around 600 ms in the user group, analyses of mean amplitudes over 50 ms and 100 ms intervals failed to detect differences between groups beyond 400 ms. An analysis of the mean amplitude over 200 to 600 ms, however, did reveal a significant difference between users and controls as an interaction with hemisphere [$F(1,16) = 5.06$, $p < 0.0389$], whereby the difference between groups was largest in the ipsilateral hemisphere. This difference is evident in Figure 7.5. Towards the end of the epoch, there were no significant differences between the two groups on the late component of PN to pitch relevant tones and the inappropriately large PN to irrelevant pitch tones did not continue beyond 600 ms in users.

These differences between groups are also replicated in the pitch difference
waveforms presented in Figure 7.6. The difference waveforms, representing Nd, were
created by subtracting the L+ irrelevant pitch ERP from the L+ relevant pitch ERP. The
resulting waveforms in Figure 7.6 emphasize the large separation between the relevant
and irrelevant pitch traces in controls, whereas in users the separation is much smaller.
This separation can be seen to commence with a sharp rise in Nd around 200 ms,
particularly in the control group, while the earlier portion of the difference wave reflects
smaller stimulus differences in the early ERP components; the lack of Nd (or positivity)
prior to 200 ms in the users reflects greater negativity in the irrelevant pitch trace (as
discussed for N1 above). The latency and amplitude of the largest peak in Nd within the
50 to 400 ms range was analysed. This indicated the point of maximum separation of
the relevant and irrelevant pitch ERPs but no differences were found between groups in
the latency of this point [F(1,16) = 2.18, p > 0.15]. There was a trend toward
significantly larger separation in the control group reflected in larger amplitude peak Nd
[F(1,16) = 3.43, p < 0.0827].
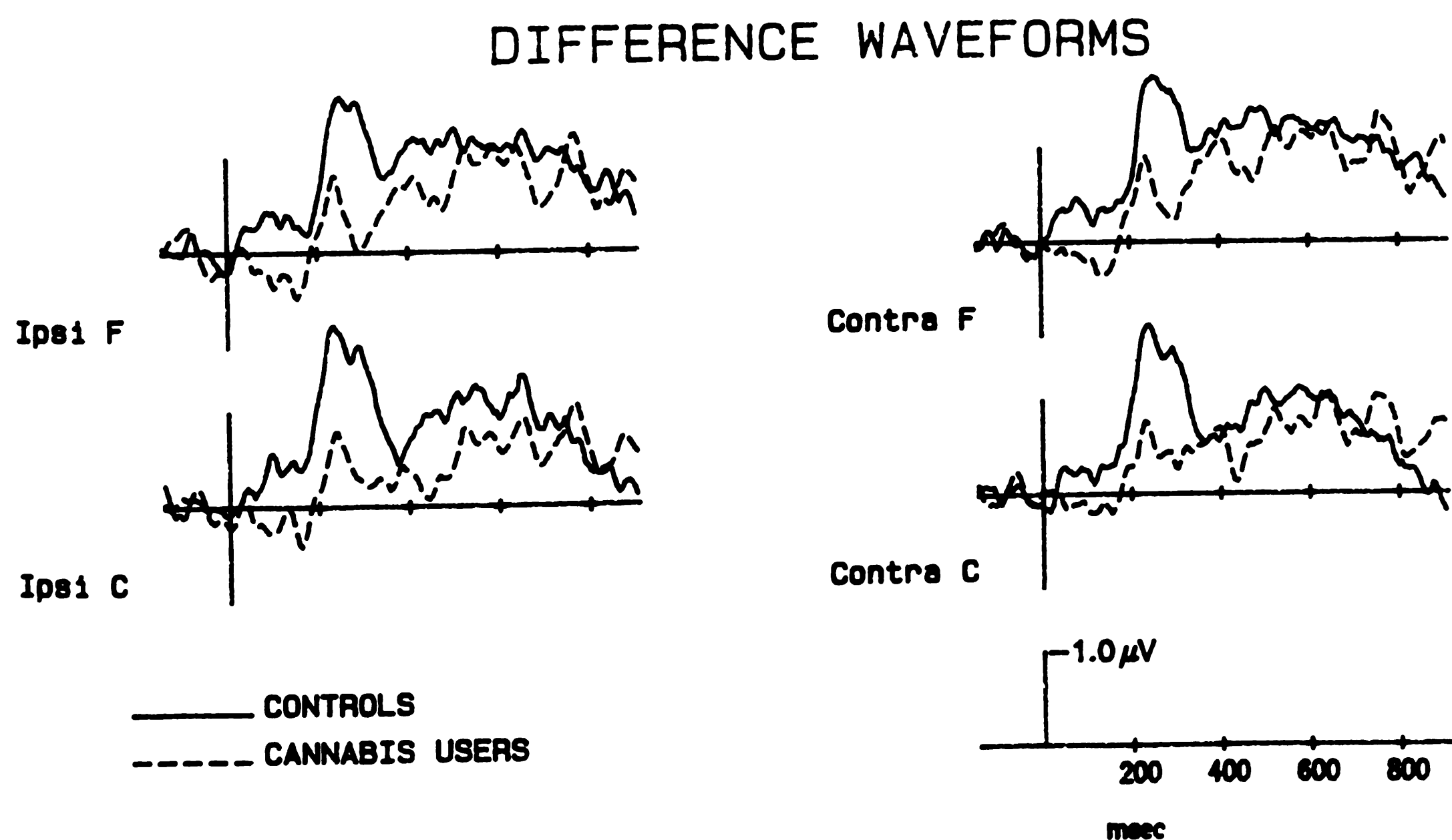
**Figure 7.6 Pitch difference waveforms (L+ relevant pitch minus L+
irrelevant pitch) for cannabis users and controls.**

Visual inspection of the raw ERPs of Figure 7.5 indicated clearly that the largest differences between groups were due to the reduced early PN to relevant pitch stimuli and the inappropriately large PN to irrelevant pitch stimuli in the user group. These observations were to an extent supported by statistical analyses, which would probably have been more robust had a larger sample been tested. Analysis of Nd measured in the difference waveforms contributed no further useful information regarding the nature of group differences. [The remainder of the studies in this thesis will therefore concentrate on analyses of PN and not Nd]. This pattern of results is indicative of an inability to select and filter out stimuli on the basis of complex stimulus attributes (eg. pitch).

7.2.3 Discussion

The differences found between cannabis user and control groups in this experiment indicate that users may have some difficulty in setting up an accurate focus of attention and in filtering out irrelevant information.

Cannabis users displayed a similar pattern to controls in the early filtering of stimuli which did not match the targets on the dimension of location, as evidenced by the separation of the L+ and L- waveforms. However, both the presence of the N200 component in the ERPs to long duration irrelevant pitch tones in the attended ear and the large PN elicited by short duration irrelevant pitch stimuli in the attended ear, imply that users were unable to effectively reject stimuli on the basis of pitch attributes.

The largest differences between users and controls were apparent in the early part of the PN component. According to Näätänen (1982), this part of the PN reflects a matching process between the sensory information contained in the stimulus and an

"attentional trace", an active voluntarily maintained neuronal representation of the physical features defining the stimuli which are the focus of attention. Thus, it appears to be the process of the selection and setting up of the attentional trace that is impaired, rather than its maintenance or rehearsal as would be reflected in the late component of PN according to Näätänen's theory. Further, the reduced P300 amplitude suggests a dysfunction in the allocation of attentional resources and stimulus evaluation strategies (Isreal et al, 1980; Pritchard, 1981).

The behavioural results of this study are important in demonstrating the value of examining the underlying mechanisms involved in processing information. Although users were no slower to respond than controls, their performance was significantly worse. It is not surprising then, that tests measuring reaction time alone may fail to detect deficits in task performance. Further, performance measures alone would not reveal the nature of the attentional deficits revealed by examining the event-related potential measures. Taken together, both the performance and the ERP results of these studies imply that long term cannabis use may impair the ability to efficiently process information.

At this stage it was not possible to assess to what extent this deficit may be due to a chronic build up of cannabinoids and whether functioning would return to normal upon discontinuation of use. The following experiments were designed to address these questions and to examine the quantity and duration of use at which dysfunction is first manifest. The differences found in this relatively small diverse sample warranted further investigation of cognitive functioning in long term cannabis users.

CHAPTER 8

AN INVESTIGATION OF THE EFFECTS OF FREQUENCY AND DURATION OF CANNABIS USE

8.1 Experiment three: The effects of frequency and duration of cannabis use on auditory selective attention

In Experiment 2, ERPs recorded during a complex auditory selective attention task were compared between a small and heterogeneous group of long term cannabis users and a non-user control group. The results indicated that compared to controls, cannabis users showed larger processing negativity to an irrelevant source of information, reflecting an inability to filter out extraneous information at an early stage of processing. Cannabis users also showed reduced P300 amplitude which was interpreted as a dysfunction in the allocation of attentional resources. The current study was designed to replicate these findings with a larger sample and to examine the effects of frequency and duration of cannabis use.

8.1.1 Method

Subjects

Subjects were recruited from the general community through advertising and gave written informed consent (see Appendix A). The minimum requirement for participation as a cannabis user was regular use of at least once a month for three years. The cannabis user group (N=32) had used cannabis for a mean of 6.69 years (range: 3 to 28 years) at a mean frequency of 12 days per month (range: once/month to daily use). The characteristics of the entire sample and subgroups are presented in Table 8.1.

The user group was split at the median on both frequency (light: $\leq$ 2/week vs. heavy: $\geq$ 3/week) and duration (short: 3-4 years vs. long: $\geq$ 5 years) of cannabis use. Mean levels of use for each group are provided in Table 8.1. Equal numbers of heavy and light users contributed to the long and short duration user groups and vice versa. A group of non-user controls (N=16) were selected to cover the range of age, years of education and sex distribution in the user groups. No control subject had ever used cannabis on a regular basis. The mean number of lifetime experiences with cannabis in the control group was 9 ($\pm$ 11.2).

Due to the inevitable relationship between age and duration of use, long duration users were older than short duration users [$F(1,30) = 18.01$, $p < 0.0002$]. While controls did not differ in age from cannabis users overall [$F(1,46) = 0.75$, $p > 0.39$], it was ensured that they did not differ in age from long duration users [$F(1,30) = 0.90$, $p > 0.35$]. This resulted in controls being significantly older than short duration cannabis users [$F(1,30) = 12.60$, $p < 0.0013$]. Cannabis users consumed more alcohol per month than controls [$F(1,46) = 7.43$, $p < 0.0090$]. Age and alcohol consumption were accordingly included as covariates in the analyses (where appropriate).

Seventy five percent of the sample were male and most had completed some tertiary education. Controls had slightly more years of education than users [$F(1,46)$ = 9.54, p < 0.0034] (equivalent to one or two more years at tertiary level). Full scale IQ, assessed by the NART (Nelson 1984) did not differ between groups based on duration of use relative to controls [$F(2,45)$ = 2.04, p > 0.14], nor between groups based on frequency of use [$F(2,45)$ = 2.30, p > 0.11]. A trend toward lower IQ overall in the cannabis users compared to controls [$F(1,46)$ = 3.56, p > 0.06] indicated that the relationships between IQ and ERP components needed to be examined in light of any group differences. The actual difference in IQ was very small, at 116.3 for users, compared to 119.5 for controls. These levels are in the superior to high average range for Full Scale IQ.

Subjects were excluded from the sample if they had a history of any psychiatric or neurological disorders, head injury or significant use of any other drugs ($\geq$ once/month) or alcohol abuse. Cannabis users were instructed to abstain from cannabis and alcohol for 24 hours prior to testing and to provide urine samples the night before testing and during the test session to ensure that they had not consumed cannabis in the intervening period. Users were excluded if the level of metabolites detected in the second urine sample was substantially higher than that in the first.

The mean level of the cannabinoid metabolite THC-COOH detected in the evening urine sample was 100.91 ng/ml (39.03 ng/ml normalised) and that on the day of testing 90.72 ng/ml (19.84 normalised). There was much variability in levels detected across subjects and approximately 60% showed zero levels of urinary cannabinoids. The control group provided a urine sample during the test session and any subject returning a positive urine for other drugs was excluded. (The 32 cannabis users and 16 controls reported here represent the final sample after all exclusion criteria were applied).

Table 8.1. Sample characteristics: mean and (SD)

Group	Sex	Age	Years of Education	NART Score	Alcohol Consumption (standard drinks per month)	Cannabis Duration (years of use)	Cannabis Frequency (days per month)
Long N=16	13M 3F	28.9 (8.2)	14.1 (2.1)	36.8 (8.4)	60.9 (48.4)	10.1 (6.8)	13.7 (9.0)
Short N=16	12M 4F	19.9 (2.0)	13.2 (1.2)	35.0 (5.8)	47.8 (38.8)	3.3 (0.5)	10.3 (6.5)
Heavy N=16	12M 4F	23.5 (7.4)	13.2 (1.8)	34.7 (7.6)	68.6 (46.9)	6.69 (5.6)	17.9 (6.9)
Light N=16	13M 3F	25.3 (7.7)	14.2 (1.7)	37.0 (6.7)	40.1 (36.2)	6.69 (6.3)	6.0 (2.6)
Overall Cannabis users	25M 7F	24.4 (7.5)	13.7 (1.8)	35.9 (7.2)	54.4 (43.7)	6.69 (5.8)	12.0 (7.9)
Controls N=16	12M 4F	26.3 (7.0)	15.6 (2.4)	39.7 (5.2)	23.4 (17.0)	____ ____	____ ____

Procedure and stimuli

Subjects were paid for their participation in a three hour test session. They provided written consent. A detailed drug history was taken (see Appendices A and B) and they completed questionnaires assessing dependence on cannabis, psychiatric symptomatology and state/trait anxiety (these will be discussed in Chapter 10). Subjects were seated in a darkened sound-attenuated room and were tested for normal hearing by standard audiometric assessment. They were trained on the selective attention task until they reached a level of performance of 50% correct responses and less than 25% errors. As for experiment two, this usually was achieved within two practice runs.

The task and stimulus parameters were the same as that of experiment two, adapted from the auditory selective attention paradigm of Hansen and Hillyard (1983), with the presentation through headphones (TDH 49) of a random series of tone pips which varied in location (left ear vs.right ear), pitch (high: 1319 Hz vs. low: 1047 Hz) and duration (long: 102 ms vs.short: 51 ms), having a rise and fall time of 10 ms. The stimuli were presented as a random sequence lasting 160 seconds per run with a random SOA of 200 to 500 ms (mean 350 ms). Fifty percent of the stimuli occurred in each ear with equal numbers of each pitch. Most of the tones (76%) of each type were of short duration, while a small percentage (24%) were long.

Subjects were instructed to attend to a particular ear and pitch, and respond with a button press to the infrequent long tones (the targets). The four attention conditions were left high, left low, right high and right low. Subjects completed eight runs, two of each attention condition responding with either the left or right hand. The order of attention conditions and responding hand was randomized among subjects.

ERP recording and data analysis

ERPs were recorded using an electrode cap (Electro-cap International) from midline (Fz, Cz, Pz) and lateral scalp sites (F3, F4, P3, P4) referenced to linked ears. Vertical eye movement was recorded by tin electrodes placed above and below the left eye. The data were amplified using Neomedix NT114-A amplifiers with a system bandpass of 0.016 and 50 Hz (3dB down). Data were digitised at a rate of 5.33 ms per channel. Overlapping epochs of 1350 ms including a 150 ms pre-stimulus baseline were extracted and epochs containing ocular artefact were rejected prior to averaging.

Separate averages were created for long and short duration stimuli, excluding those with an incorrect response, and collapsed across runs according to attention condition. Thus, ERPs were classified according to whether they matched the target on location and pitch for each run, resulting in attended (L+) and unattended ear (L-) ERPs for relevant and irrelevant pitch stimuli, as described in Chapter 7. ERPs were sorted according to whether they were recorded from the hemisphere ipsilateral or contralateral to the stimulated ear.

The processes of selective attention were assessed by comparing groups on the mean amplitude of processing negativity to short tones and the amplitude and latency of the P300 component to targets. These measures were subjected to analyses of variance (ANOVA) with frequency and duration of cannabis use as factors and repeated measures on stimulus type and electrode site.

Responses were classified as correct detections if they occurred within 200 to 1200 ms after a target stimulus. Reaction time was measured as the latency of the response from the onset of the target. Hit rate was calculated as a ratio of the total number of targets. A target not followed by a response was classified as an error of omission or "miss", while responses occurring at other times were classified as errors of commission or "false alarms". False alarm rate was calculated as a ratio of the total number of non-targets.

8.1.2 Results

Performance data

Performance data from the groups of cannabis users and controls are presented in Table 8.2. Analyses of variance indicated that reaction time to targets was longer [$F(1,46) = 4.56$, $p < 0.0380$] and the proportion of correctly detected targets was lower [$F(1,46) = 11.26$, $p < 0.0016$] in the cannabis user group overall by comparison with controls, with the largest difference between heavy cannabis users and controls (reaction time: heavy users vs. controls [$F(1,30) = 7.21$, $p < 0.0117$; hit rate: heavy users vs. controls [$F(1,30) = 16.25$, $p < 0.0004$]. Differences in false alarm rate did not reach significance [$F(1,46) = 1.34$, $p = 0.2531$]. Cannabis user groups did not differ significantly on any of the performance measures.

Table 8.2. Performance measures of reaction time, hit rate and false alarm rate for cannabis user groups and controls: means and (SD).

	Cannabis Users (overall)	Long Duration users	Short Duration users	Heavy Frequency users	Light Frequency users	Control Group (non-users)
Reaction time (ms)	644.84 (90.56)	650.83 (98.11)	638.86 (85.13)	664.72 (81.01)	624.97 (97.68)	587.42 (81.79)
Hit rate (%)	73.71 (11.05)	74.22 (12.55)	73.21 (9.72)	70.86 (10.35)	76.56 (11.32)	84.23 (8.30)
False alarm rate (%)	0.77 (0.80)	0.83 (1.01)	0.72 (0.54)	0.80 (0.63)	0.75 (0.96)	0.50 (0.69)

ERP data

Processing negativity

Inspection of the ERP waveforms to short tones suggested that the results of experiment two had been replicated: cannabis users showed increased processing negativity (PN) to tones which matched the target on location but not pitch. When the cannabis user group was split according to frequency and duration of use, it became apparent that PN was greatly affected by duration of use.

Long versus short duration users versus controls

Grand average ERPs to short tones at all scalp sites are depicted in Figures 8.1, 8.2 and 8.3 respectively for long duration users, short duration users and controls. For easier comparison across groups, frontal and central sites only are presented in Figure 8.4 for all three groups.

Visual inspection of the waveforms suggested a difference between groups in N1 amplitude, however analyses of the peak between 50 and 250 ms at frontal and central sites revealed this not to be significant [$F(2,45) = 1.50$, $p > 0.23$] and groups did not differ in N1 latency [$F(2,45) = 0.90$, $p > 0.41$]. P1 and P2, measured as the most positive peaks between 20 and 100 ms, and 100 and 300 ms respectively, at frontal and central sites did not differ between groups in amplitude [P1: $F(2,45) = 0.73$, $p > 0.48$; P2: $F(2,45) = 0.85$, $p > 0.43$] or latency [P1: $F(2,45) = 1.30$, $p > 0.28$; P2: $F(2,45) = 0.62$, $p > 0.54$].

Preliminary analyses of mean amplitude measures over 100 ms intervals at frontal and central scalp sites indicated significant differences between groups based on duration of use over the range from 300 to 600 ms for tones in the attended ear (L+) only, with no significant differences occurring outside this latency range: [300-400 ms: stimulus x electrode x group $F(6,135) = 2.67$, $p < 0.0512$; 400-500 ms: group $F(2,45) = 5.83$, $p < 0.0056$, electrode x group $F(6,135) = 2.84$, $p < 0.0369$, stimulus x electrode x group $F(6,135) = 2.74$, $p < 0.0416$; 500-600 ms: group $F(2,45) = 4.10$, $p < 0.0231$, electrode x group $F(6,135) = 3.37$, $p < 0.0207$, stimulus x electrode x group $F(6,135) = 2.78$, $p < 0.0333$].

On the basis of this analysis, PN was measured as the mean amplitude over 300 to 600 ms and subjected to a repeated measures ANOVA (BMD-P2V). The results confirmed that there were no differences between groups in the processing of tones in the unattended ear (L-) [group $F(2,45) = 0.90$, $p > 0.41$; stimulus x electrode x group $F(6,135) = 0.72$, $p > 0.57$]. Analysis of PN to tones of relevant and irrelevant pitch in the attended ear (L+) for groups based on duration of use (long duration users, short duration users and controls), revealed a significant effect of group [$F(2,45) = 5.11$, $p < 0.0100$] and an interaction between group, stimulus and scalp site [$F(6,135) = 3.08$, $p < 0.0266$]. Group multiple comparisons at each scalp site were carried out using the Bonferroni procedure.

The long duration user group showed significantly larger PN to pitch irrelevant tones in the attended ear than controls at all frontal sites [Fz: $F(1,30) = 9.86$, $p < 0.0038$, ipsilateral: $F(1,30) = 10.35$, $p < 0.0031$; contralateral: $F(1,30) = 12.94$, $p < 0.0011$] and at Cz [$F(1,30) = 6.68$, $p < 0.0149$]. Long duration users also showed significantly larger PN than short duration users at all frontal sites [Fz: $F(1,30) = 13.39$, $p < 0.0010$; ipsilateral: $F(1,30) = 12.80$, $p < 0.0012$; contralateral: $F(1,30) = 15.82$, $p < 0.0004$], but did not differ from short users at Cz [$F(1,30) = 1.00$, $p > 0.32$]. These results were essentially unaltered when age and alcohol consumption were used as covariates (but see analysis of covariance for heterogeneous regression slopes, below).

Short duration users did not differ from controls at frontal sites [Fz: $F(1,30) = 0.12$, $p > 0.73$; ipsilateral: $F(1,30) = 0.07$, $p > 0.79$; contralateral: $F(1,30) = 0.01$, $p > 0.91$], but there was a trend toward larger PN to pitch irrelevant tones in short duration users at Cz [$F(1,30) = 3.47$, $p < 0.0722$], and this difference became significant when age was used as a covariate [$F(1,29) = 5.78$, $p < 0.0228$]. These differences between long and short duration user groups and nonuser controls are clearly apparent in Figure 8.4.

LONG DURATION USERS

Ipsi F

Fz

Contra F

Cz

Ipsi P

Pz

Contra P

L+ relevant pitch
L+ irrelevant pitch
L- relevant pitch
L- irrelevant pitch

-2.0µV

200 400 600 800 1000 1200

msec
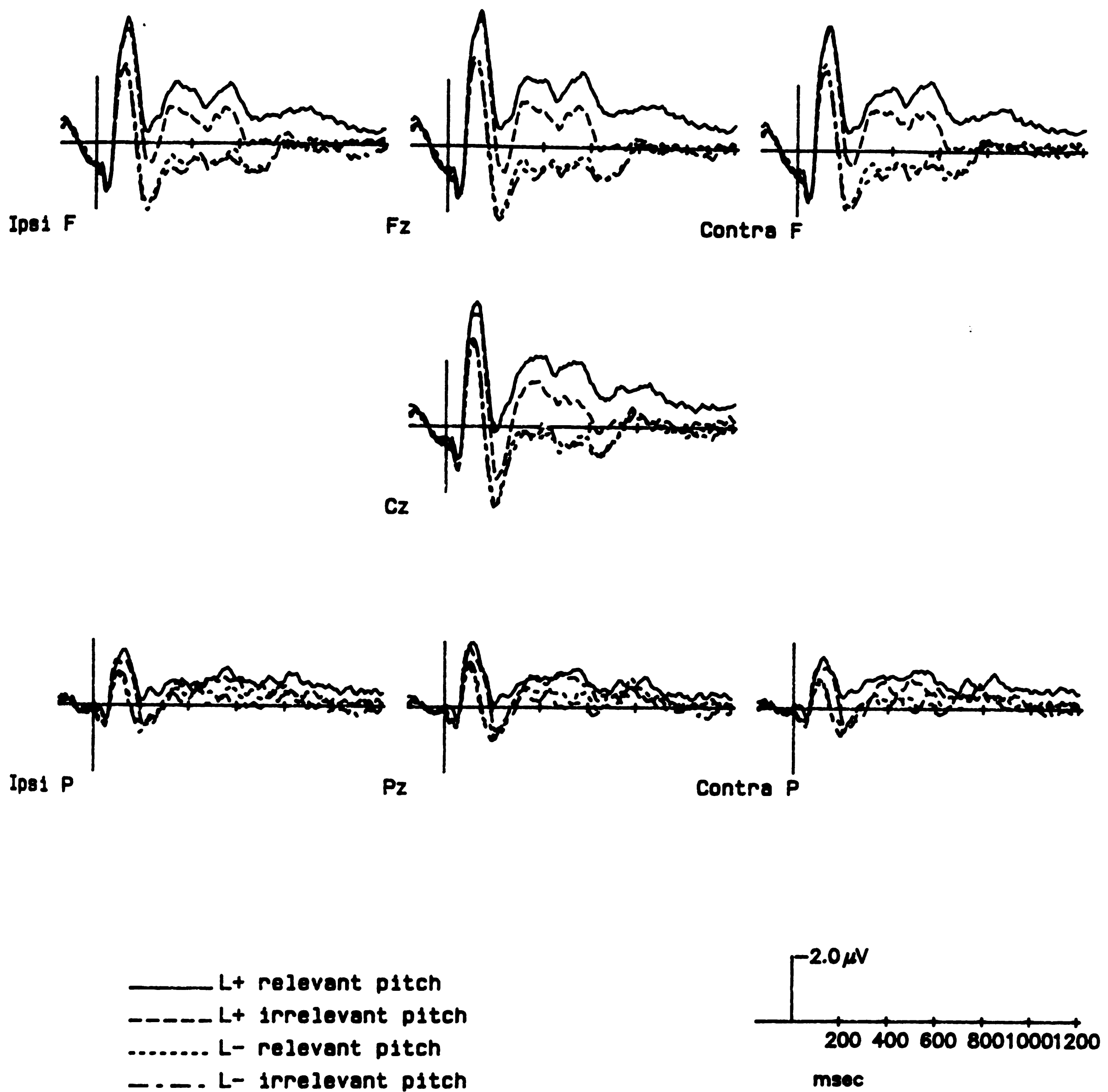
Figure 8.1 Grand average ERPs to short tones recorded at frontal (F), central (C) and parietal (P) scalp sites from long duration cannabis users. (L+ and L- refer to attended and unattended location (ear) respectively).

SHORT DURATION USERS

Ipsi F   Fz   Contra F

Cz

Ipsi P   Pz   Contra P

——— L+ relevant pitch
— — — L+ irrelevant pitch
········ L- relevant pitch
— · — · L- irrelevant pitch

-2.0 μV

200 400 600 80010001200
msec
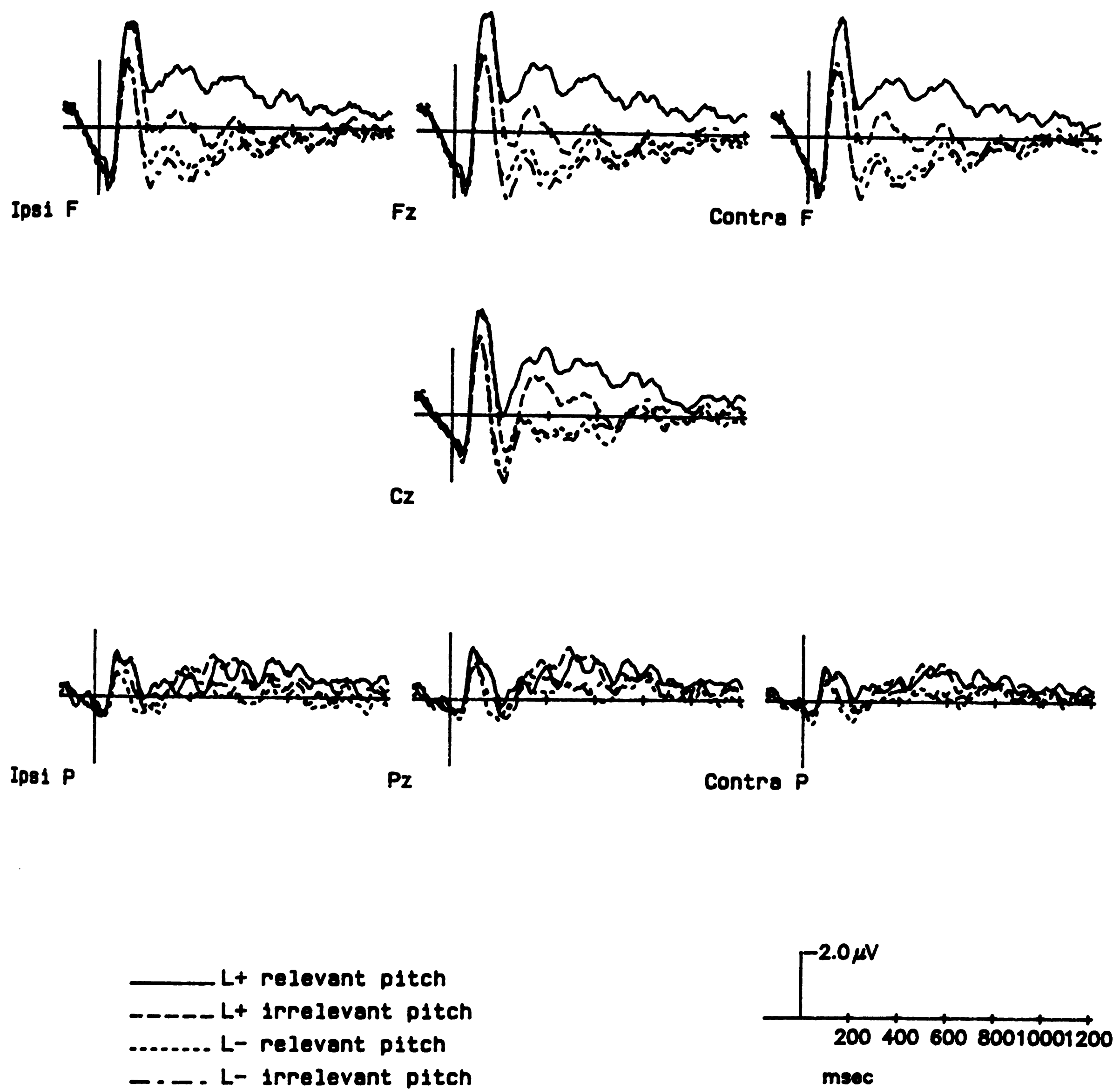
Figure 8.2   Grand average ERPs to short tones recorded at frontal (F), central (C) and parietal (P) scalp sites from short duration cannabis users.   (L+ and L- refer to attended and unattended location (ear) respectively).
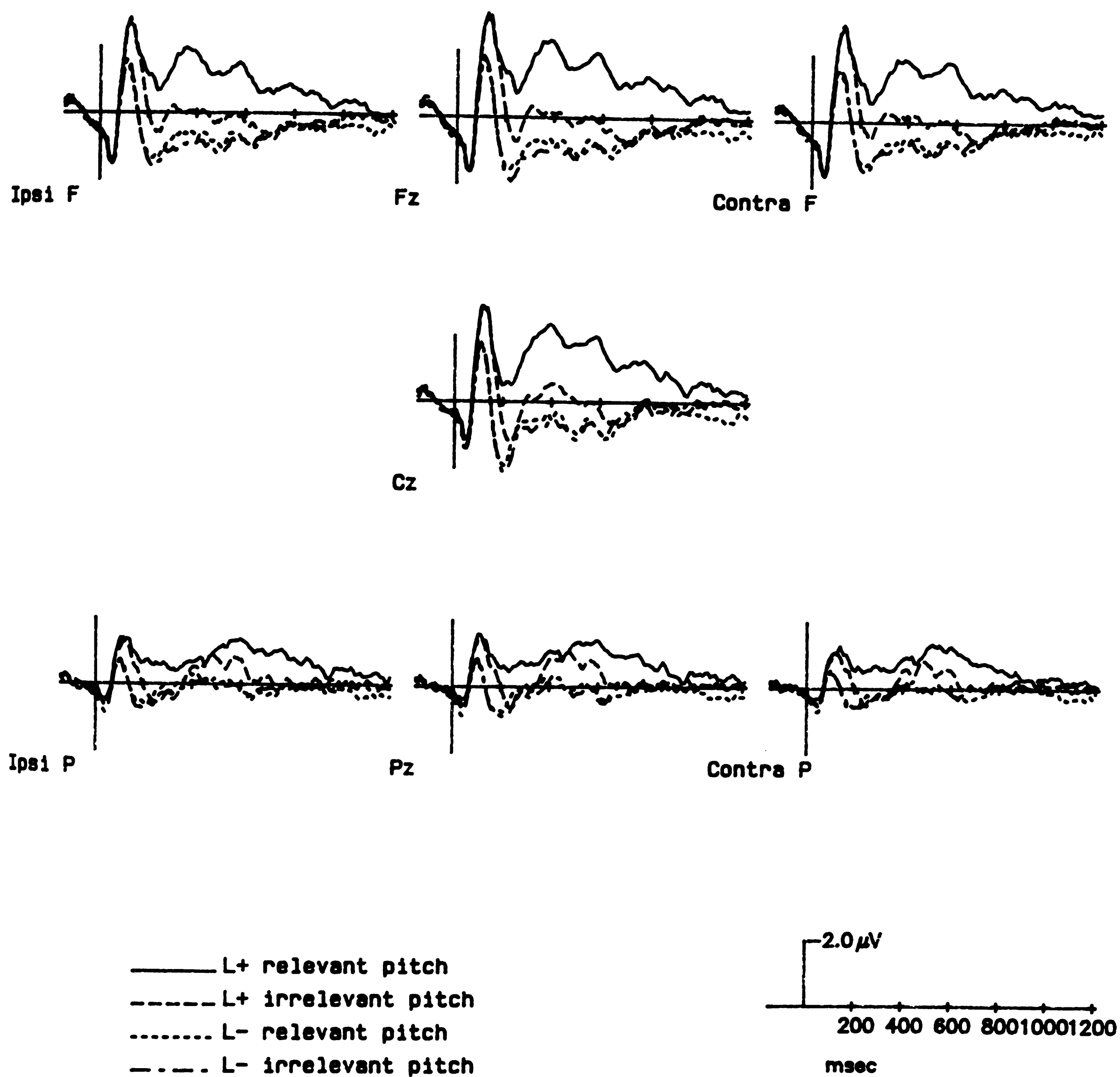
CONTROLS

Figure 8.3 Grand average ERPs to short tones recorded at frontal (F), central (C) and parietal (P) scalp sites from controls. (L+ and L- refer to attended and unattended location (ear) respectively).

LONG DURATION USERS

Ipsi F   Fz   Contra F

Cz

SHORT DURATION USERS

Ipsi F   Fz   Contra F

Cz

CONTROLS

Ipsi F   Fz   Contra F

Cz

————— L+ relevant pitch
– – – – – L+ irrelevant pitch

⌐2.0 µV

200 400 600 8001000 1200
msec
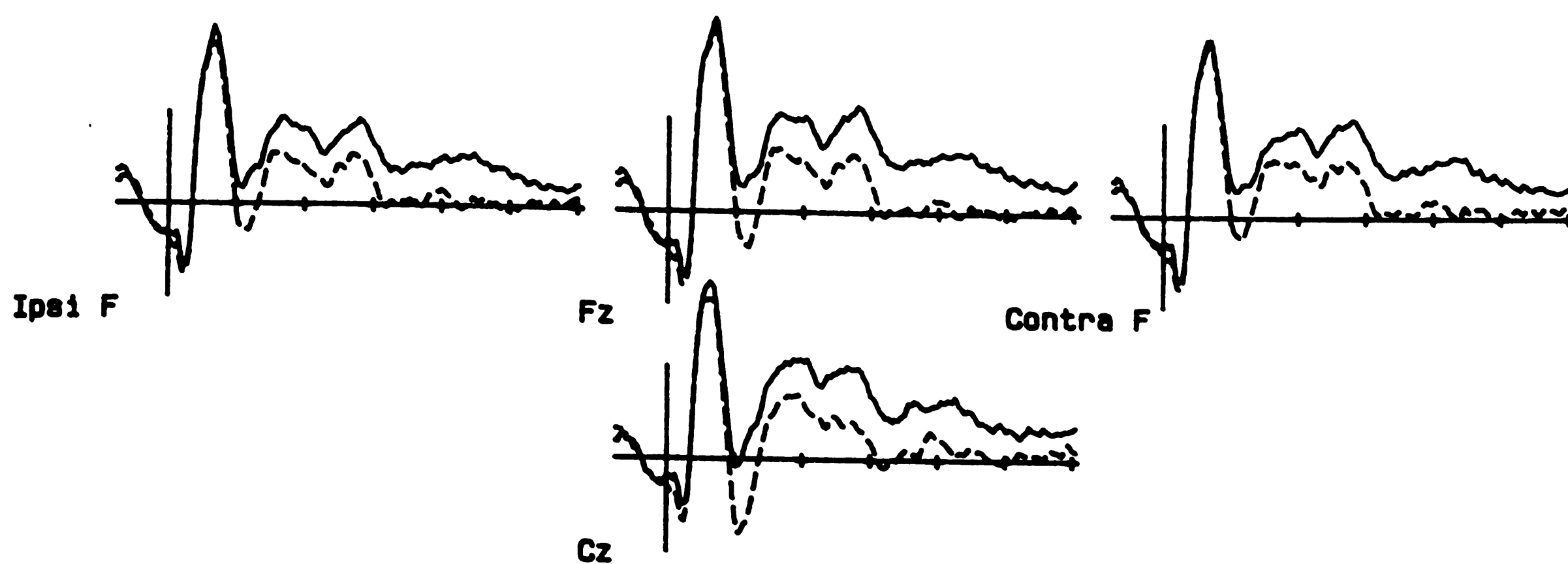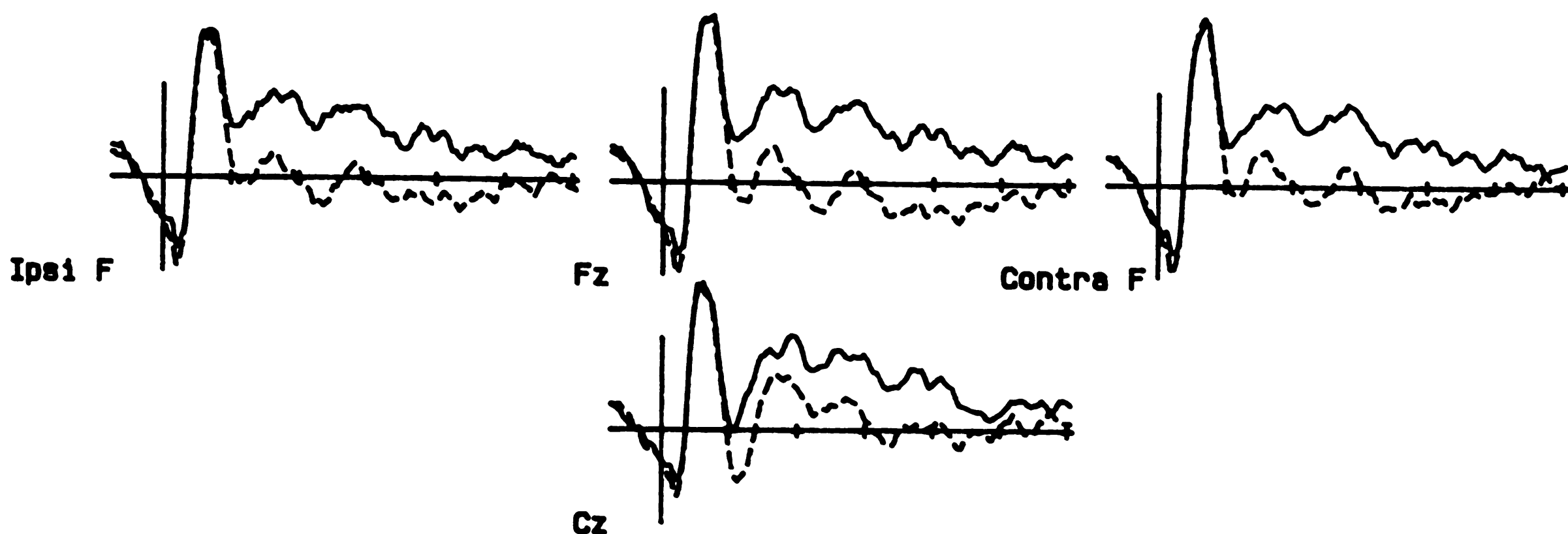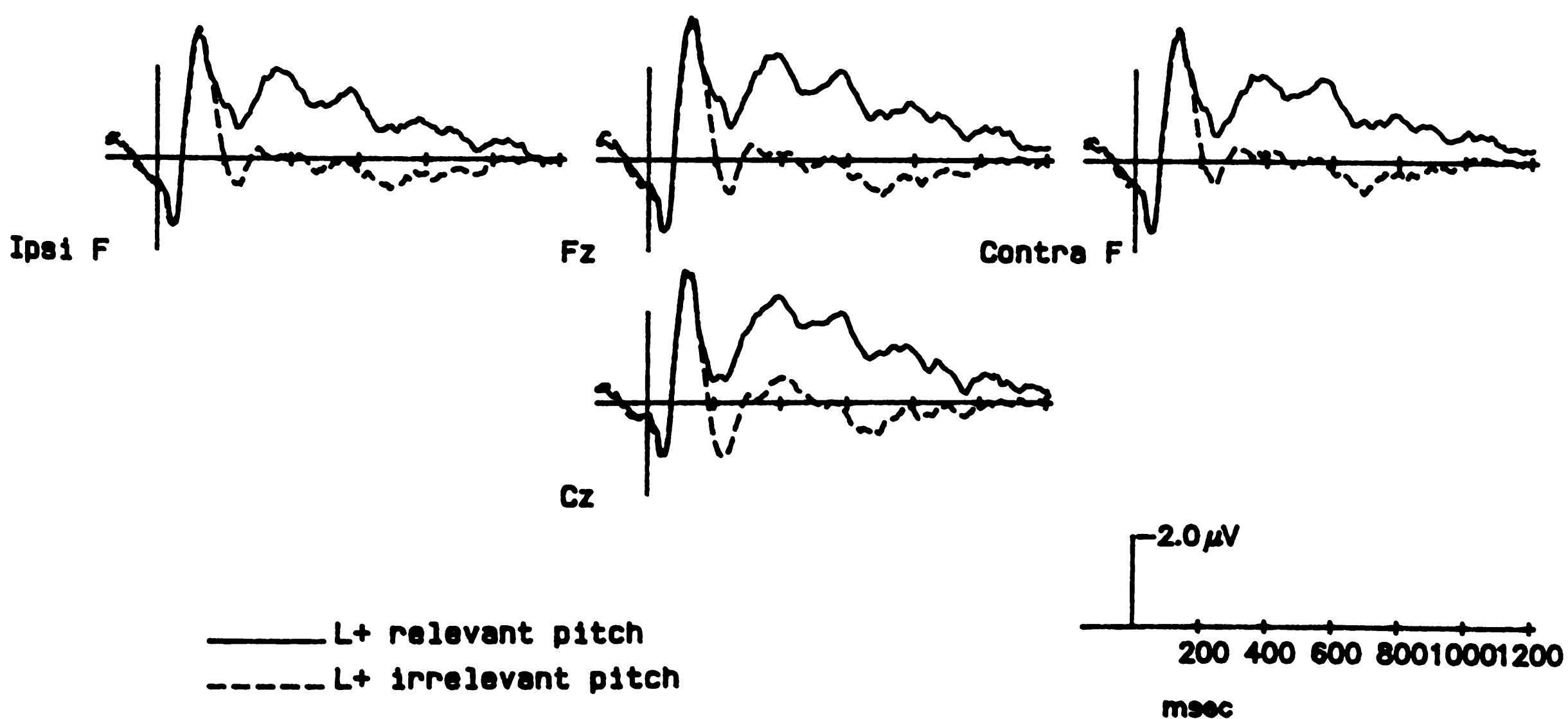
Figure 8.4   Grand average ERPs to short tones recorded at frontal (F) and central (C) scalp sites from long and short duration cannabis users and controls.   (L+ attended location only).

Correlational analyses within the user group indicated that the ability to filter out irrelevant information, as indexed by PN, was increasingly impaired with the number of years of cannabis use (see Figure 8.5). The relationship was not initially significant in the entire sample (Figure 8.5.A), however, it was apparent that the majority of the sample had used cannabis for up to twelve years, while the two subjects with deviant results had used cannabis for 25 and 28 years. A t-test for outliers (Barnett and Lewis, 1984) determined that these two subjects were statistical outliers in terms of their duration of use compared to the rest of the sample (t = 6.80, p < 0.01). When these two outliers were excluded from the correlational analysis, the relationship between PN and duration of cannabis use became highly significant (r = 0.65, p < 0.0001) (Figure 8.5.B). One interpretation of this result is that some kind of tolerance may develop after using for a very long number of years, producing a non-linear relationship. On the other hand, perhaps a significant linear relationship would remain if more subjects with durations of use of between 12 and 30 years were tested. Nevertheless, from Figure 8.3.B it is clear that a strong relationship appears to exist between the duration of cannabis use and the amplitude of processing negativity to irrelevant information.

Since an inevitable relationship existed between years of cannabis use and increasing age (r = 0.77, p < 0.0001), a partial correlational analysis was carried out. This indicated that the significant relationship between duration of cannabis use and PN remained after controlling for the effect of age (r = 0.54, p < 0.005), whereas there was no relationship between age and PN after controlling for duration of use (r = -0.11). Thus, the ability to filter out irrelevant information reflected in processing negativity to pitch irrelevant tones, was progressively impaired as a function of the number of years of cannabis use.
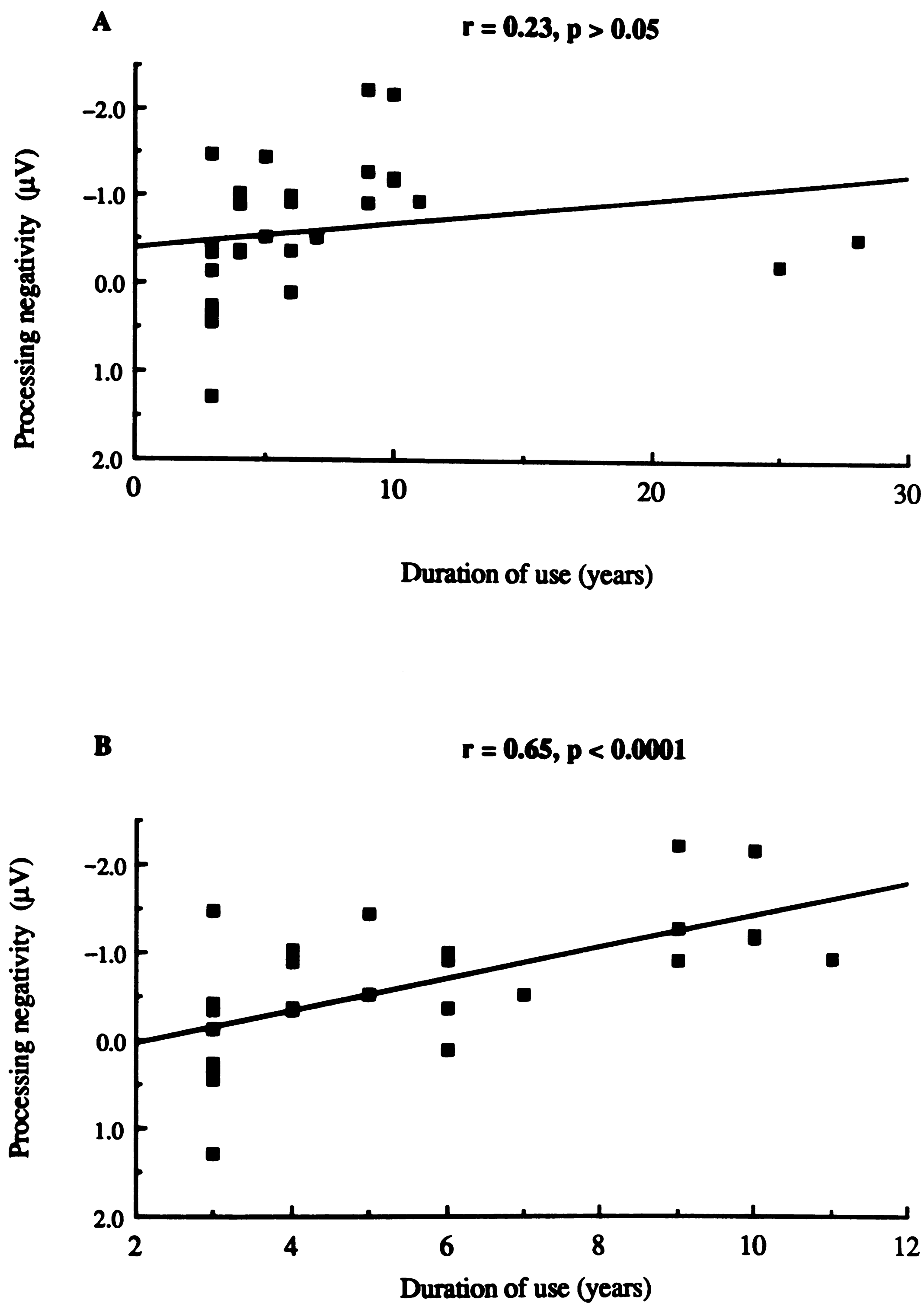
Figure 8.5 **A. Mean amplitude of PN (μV) to pitch irrelevant tones as a function of duration of cannabis use in the entire sample, and B. with two outliers excluded.**

Correlational analyses over all groups (and for each group separately) indicated that alcohol consumption was not related to PN (r = 0.03). A relationship between age and PN was found in the control group only (r = 0.51, p < 0.05), as was a relationship between IQ and PN in the control group only (r = 0.68, p < 0.005), but age and IQ were also correlated in the controls (r = 0.68, p < 0.005). Partial correlational analyses revealed that the relationship between IQ and PN remained significant after controlling for the effects of age (r = 0.52, p < 0.05), whereas there was no relationship between age and PN after controlling for IQ (r = 0.10). PN and IQ were unrelated in the cannabis user group (r = -0.10).

An analysis of covariance technique for heterogeneous regression slopes (Johnson-Neyman technique (Huitema, 1980)) using IQ as the covariate, determined significant PN differences between groups below a certain NART score cut off. Long duration users differed significantly from controls at frontal and central sites below a NART score of 42 (estimated Full Scale IQ 121) [F(1,28) = 4.20, p < 0.05]. Short duration users were also found to differ significantly from controls below a NART score of 35 (estimated Full Scale IQ of 115). These results raise the possibility of more severe consequences from cannabis use for those of lower IQ. However, the cut off levels below which group differences are apparent are within the superior range of IQ for the long duration user group and the high average range for IQ for short term users. This indicates that the effects of cannabis use are more apparent in users of low IQ when cannabis has only been used for a few years, but when cannabis has been used for many years, its effects on selective attention override any effect of IQ. This might also be interpreted to suggest that only users of superior IQ may be able to compensate and overcome subtle impairments. The positive relationship between PN and IQ in controls is puzzling. One interpretation of this relationship is that brighter subjects may be better able to process multiple sources of stimuli without any resultant loss of performance.

Heavy versus light users versus controls

Analysis of groups based on frequency of use indicated no differences between heavy users, light users and controls on any measure derived from their ERPs to short tones. Grand average ERPs to short tones recorded from heavy users and light users are depicted in Figures 8.6 and 8.7 respectively. As to be expected from inspection of these figures compared with controls (Figure 8.3), groups did not differ in the amplitude or latency of the major early components of the epoch [Amplitude, P1: $F(2,45) = 0.73$, $p > 0.89$; N1: $F(2,45) = 1.71$, $p > 0.19$; P2: $F(2,45) = 1.94$, $p > 0.15$; Latency, P1: $F(2,45) = 1.41$, $p > 0.25$; N1: $F(2,45) = 0.29$, $p > 0.74$; P2: $F(2,45) = 0.09$, $p > 0.91$].

PN did not differ between groups in the processing of tones in the unattended ear (L-) [group: $F(2,45) = 0.12$ $p > 0.88$; stimulus x electrode x group: $F(6,135) = 0.40$, $p > 0.79$]. Analysis of PN to tones of relevant and irrelevant pitch in the attended ear (L+) also revealed no difference between heavy users, light users and controls [group: $F(2,45) = 1.24$, $p > 0.30$; stimulus x electrode x group: $F(6,135) = 0.76$, $p > 0.52$].

Correlational analysis showed no relationship to exist between PN to pitch irrelevant tones and frequency of cannabis use ($r = 0.19$, $p > 0.28$). A two way analysis of variance with frequency and duration as factors found no interaction between frequency and duration of use [$F(1,28) = 0.20$, $p > 0.62$] and no frequency x duration x stimulus x electrode interaction [$F(3,84) = 0.04$, $p > 0.51$]. These results imply that the large PN to pitch irrelevant tones observed in cannabis users in both this experiment and in experiment two, is not related to frequency of cannabis use, but increases as a function of cumulative exposure to cannabis.

HEAVY USERS
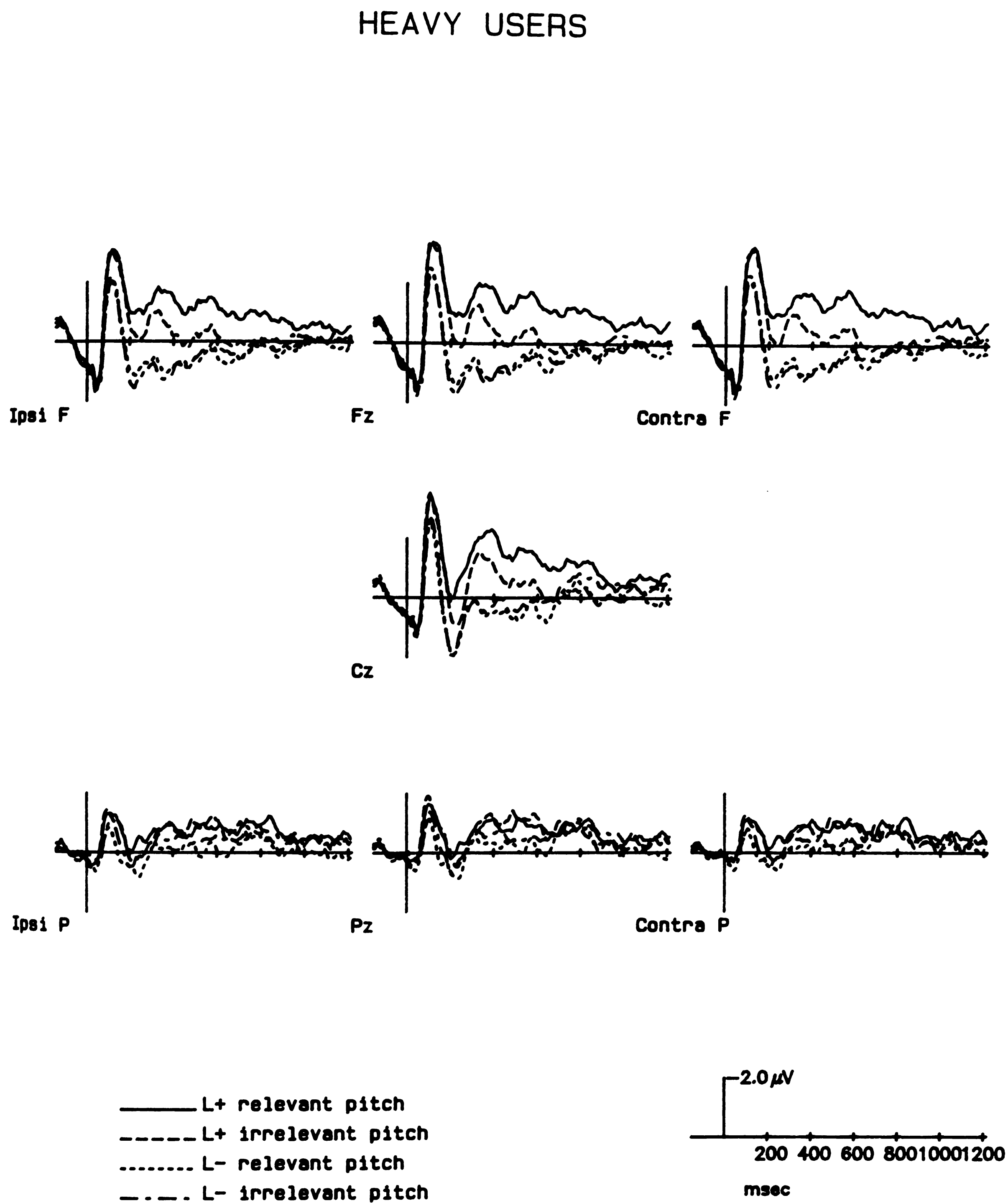
Figure 8.6 Grand average ERPs to short tones recorded at frontal (F), central (C) and parietal (P) scalp sites from heavy cannabis users. (L+ and L- refer to attended and unattended location (ear) respectively).

LIGHT USERS

Ipsi F   Fz   Contra F

Cz

Ipsi P   Pz   Contra P

─────── L+ relevant pitch
─ ─ ─ ─ L+ irrelevant pitch
········ L- relevant pitch
─ · ─ · L- irrelevant pitch

┌─2.0 μV

200 400 600 80010001200
msec
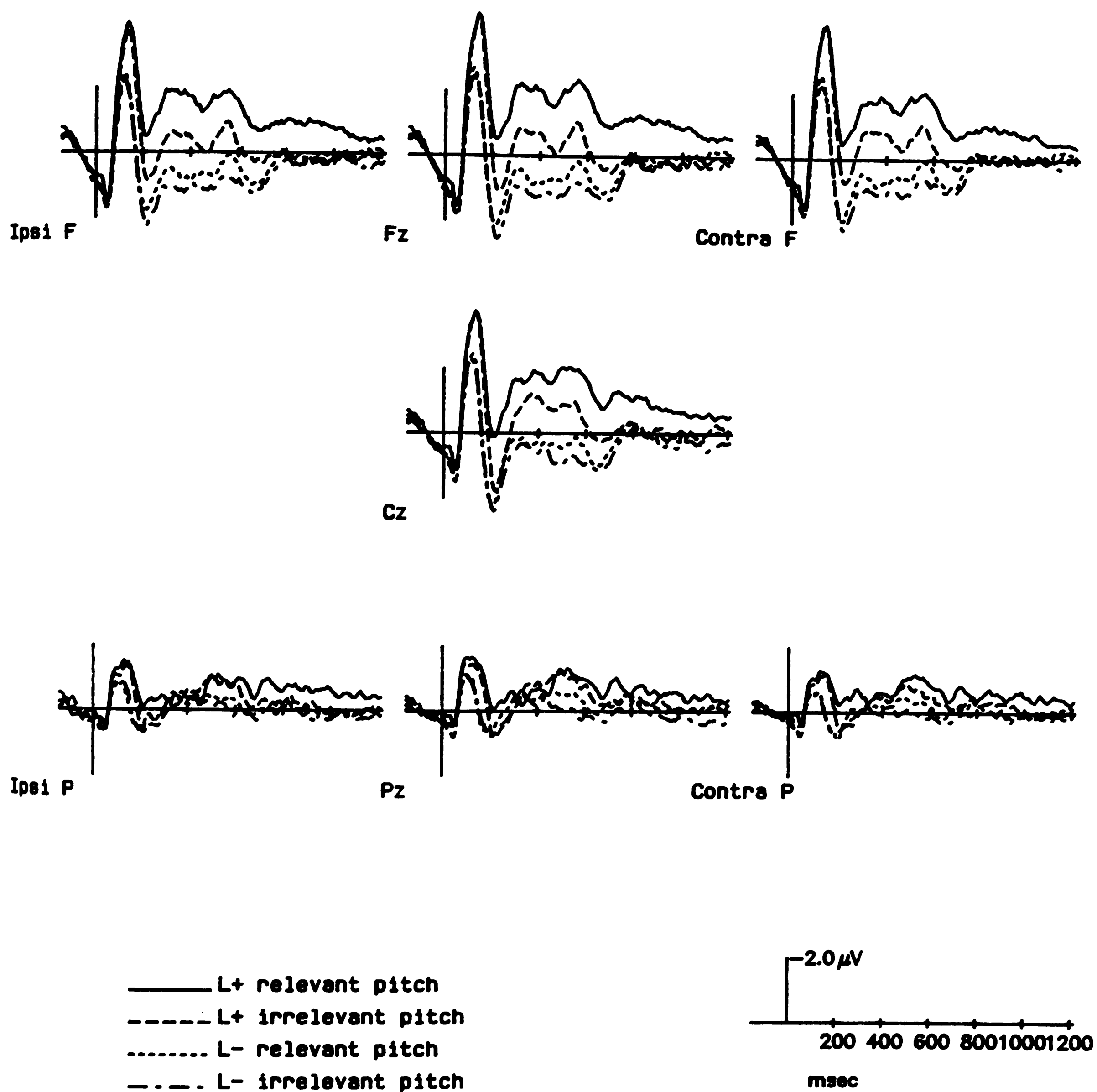
Figure 8.7 Grand average ERPs to short tones recorded at frontal (F) central (C) and parietal (P) scalp sites from light cannabis users. (L+ and L- refer to attended and unattended location (ear) respectively).

One final possibility was explored with regard to effects on PN and that was exposure to tobacco smoke. Cannabis user groups and controls were divided into cigarette smokers and non smokers: fifteen of the cannabis users were tobacco smokers (9 long, 6 short term users), while only 2 of the controls were smokers. An analysis of variance comparing smokers and nonsmokers in the cannabis users only, found no effect of cigarette smoking on PN [$F(1,28) = 0.27$, $p > 0.60$]. Since long term cannabis users had differed significantly from short term cannabis users in PN, this analysis confirmed that the large PN to irrelevant stimuli was related to exposure to cannabis smoke and not the result of smoking per se.

P300

The P300 component to target tones was measured as the most positive peak occurring between 200 and 1000 ms at parietal scalp sites. Subjects with poorly defined P300 components or no measurable peak were excluded from the analyses (4 long users, 1 short and 1 control; 2 heavy users, 3 light users and 1 control). Inspection of the waveforms suggested that, contrary to our previous findings, there were no differences between cannabis users and controls in the amplitude of P300. This was confirmed by analysis of P300 peak amplitude for cannabis users overall compared to controls [$F(1,40) = 1.54$, $p > 0.22$] and for groups based on frequency [$F(2,39) = 0.81$, $p > 0.45$] and duration [$F(2,39) = 1.42$, $p > 0.25$] of use. However, when the cannabis user group was split according to frequency and duration of use, it became apparent that P300 latency was greatly affected by frequency of use.

Heavy versus light users versus controls

The ERPs to long duration (target) tones recorded from heavy cannabis users, light

cannabis users and controls are depicted in Figures 8.8, 8.9 and 8.10 respectively. Figure 8.11 shows parietal ERPs to the L+ relevant pitch target tone overlaid for heavy users, light users and controls. The morphology of these ERP waveforms appears quite different to the target ERPs of experiment two (Figure 7.4). This is primarily due to the longer time constant used for recording data in this experiment (10 ms vs 5 ms in experiment two). The most striking difference is in the large frontal negativity to the L+ relevant pitch tones. Analysis of the peak of this frontal negativity indicated no differences between groups [$F_{(2,45)} = 0.22$, $p > 0.80$].

The P300 component appeared to be delayed by over 100 ms in the heavy user group compared to both light users and controls. The mean latency of the peak measured at parietal sites was analysed and revealed a significant group effect [$F_{(2,39)} = 4.68$, $p < 0.0150$] and an interaction between group and electrode site [$F_{(4,78)} = 3.68$, $p < 0.0089$].

Group multiple comparisons at each site revealed that P300 was significantly delayed in heavy users compared to light users and controls at Pz and at the parietal site contralateral to the stimulated ear: heavy vs. light users:[Pz: $F_{(1,25)} = 4.71$, $p < 0.0397$; ipsilateral: $F_{(1,25)} = 1.73$, $p > 0.20$; contralateral: $F_{(1,25)} = 17.49$, $p < 0.0003$]; heavy users vs. controls:[Pz: $F_{(1,27)} = 6.41$, $p < 0.0175$; ipsilateral: $F_{(1,27)} = 2.35$, $p > 0.13$; contralateral: $F_{(1,27)} = 5.15$, $p < 0.0314$]. Light users did not differ from controls at any site [Pz: $F_{(1,26)} = 0.92$, $p > 0.34$; ipsilateral: $F_{(1,26)} = 0.12$, $p > 0.73$; contralateral: $F_{(1,26)} = 2.25$, $p > 0.14$]. These results are apparent in Figure 8.11.

There was a significant linear relationship between P300 latency and frequency of cannabis use ($r = 0.50$, $p < 0.0083$) as shown in Figure 8.12. Age did not differ between groups [$F_{(2,45)} = 0.60$, $p > 0.55$] and P300 latency was unrelated to alcohol consumption ($r = 0.23$, $p > .24$) or IQ ($r = 0.21$, $p > 0.29$).

HEAVY USERS
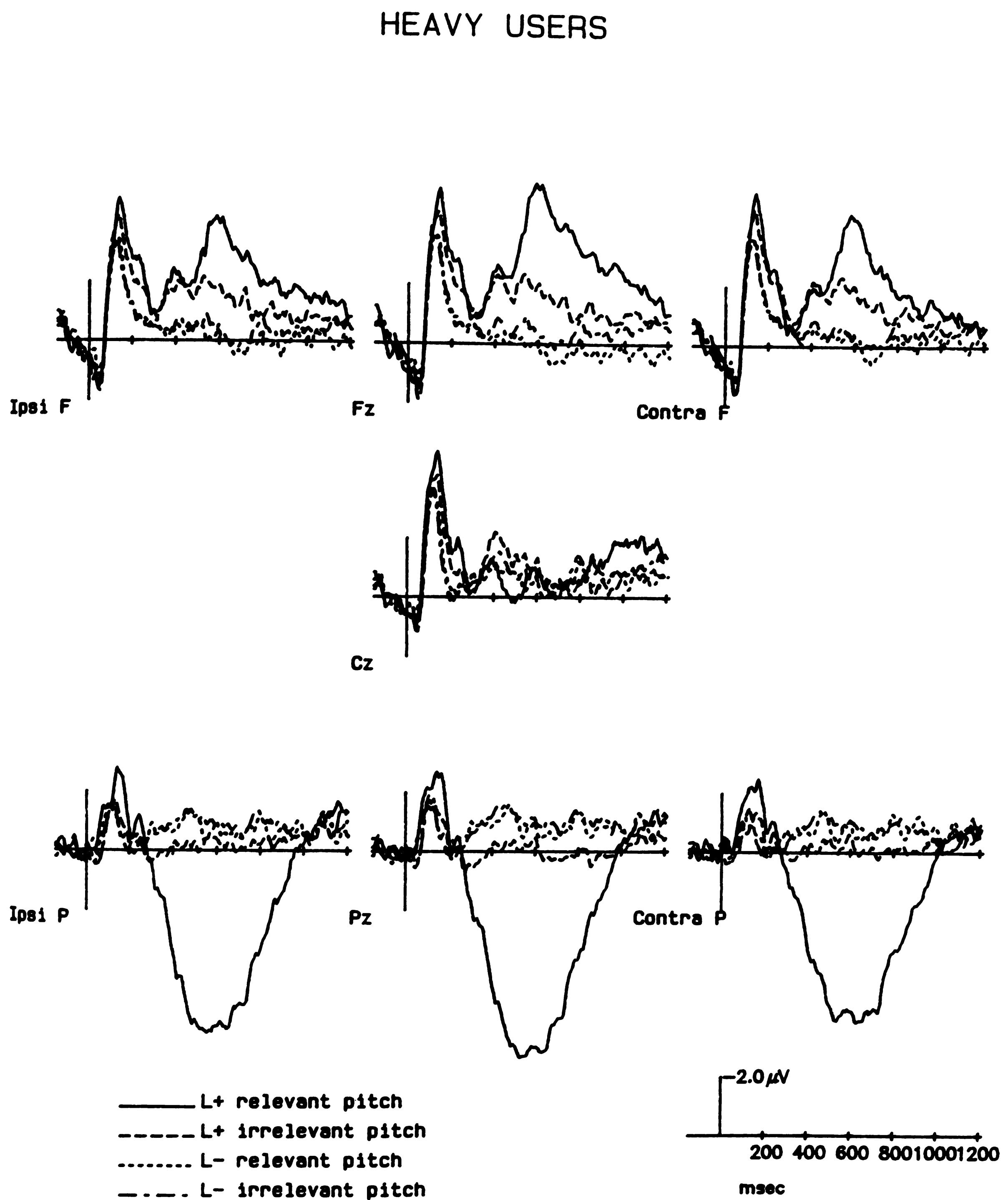
Figure 8.8 **Grand average ERPs to long tones recorded at frontal (F), central (C) and parietal (P) scalp sites from heavy cannabis users. (L+ and L- refer to attended and unattended location (ear) respectively).**

LIGHT USERS

Ipsi F   Fz   Contra F

Cz

Ipsi P   Pz   Contra P

———— L+ relevant pitch
———— L+ irrelevant pitch
········ L- relevant pitch
—·—· L- irrelevant pitch

⌐2.0 μV

200 400 600 80010001200
msec
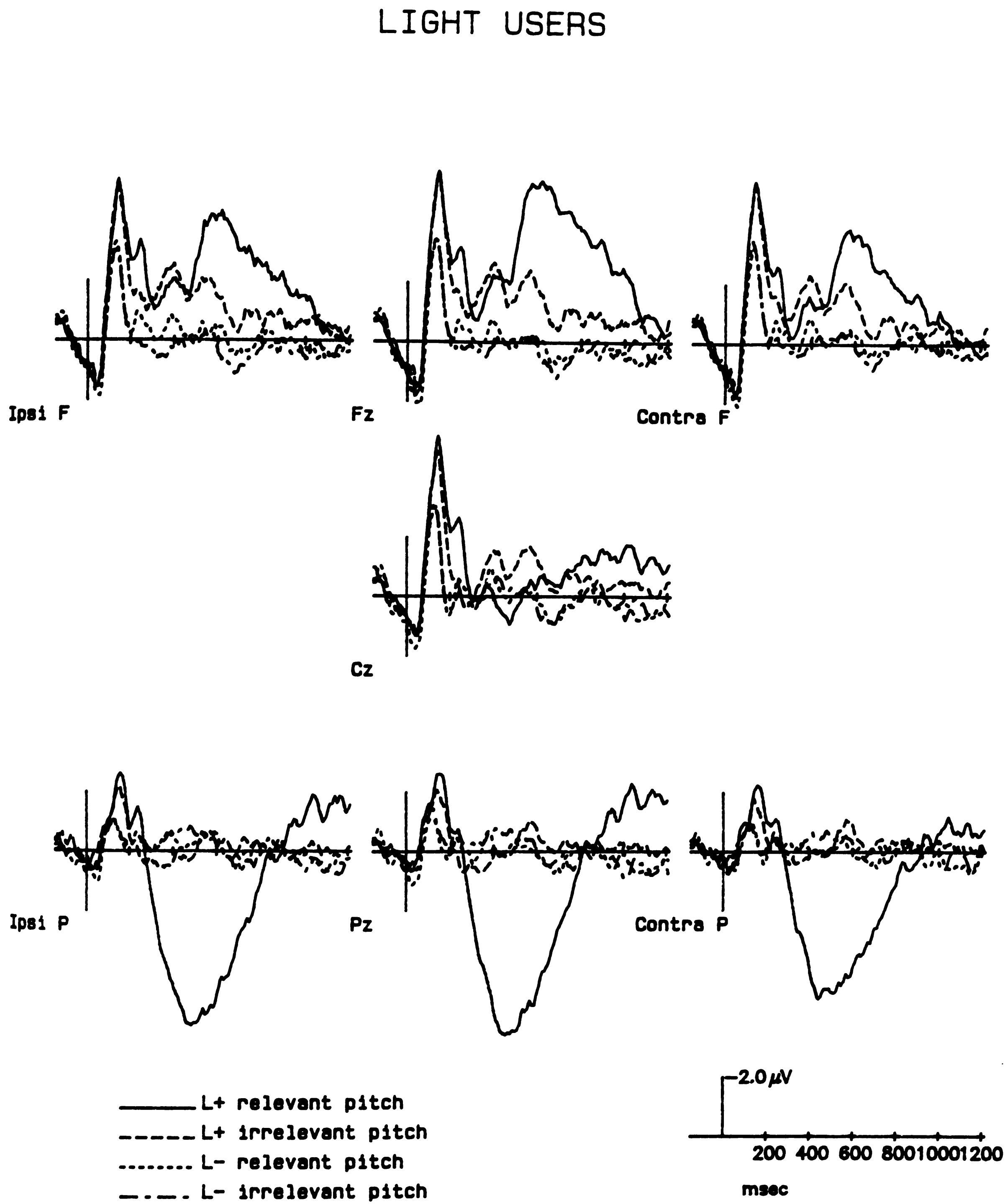
Figure 8.9   Grand average ERPs to long tones recorded at frontal (F), central (C) and parietal (P) scalp sites from light cannabis users. (L+ and L- refer to attended and unattended location (ear) respectively).
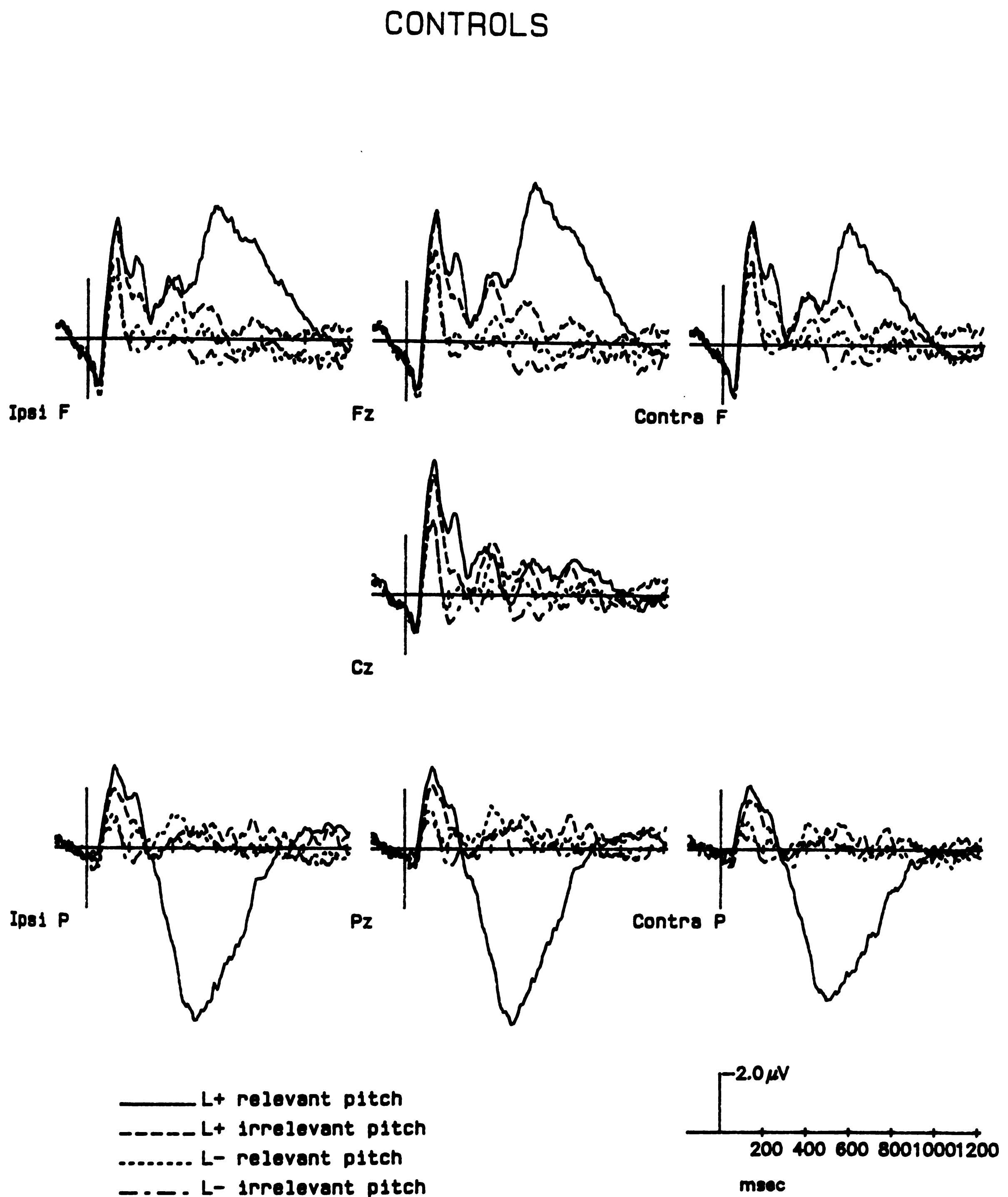
CONTROLS

Figure 8.10   Grand average ERPs to long tones recorded at frontal (F), central (C) and parietal (P) scalp sites from controls. (L+ and L- refer to attended and unattended location (ear) respectively).

Ipsi P

Pz

Contra P

$-4.0\,\mu$V

200 400 600 800 1000 1200

msec

HEAVY
LIGHT
CONTROLS
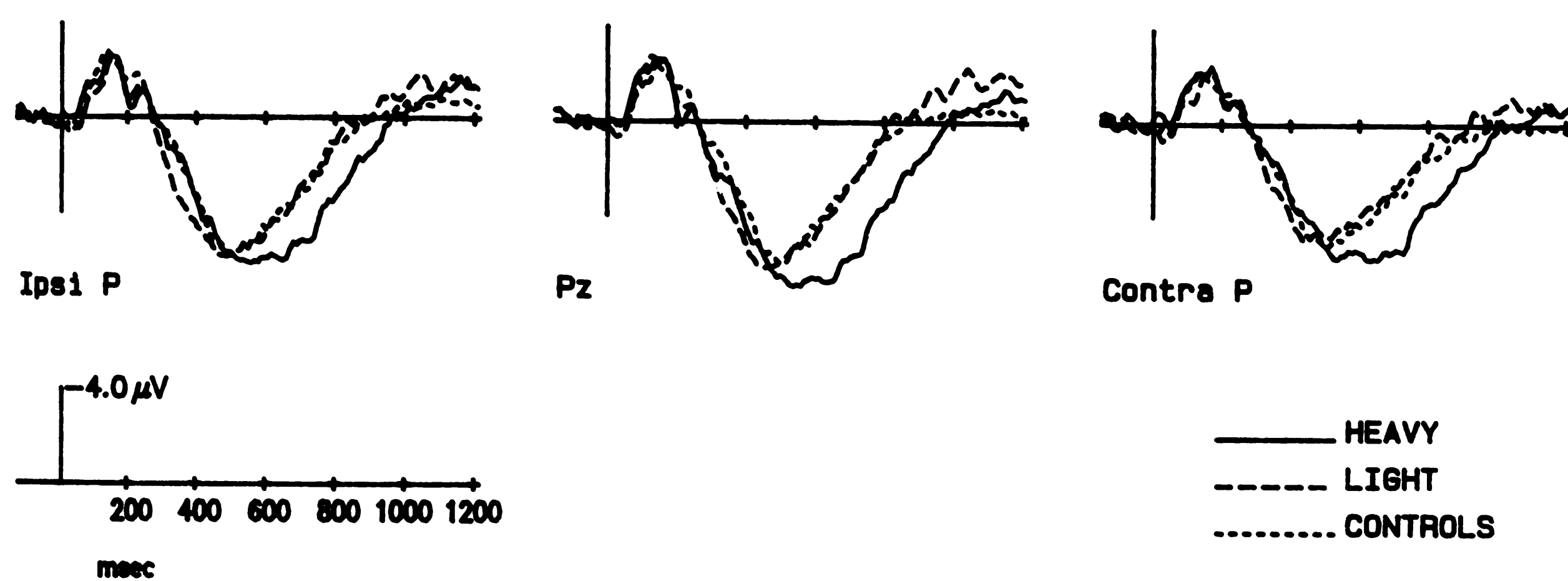
Figure 8.11   Grand average ERPs to target tones recorded at the contralateral parietal scalp site from heavy and light cannabis users and controls.
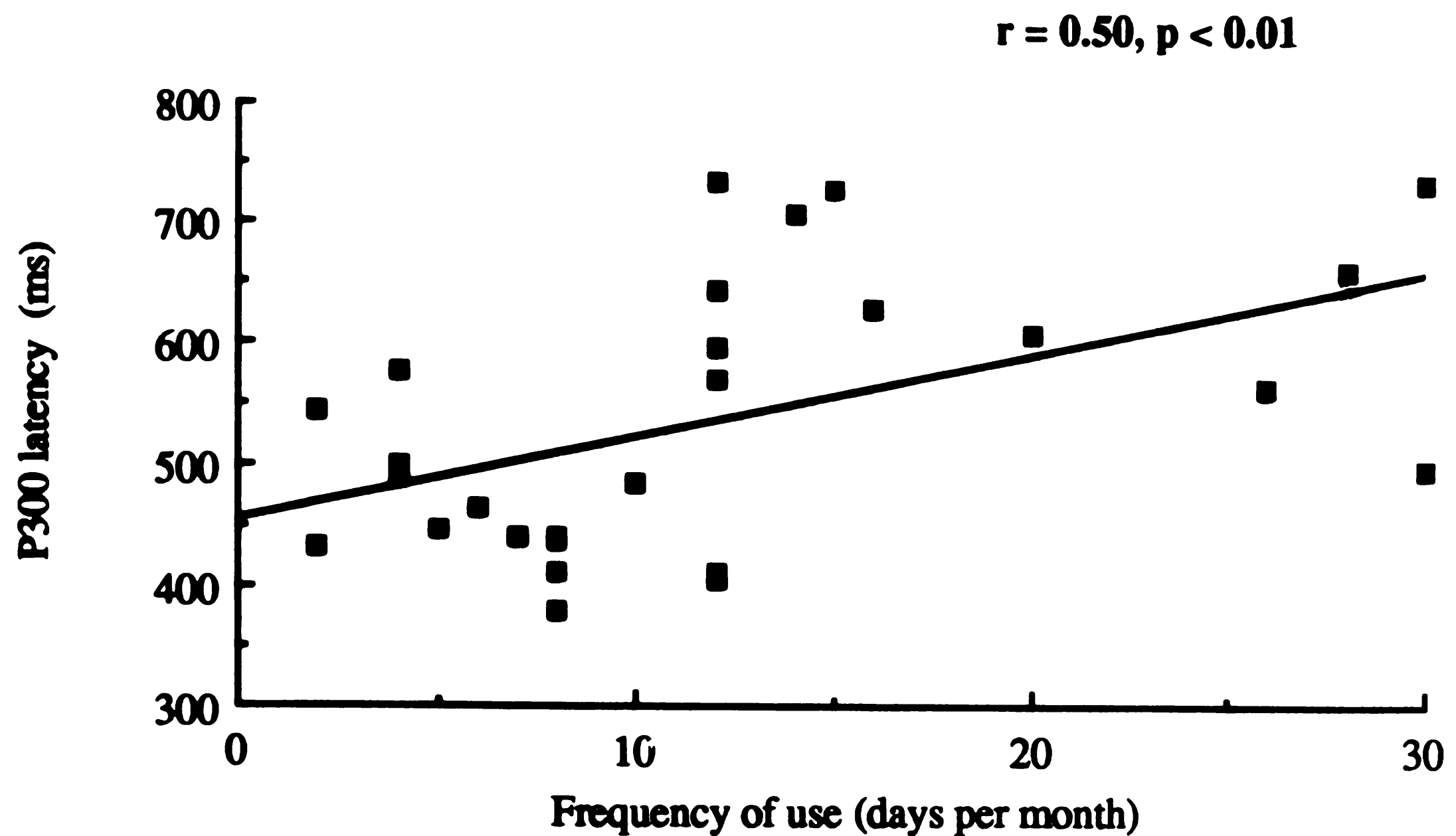
Figure 8.12   Peak latency of P300 (ms) at the contralateral parietal scalp site as a function of frequency of cannabis use.

Long versus short users versus controls

Grand average ERPs to long tones from long and short term cannabis users are depicted in Figures 8.13 and 8.14 respectively. Analysis of the late frontal negativity to targets revealed no differences between groups based on duration of use [$F(2,45)$ = 1.80, $p > 0.18$]. Nor did groups differ in the latency of P300 measured at parietal scalp sites [group: $F(2,39)$ = 1.20, $p > 0.31$; electrode x group: $F(4,78)$ = 0.99, $p > 0.41$]. Correlational analysis revealed that duration of cannabis use was unrelated to P300 latency ($r = 0.14$). There was no interaction between frequency and duration [$F(1,23)$ = 1.93, $p > 0.17$] nor between frequency, duration and electrode site [$F(2,46)$ = 0.70. $p > 0.46$]. Thus, the latency of P300, which reflects the time required to evaluate a stimulus, was delayed with increasing frequency of cannabis use, regardless of the number of years of use.

LONG DURATION USERS

Ipsi F   Fz   Contra F

Cz

Ipsi P   Pz   Contra P

─────── L+ relevant pitch
── ── ── L+ irrelevant pitch
········ L- relevant pitch
─ · ─ · ─ L- irrelevant pitch

┌─2.0 µV

200 400 600 80010001200

msec
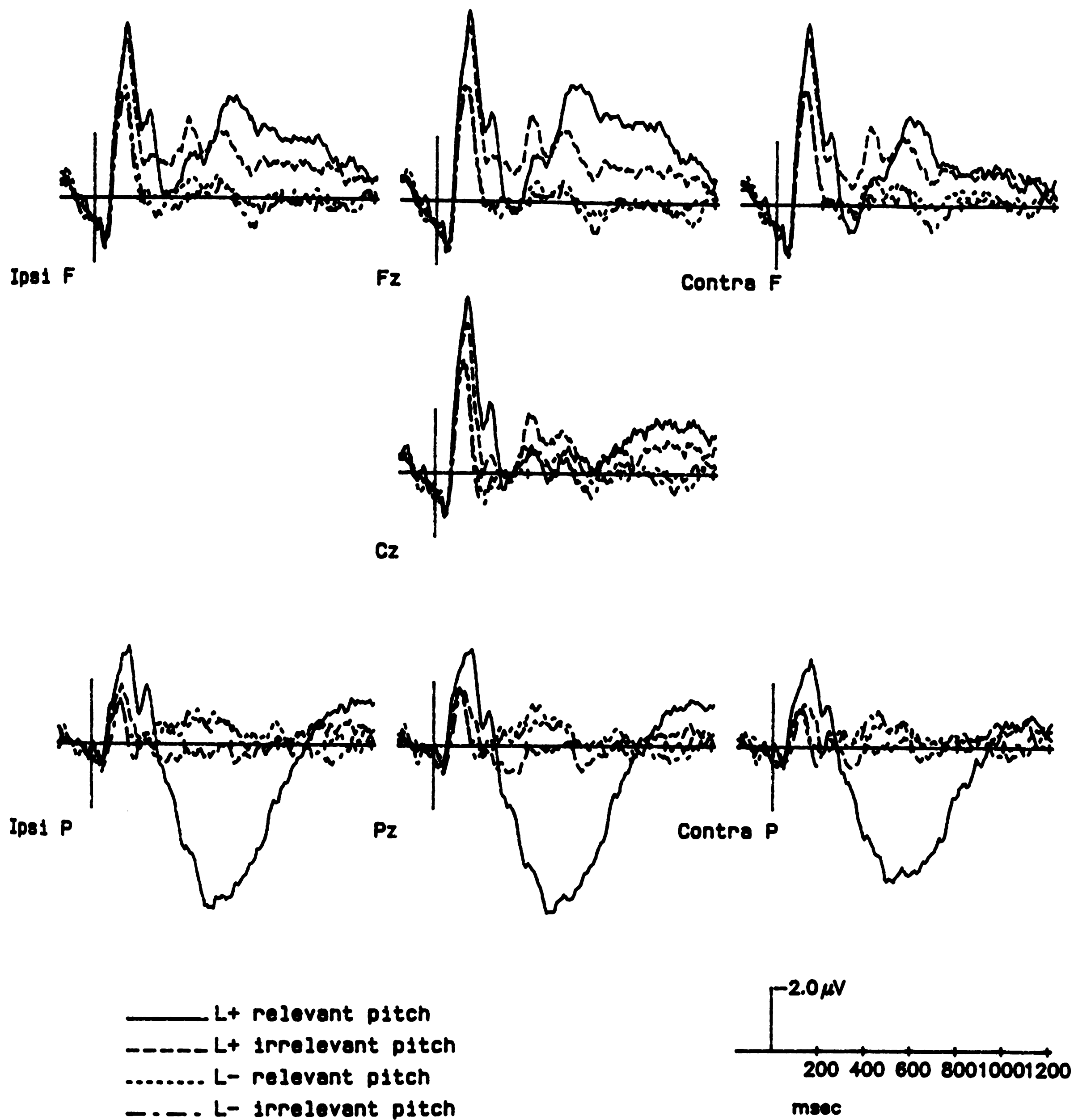
Figure 8.13 Grand average ERPs to long tones recorded at frontal (F), central (C) and parietal (P) scalp sites from long duration cannabis users. (L+ and L- refer to attended and unattended location (ear) respectively).

SHORT DURATION USERS
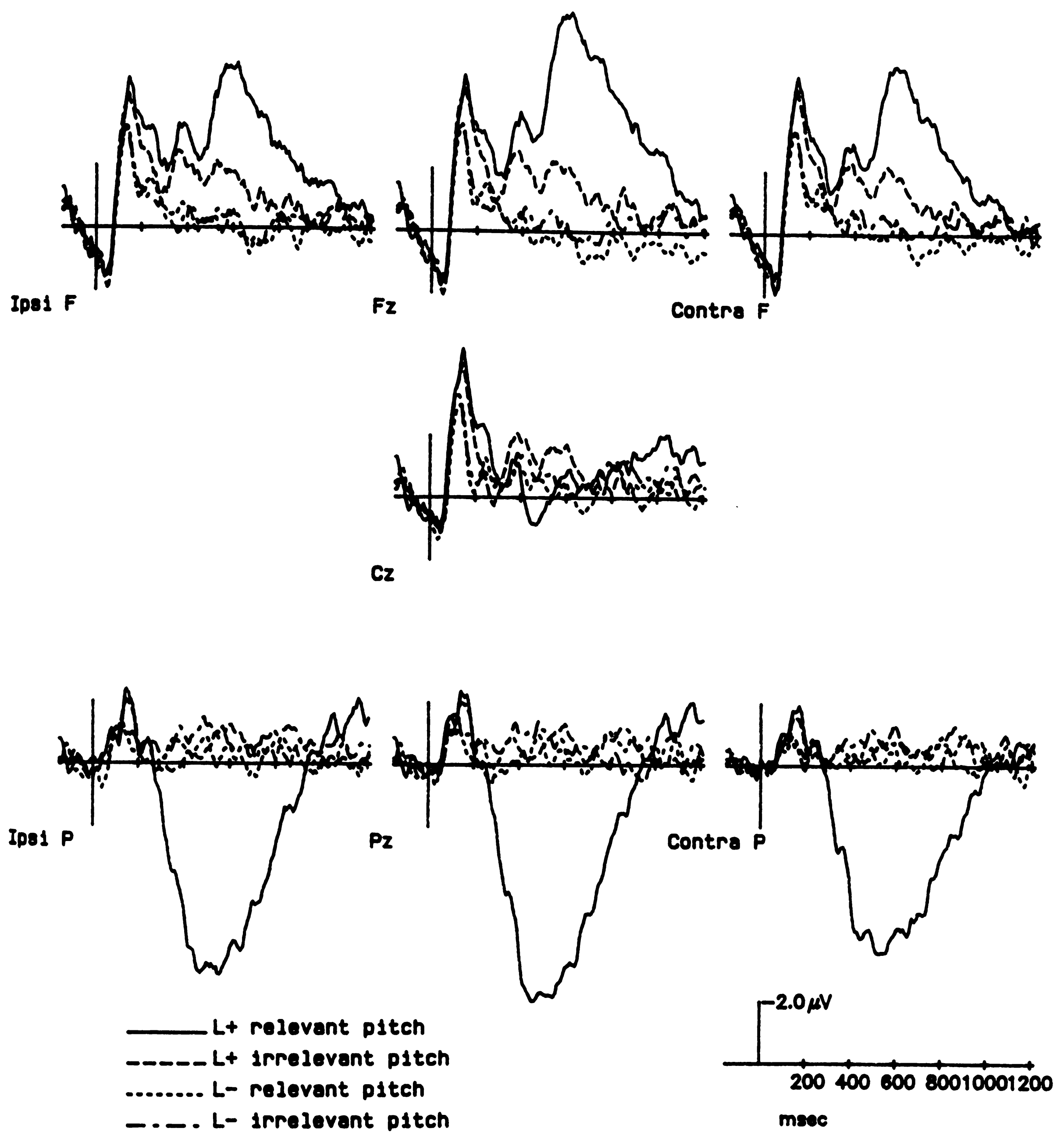
Figure 8.14 **Grand average ERPs to long tones recorded at frontal (F), central (C) and parietal (P) scalp sites from short duration cannabis users. (L+ and L- refer to attended and unattended location (ear) respectively).**

8.1.3   Discussion

It appears that frequency and duration of cannabis use differentially affect brain function in this selective attention task: heavy frequency use was found to prolong stimulus evaluation time, measured by P300 latency; long duration use impaired the ability to effectively focus attention and ignore irrelevant information, evidenced by increased processing negativity to irrelevant stimuli. Large processing negativity to pitch irrelevant tones in the long duration users indicates unnecessary processing of, and hence an inability to effectively reject pitch irrelevant information. This could be interpreted as either a failure to habituate to irrelevant stimuli (Miller and Branconnier, 1983), as faulty gating mechanisms (Hillyard and Mangun, 1987) or as the result of using inefficient information processing strategies (Hillyard and Hansen, 1986).

The increased PN to pitch irrelevant tones replicated the result of experiment two. But experiment two also found P300 amplitude to be smaller in cannabis users, a finding which was not replicated in experiment three. Careful scrutiny of the ERP waveforms, however, suggests that it was the control group that differed in the two studies. The control group in the original study showed a much larger P300 than did controls of the current study, as can be seen by comparing the amplitudes of controls in Figures 7.4 and 8.10. No apparent differences in the characteristics of the two samples could explain this, indicating that effects of cannabis use on P300 amplitude are less robust than effects on PN. Similarly, P300 latency was not significantly delayed in the original study (there was a nonsignificant trend), but the larger sample of this experiment provided more power to detect differences between groups. In the current study, there were no interactions between frequency and duration of use on either measure of brain function, suggesting that each affects different mechanisms or pathways in the brain.

The lack of an effect of duration of cannabis use on P300 latency suggests that the observed delay is temporary in nature and could be eliminated by reducing frequency of use. Cannabis may slow information processing by producing some (reversible) cell toxicity or disruption of brain messenger coordination. Cannabinoid compounds are lipophilic and alter membrane fluidity parameters, which may in turn alter the binding parameters of non-cannabinoid receptors, inhibit adenylate cyclase and cause perturbation of mechanisms of neurotransmitter uptake or release (Makriyannis and Rapaka, 1990; Martin, 1986).

Cannabinoids accumulate in fatty tissues (and thus probably in brain) (Hollister, 1986), and may be detectable in urine for more than two months after use (Ellis et al, 1985). While all subjects were required to abstain from cannabis for at least 24 hours (the range being 1 to 30 days of abstinence), the heavy users (using 3 times per week to daily) have considerably more cannabinoids continuously present in the body. Analyses confirmed that heavy cannabis users had significantly greater cannabinoid levels detected in their urines than light users [167 ng/ml vs. 24 ng/ml respectively; $F(1,30) = 8.06$, $p < 0.0081$] (long users appeared to have greater levels than short term users, 114 ng/ml vs. 77 ng/ml, but this difference was not significant ($F(1,30) = 0.45$, $p > 0.50$)). It is possible that the continual presence of cannabinoids at these levels in heavy cannabis users may affect their performance, even when they are not acutely intoxicated.

This hypothesis is in accord with the results of a study which found aircraft pilots' simulation performance to be impaired as long as 24 hours after smoking a single moderate dose of cannabis in the absence of any awareness of the drug's influence (Leirer et al, 1991; Yesavage et al, 1985). Acutely, cannabis has been shown to slow complex reaction time (see Chapter 3). In this study, reaction times were significantly slower in heavy users compared to controls and there was a nonsignificant trend toward

longer reaction times in the heavy users compared to light users. More importantly, the speed of information processing in the brain, P300 latency, was significantly delayed in the heavy user group compared to both light users and controls. This result emphasizes the sensitivity of ERP measures in detecting impairments in covert cognitive processes, otherwise undetected by overt measures of performance.

If the delay in P300 was a residual (hangover) effect, one would expect P300 latency to vary as a function of time since last use of cannabis or a measure of the level of cannabinoids present in the body. This hypothesis was tested by correlational analyses. As apparent in Figure 8.14.A, the relationship between P300 latency and self-reported most recent use was nonsignificant, although the trend was in the expected direction (r = -0.23). It is possible that more precise measures of quantity and time since last use with controlled verification would provide evidence of a stronger relationship.

In Figure 8.14.B, P300 latency plotted against the normalised urinary cannabinoid metabolite (THC-COOH) also showed a nonsignificant trend in the expected direction (r = 0.23). As mentioned above, 60% of the sample had no detectable cannabinoid metabolites in their urines. Such measures are subject to great variability (Ellis et al, 1985), and while weak traces of metabolised cannabinoids may be detected, the extent of storage of THC is unknown. It has been suggested that approximately 70% of ingested THC is taken up by tissues while only 30% is converted to metabolites measurable in urine, and that particularly following chronic use, there is a significant decrease in metabolites extracted in urine and a relative increase in unextracted metabolites (Hunt and Jones, 1980).

A

r = -0.23, p > 0.25

B

r = 0.23, p > 0.25
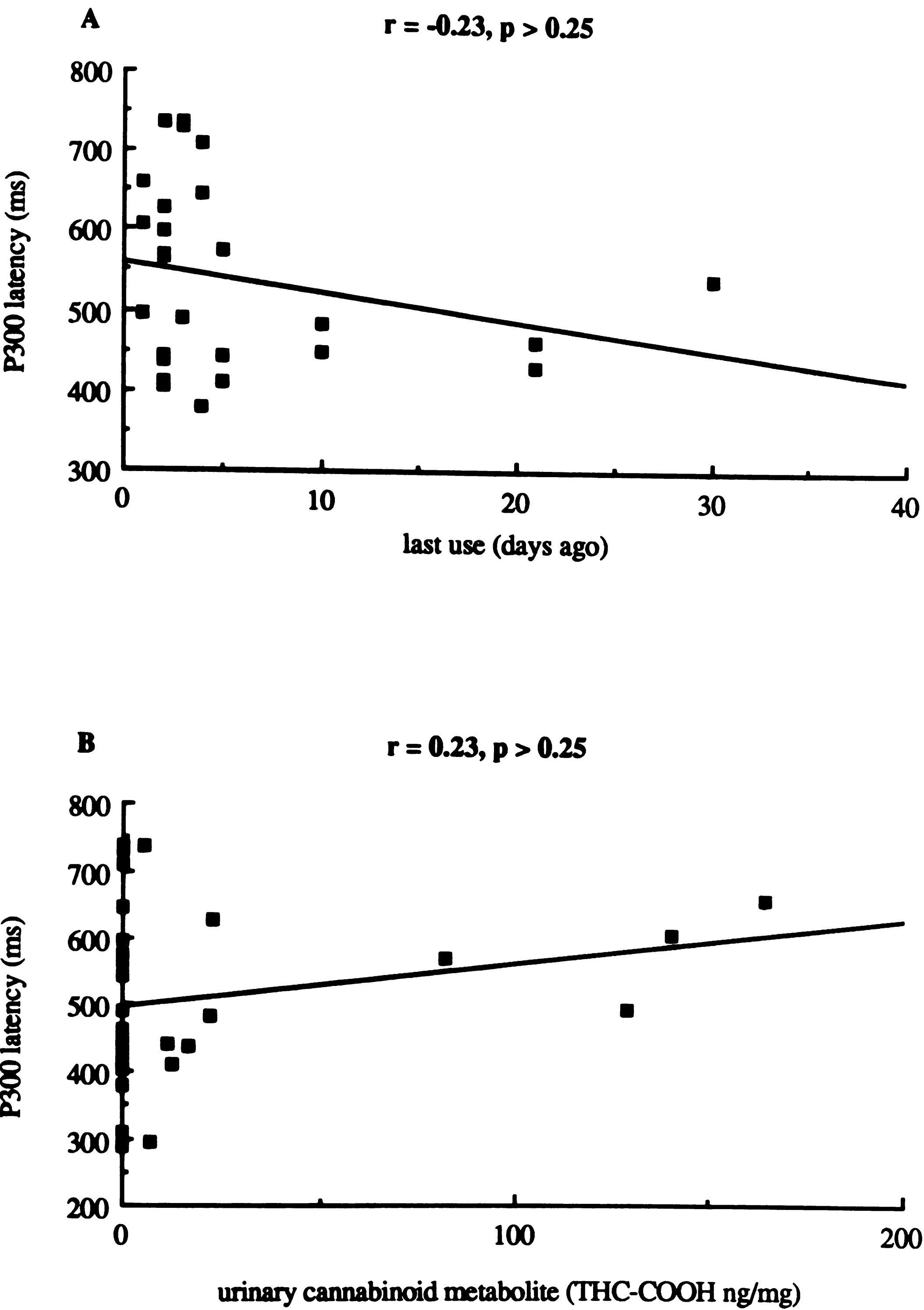
Figure 8.15 P300 latency (ms) at the contralateral parietal scalp site as a
function of A. time since last use of cannabis (days ago), and B.
normalized cannabinoid metabolite extracted from urine on the day of
testing.

The effect of duration of cannabis use on the rejection of irrelevant information reflects a very different mechanism. Neither time since last use (r = 0.03), nor urinary cannabinoid metabolite levels (r = 0.16) correlated with increased processing negativity to pitch irrelevant stimuli, implying that increasing years of use leads to long term changes that do not resolve with a short period of abstinence. These changes may occur at the cannabinoid receptor site.

Such an hypothesis is consistent with the high density of cannabinoid receptors in hippocampus, and the role of the hippocampus in the cognitive requirements of this task, particularly in the exclusion of extraneous information (Miller and Branconnier, 1983). Further, hippocampal neurons have been shown to be sensitive to spatial, temporal and discriminatory properties of stimuli, being activated by the learned significance of relationships among multiple stimuli, rather than by their particular sensory or physical properties (Eichenbaum and Cohen, 1988). Cannabinoid receptors occur in high density in other regions known to be involved in attention, such as the globus pallidus, frontal cortex, particularly anterior cingulate cortex, and the cerebellum (see Chapter 2). While much research is required to determine the functional properties of the endogenous cannabinoid-like constituent anandamide, it may be that this substance plays a role in the modulation of attention.

It has recently been demonstrated that chronic administration of cannabinoids results in receptor down-regulation with a reduction in the number of receptors in rat brain (Oviedo et al, 1993). Previous research with animals has not established that alterations in the properties of the cannabinoid receptor are irreversible (Westlake et al, 1991), although the duration of exposure in such studies has generally been for one year or less. The results of the present study suggest that long term effects may only become

readily apparent after 5 years of exposure, given the significant difference between the long term users of this study and controls, in contrast to the lack of robust differences between the short term users and controls. Nevertheless, the linear relationship observed implies not only progressive impairment, but also the possibility for early detection of subtle impairments with the use of more sensitive techniques.

The precise mechanisms of cannabinoid toxicity warrant further research. Whatever the mechanisms, these data provide evidence that increasing duration of cannabis use leads to a progressively impaired mode of information processing, whereby complex irrelevant information is not filtered out at an early stage of processing. In the real world, this may lead to distractibility and hence impairment in any situation where concentration and focussed attention are essential. The question that remained was: to what extent are these changes reversible after a longer period of abstinence? The next experiment was designed to assess the extent of reversibility in long term cannabis users who had ceased using.

CHAPTER 9

AN INVESTIGATION OF THE REVERSIBILITY OF COGNITIVE IMPAIRMENT IN EX-CANNABIS USERS

9.1 Experiment four: Reversibility of attentional deficits in ex-cannabis users

The previous experiment established that the large processing negativity elicited by pitch irrelevant stimuli in long term cannabis users performing a selective attention task, increased with the duration of cannabis use. This was interpreted as a progressive impairment in the ability to focus attention and ignore complex irrelevant information, and suggested that long term changes may occur as a result of cumulative exposure to cannabis.

This experiment was designed to assess the extent of reversibility of these changes with prolonged abstinence from cannabis use, and as such, examined the ERP response in the same selective attention task of a group of long term cannabis users who had ceased using cannabis. It was hypothesised that PN to pitch irrelevant stimuli may gradually resolve over time as the duration of abstinence from cannabis increases.

A power analysis based on the data of experiment three determined an effect size greater than one standard deviation unit. With a sample of 32 ex-users there would be an 80% chance of detecting a difference between groups of 0.7 standard deviation units at an alpha level of 0.05 (2-tailed test).

9.1.1 Method

Subjects

Subjects were recruited from the general community by advertising on university campuses and in popular youth magazines. The criteria for inclusion were to have used cannabis for at least 5 years and to have given up using cannabis within the past few years and at the very least 6 weeks prior to testing (this would allow any accumulated cannabinoids to be eliminated from the body). Attempts were made to select ex-users matched as closely as possible on sex, age and educational status to the long term users and controls of experiment three, and to ensure that the past duration of cannabis use was equivalent among long term users and ex-users. Thirty two cannabis users initially met the criteria for inclusion, but after taking a detailed drug use history it became apparent that two subjects had not quite used cannabis for 5 years, and were therefore excluded from comparative analyses with groups from experiment three. A further two subjects were excluded from the analyses due to high levels of cannabinoids detected in their urines at the time of testing. Therefore the final sample consisted of 28 ex-users whose characteristics are presented in Table 9.1.

Ex-users were well matched to the long term users of experiment three; the groups did not differ in age [$F(1,42) = 0.31$, $p > 0.58$], years of education [$F(1,42) = 0.91$, $p > 0.34$], NART scores [$F(1,42) = 1.09$, $p > 0.30$] or alcohol consumption [$F(1,42) = 2.31$, $p > 0.13$]. Further, they did not differ in their mean duration of cannabis use [$F(1,42) = 0.42$, $p > 0.52$] which ranged from 5 to 20 years, and the two groups were equivalent in their frequency of cannabis use [$F(1,42) = 2.86$, $p > 0.09$]. The mean frequency of use for the ex-users reflects their usage during the longest phase of their use, but many had gradually diminished their frequency of use prior to ceasing altogether. 40% had stopped "cold turkey" during the heaviest period of their use.

Table 9.1. Sample characteristics: mean and (SD) compared with groups from experiment three.

Group	Sex	Age	Years of Education	NART Score	Alcohol Consumption (standard drinks per month)	Cannabis Duration (years of use)	Cannabis Frequency (days per month)
Ex-users N=28	22M 6F	27.8 (5.2)	14.8 (2.3)	34.3 (7.0)	39.4 (43.2)	9.0 (3.8)	19.1 (10.9)
Long N=16	13M 3F	28.9 (8.2)	14.1 (2.1)	36.8 (8.4)	60.9 (48.4)	10.1 (6.8)	13.7 (9.0)
Short N=16	12M 4F	19.9 (2.0)	13.2 (1.2)	35.0 (5.8)	47.8 (38.8)	3.3 (0.5)	10.3 (6.5)
Controls N=16	12M 4F	26.3 (7.0)	15.6 (2.4)	39.7 (5.2)	23.4 (17.0)	____ ____	____ ____

The ex-user group had consumed cannabis for significantly longer [$F(1,42) = 34.64$, $p < 0.0000$] and at a greater frequency [$F(1,42) = 8.78$, $p < 0.005$] than the short term users of experiment three, were older than short term users [$F(1,42) = 33.36$, $p < 0.0000$], had slightly more years of education [$F(1,42) = 6.31$, $p < 0.0159$], but did not

differ from short term users in IQ (estimated by their NART scores) [$F_{(1,42)} = 0.12$, p > 0.73] and did not differ in monthly alcohol consumption [$F_{(1,42)} = 0.41$, p > 0.52]. Ex-users did not differ in age from controls [$F_{(1,42)} = 0.60$, p > 0.4417], nor alcohol consumption [$F_{(1,42)} = 2.02$, p > 0.16], nor education [$F_{(1,42)} = 1.17$, p > 0.28], but ex-users had significantly lower NART scores than controls [$F_{(1,42)} = 7.24$, p < 0.0102]. This difference in IQ was taken into consideration in analyses as described below.

The same exclusion criteria applied as for experiment three. The ex-users were instructed to abstain from alcohol for 24 hours prior to testing. They provided a urine sample on the day of testing and any subject with cannabinoids (or any other drugs) detected in their urine was excluded from the sample. As stated above, two subjects were excluded on this basis. One had expressed concern about possible exposure through passive inhalation, but the cannabinoid levels detected in her urine were judged to be far too high to have resulted from passive exposure, and as a measure of prudence, it was considered essential to exclude any subject who may have been exposed to cannabis whether actively or inadvertently, as well as any subject who may have lied about their use. The 28 subjects of the final sample had no cannabinoids detected in their urines.

The mean duration of abstinence in the ex-user group was approximately 2 years (SD = 22.8 months, range 3 months to 6 years). The main reasons given by ex-users for ceasing their use of cannabis could be labelled as maturational. For example, some gave up in order to pursue further studies, some had babies, some simply stated that their lives weren't really going anywhere or that they felt they had grown out of using cannabis. Almost two thirds of the sample claimed to have felt dependent on cannabis; for the majority this was described as a "psychological dependence", while four subjects claimed to have been both physically and psychologically dependent. Dependence, in

general, was defined in various ways, encompassing the following terms: a habitual or automatic action (to smoke); a strong need to use cannabis in order to feel normal; an inability to sleep or to function without it; cannabis use as an escape from reality, an aid in the management of depression, stress, anxiety or insomnia, or an emotional or social "crutch" in navigating interpersonal relationships and social events. The 40% of subjects who claimed not to have felt dependent on cannabis when asked directly, nevertheless scored highly on a symptom checklist for dependence (see Chapter 10). One third of the sample stated that they had no intention of ever using cannabis again, while the remainder felt that they might use occasionally at social functions in the future, but none had any desire to return to regular use.

Procedure and stimuli

This was identical to that described for experiment three (see Chapter 8).

ERP recording and data analysis

This was identical to that described for experiment three (see Chapter 8). The only difference in data analysis was that the main comparisons of interest in this study were between ex-users and current long term users of experiment three, and between ex-users and controls of experiment three. The effects of past frequency of use in ex-users were also examined in correlational analyses, but with the hypothesis that past frequency of use would have no residual effect.

9.1.2 Results

Performance data

Performance measures for ex-users and all other groups are presented in Table 9.2. Analysis of variance showed that although ex-users appeared to have longer reaction times than controls, the difference was not significant [$F(1,42) = 1.08$, $p > 0.30$]. Ex-users reaction times did not differ significantly from those of long [$F(1,42) = 1.37$, $p > 0.24$] or short duration users [$F(1,42) = 0.65$, $p > 0.42$]. However, ex-users made significantly fewer correct detections than controls [$F(1,42) = 5.05$, $p < 0.0299$] but did not differ from either of the cannabis using groups in terms of "hit rate" [ex vs. long: $F(1,42) = 0.11$, $p > 0.73$; ex vs. short: $F(1,42) = 0.38$, $p > 0.53$]. There were no differences between ex-users and any other group in false alarm rate [ex vs. controls: $F(1,42) = 0.72$, $p > 0.40$; ex vs. long: $F(1,42) = 0.15$, $p > 0.70$; ex vs. short: $F(1,42) = 0.00$, $p > 0.99$].

ERP data

The grand average ERPs to short tones recorded from the 28 ex-users are depicted in Figure 9.1. Figure 9.2 depicting frontal and central midline sites only, permits direct comparison of groups. Inspection of the plots suggested that processing negativity (PN) to pitch irrelevant tones was not as large in the ex-users as that seen in the current long term users of experiment three, and PN to pitch relevant tones also appeared reduced in the ex-users compared to all other groups. PN at frontal and central sites from the 28 ex-cannabis users was measured as the mean amplitude between 300 and 600 ms at frontal and central sites and subjected to an analysis of variance.

Table 9.2 Performance measures of reaction time, hit rate and false alarm rate for ex-cannabis users compared with groups from experiment three: means and (SD).

	Long Duration users	Short Duration users	Ex-cannabis users	Controls (non-users)
Reaction time (ms)	650.83 (98.11)	638.86 (85.13)	616.20 (92.06)	587.42 (81.79)
Hit rate (%)	74.22 (12.55)	73.21 (9.72)	75.64 (13.89)	84.23 (8.30)
False alarm rate (%)	0.83 (1.01)	0.72 (0.54)	0.72 (0.88)	0.50 (0.69)

The results showed that the ex-users differed from the long duration users in the processing of both relevant and irrelevant pitch stimuli; that is, there was a significant effect of group [$F(1,42) = 11.41$, $p < 0.0016$] but no stimulus x group interaction [$F(1,42) = 0.17$, $p > 0.67$]. PN to both relevant and irrelevant stimuli in the attended ear was significantly smaller in the ex-users compared to the long term users.

EX-CANNABIS USERS

Ipsi F

Fz

Contra F

Cz

Ipsi P

Pz

Contra P

```
_____ L+ relevant pitch
_ _ _ _ _ L+ irrelevant pitch
......... L- relevant pitch
_ . _ . L- irrelevant pitch
```

```
  ┌─2.0 μV
  │
──┴───┼────┼────┼────┼────┼──
    200 400 600 80010001200
msec
```
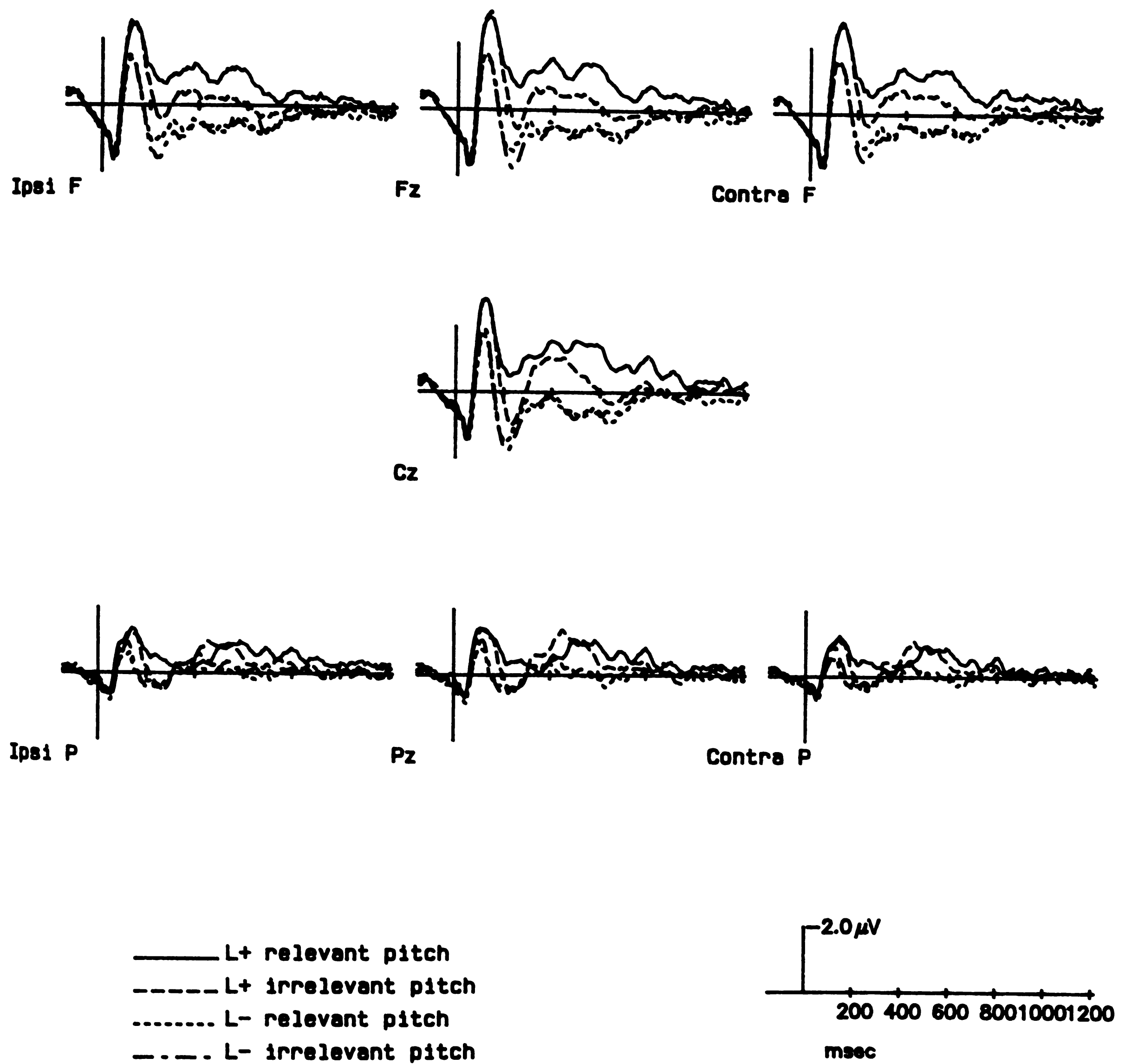
Figure 9.1 **Grand average ERPs to short tones recorded from 28 ex-cannabis users depicted at all electrode sites. (L+ and L- refer to attended and unattended location (ear) respectively).**

LONG USERS

SHORT USERS

Fz

Cz

Fz

Cz

EX-USERS

CONTROLS

Fz

Cz

Fz

Cz

—————— L+ relevant pitch
— — — — L+ irrelevant pitch

┌─2.0 μV

200 400 600 80010001200
msec
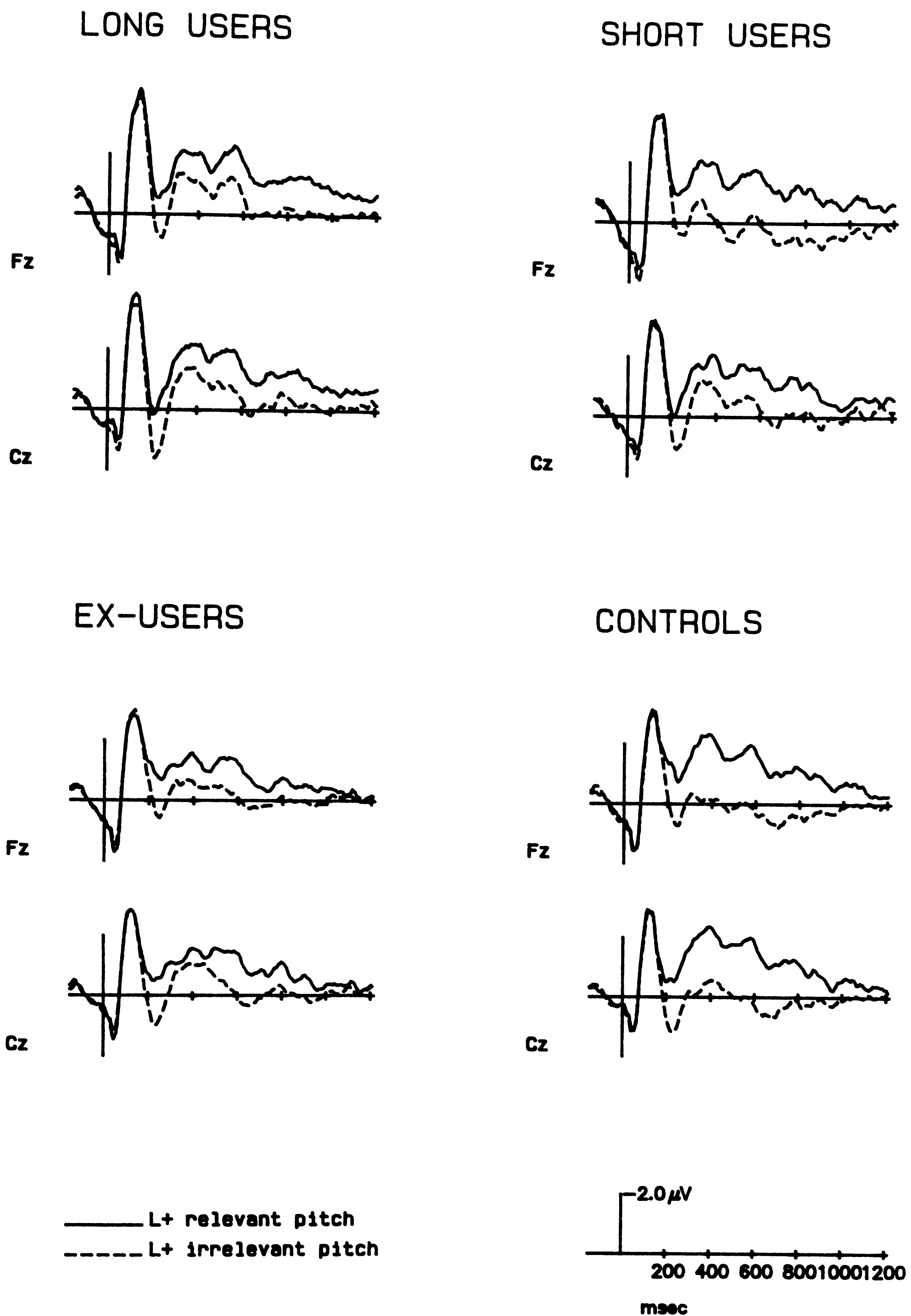
Figure 9.2 **Grand average ERPs to short duration pitch relevant and pitch irrelevant tones in the attended ear recorded at frontal (Fz) and central (Cz) midline sites from long and short duration cannabis users, ex-cannabis users and controls.**

The pattern of results was quite different when comparing ex-users with each of the other two groups: the main effect of group was not significant [ex vs short: $F(1,42)$ = 0.08, p > 0.78; ex vs controls: $F(1,42)$ = 0.39, p > 0.53] but there were significant stimulus x group interactions [ex vs. short: $F(1,42)$ = 5.30, p < 0.0264; ex vs. controls: $F(1,42)$ = 5.62, p > 0.0224]. Multiple comparisons of each group for each stimulus revealed the following differences: Ex-users vs. short duration users: relevant pitch $F(1,42)$ = 2.88, p > 0.097; irrelevant pitch $F(1,42)$ = 2.02, p > 0.162; Ex-users vs. controls: relevant pitch $F(1,42)$ = 3.86, p > 0.056; irrelevant pitch $F(1,42)$ = 2.55, p > 0.117. While none of the comparisons reached significance the trend was in the direction of smaller PN to relevant pitch stimuli in the ex-users, but also trends toward larger PN to irrelevant pitch stimuli in the ex-user group compared to both short duration users and controls. These results are apparent in Figure 9.3.
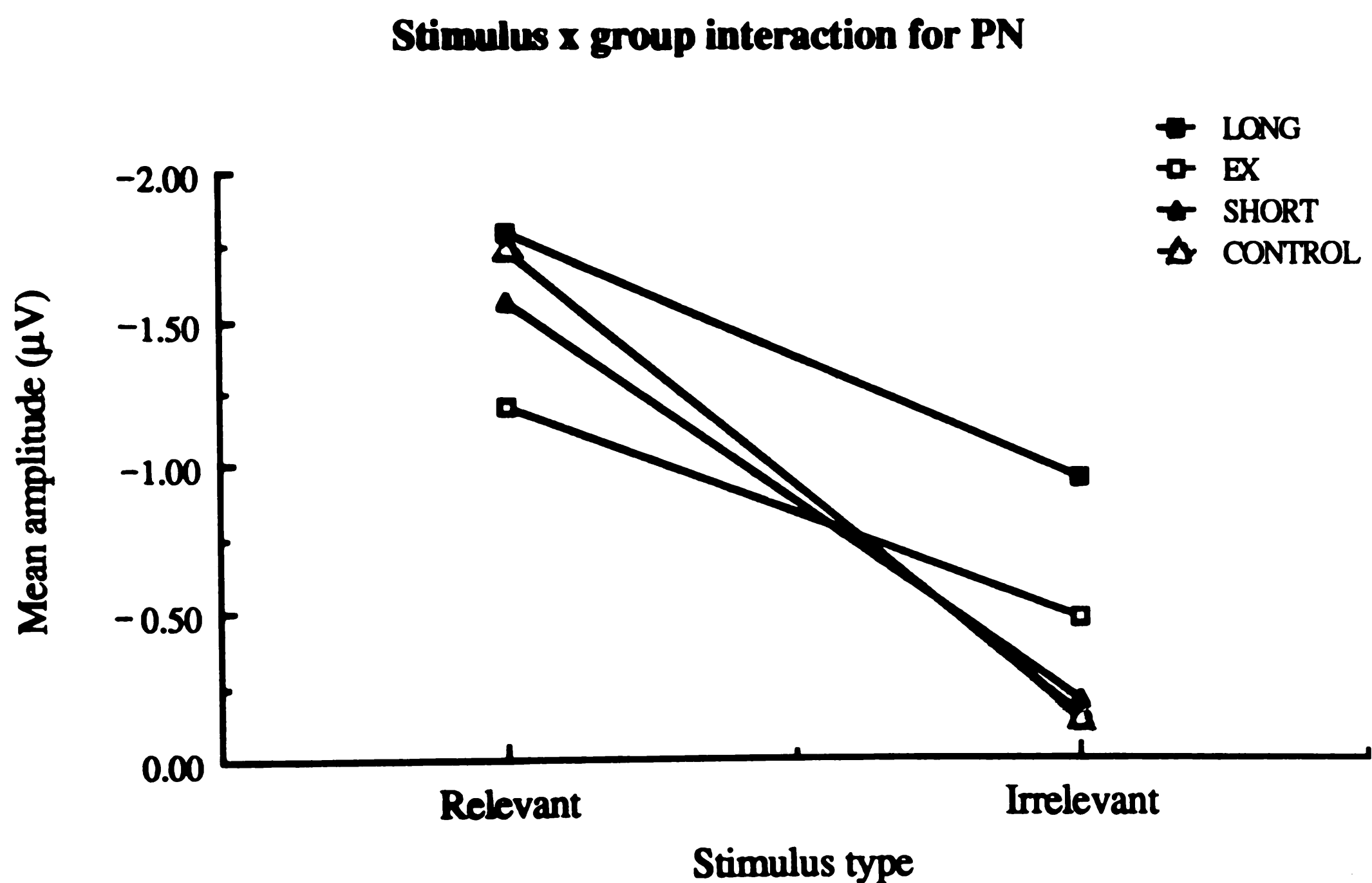
Figure 9.3 Stimulus x group interaction, depicting PN to pitch relevant and pitch irrelevant stimuli in the attended ear for long term users, short term users, ex-users and controls.

The slope for the ex-users in Figure 9.3 resembles that of the long term users, albeit reduced overall for both relevant and irrelevant pitch stimuli. This pattern is distinct from that of both short term users and controls where a much sharper reduction is seen from PN to pitch relevant, to PN to pitch irrelevant stimuli. There was also a significant interaction between stimulus, electrode and group when comparing ex-users with short term users [$F(3,126) = 3.45$, $p < 0.0359$]. The nature of this interaction is depicted in Figure 9.4: ex-users have smaller PN to pitch relevant stimuli across all sites, but larger PN to pitch irrelevant stimuli than short term users frontally but not at Cz, where short term users showed large PN to pitch irrelevant tones. Ex-users were similar to both groups of cannabis users in showing large PN at Cz (apparent in Figure 9.2), but the interaction between stimulus, electrode and group was not significant when ex-users were compared with controls [$F(3,126) = 0.74$, $p > 0.49$].

Ex-users vs short duration users: stimulus x electrode x group interaction
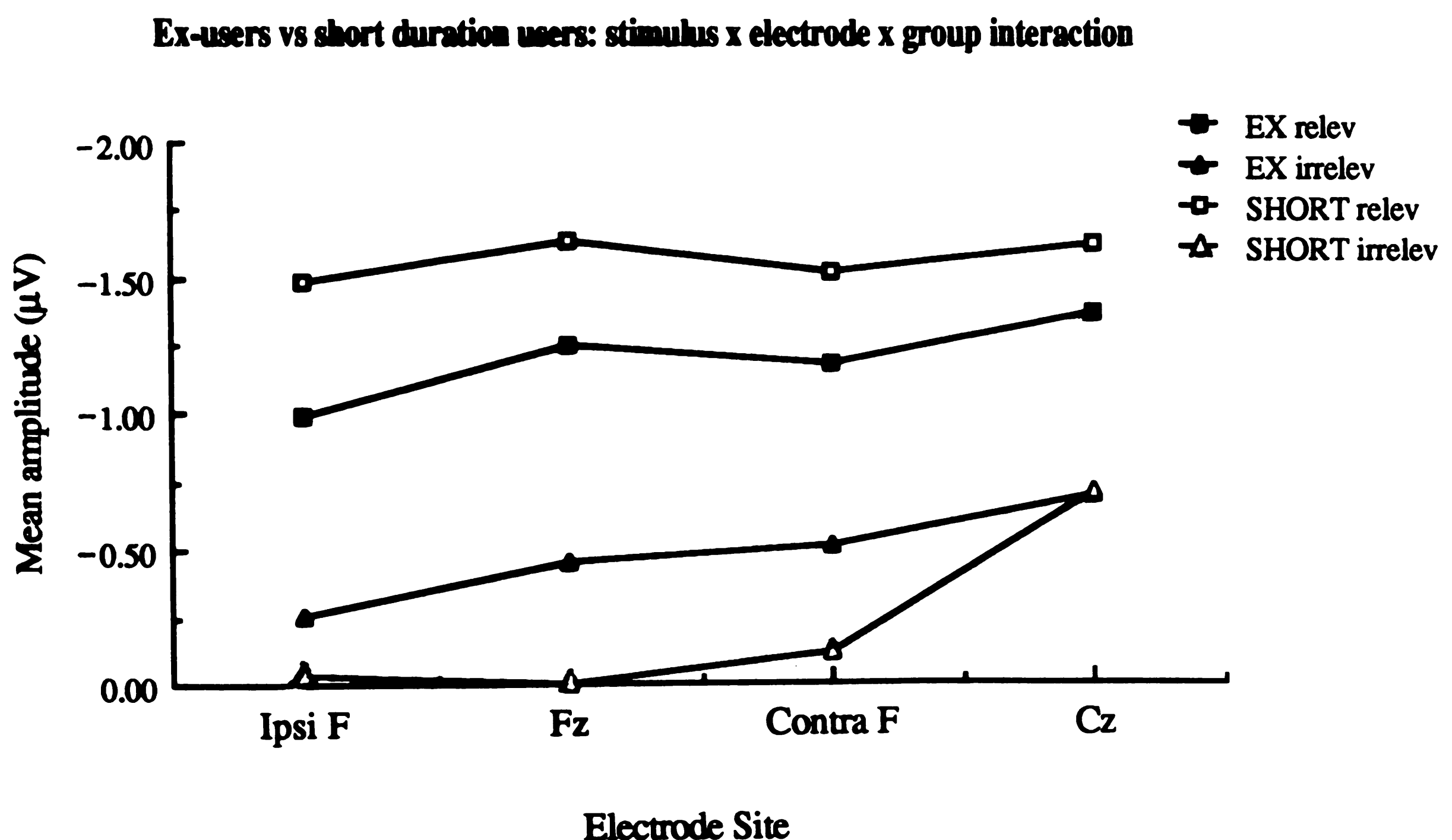
Figure 9.4 Stimulus x electrode x group interaction, depicting PN to pitch relevant and pitch irrelevant stimuli in the attended ear for ex-users and short term users across frontal and central scalp sites.

Since ex-users had significantly lower NART scores than controls, and therefore a lower mean IQ, the effects of IQ on PN to pitch irrelevant tones were examined by correlational analysis. PN was measured as the mean amplitude between 300 and 600 ms over frontal and central sites. There was no relationship between IQ and PN in the ex-user group ($r = 0.15$), however, PN increased as a function of IQ in the control group ($r = 0.68$, $p < 0.005$) (as reported in Chapter 8). The ex-users result essentially replicated that found in experiment three with current cannabis users. Hence, the Johnson-Neyman technique for the analysis of covariance for heterogeneous regression slopes (Huitema, 1980) was applied. This determined that the groups differed significantly below a NART score of 40 (estimated Full Scale IQ of 119.7), with ex-users having significantly larger PN to pitch irrelevant tones than controls at both frontal and central sites [$F(1,42) = 4.07$, $p < 0.05$]. Nineteen of the ex-users (68%) had NART scores falling below 40, thus representing the majority of the sample. As discussed in Chapter 8 concerning similar results found with current cannabis users, these analyses suggest that the long term effects of cannabis may be more apparent in users of lower IQ, or else, those of superior IQ compensate for the impairing effects of cannabis (given that the cut off IQ score falls in the superior to high average range). As argued in Chapter 8, the positive relationship between PN and IQ in the control group may reflect the ability of brighter subjects to attend to more than one source of stimuli without concomitant impairment in performance on the task. For current and ex-cannabis users, the processing of pitch irrelevant stimuli appeared to impair their task performance. These hypotheses were tested by correlational analysis of performance data and PN. While none of the tests reached significance, there were trends in the expected direction in the relationships between PN and the proportion of errors of commission (users: $r = 0.27$; ex-users: $r = 0.17$; controls: $r = -0.39$).

Correlational analysis showed a significant relationship between the past duration of cannabis use in the ex-user group, and PN to pitch irrelevant tones in the attended ear (r = 0.51, p < 0.005). This is depicted in Figure 9.5. Due to the significant relationship between age and duration of use (r = 0.84, p < 0.0001), age was also related to PN (r = 0.40, p < 0.03). However, a partial correlational analysis revealed that a relationship between duration and PN remained after removing the linear effects of age (r = 0.34, p < 0.05), whereas there was no relationship between age and PN after controlling for the effects of duration of cannabis use (r = -0.05).
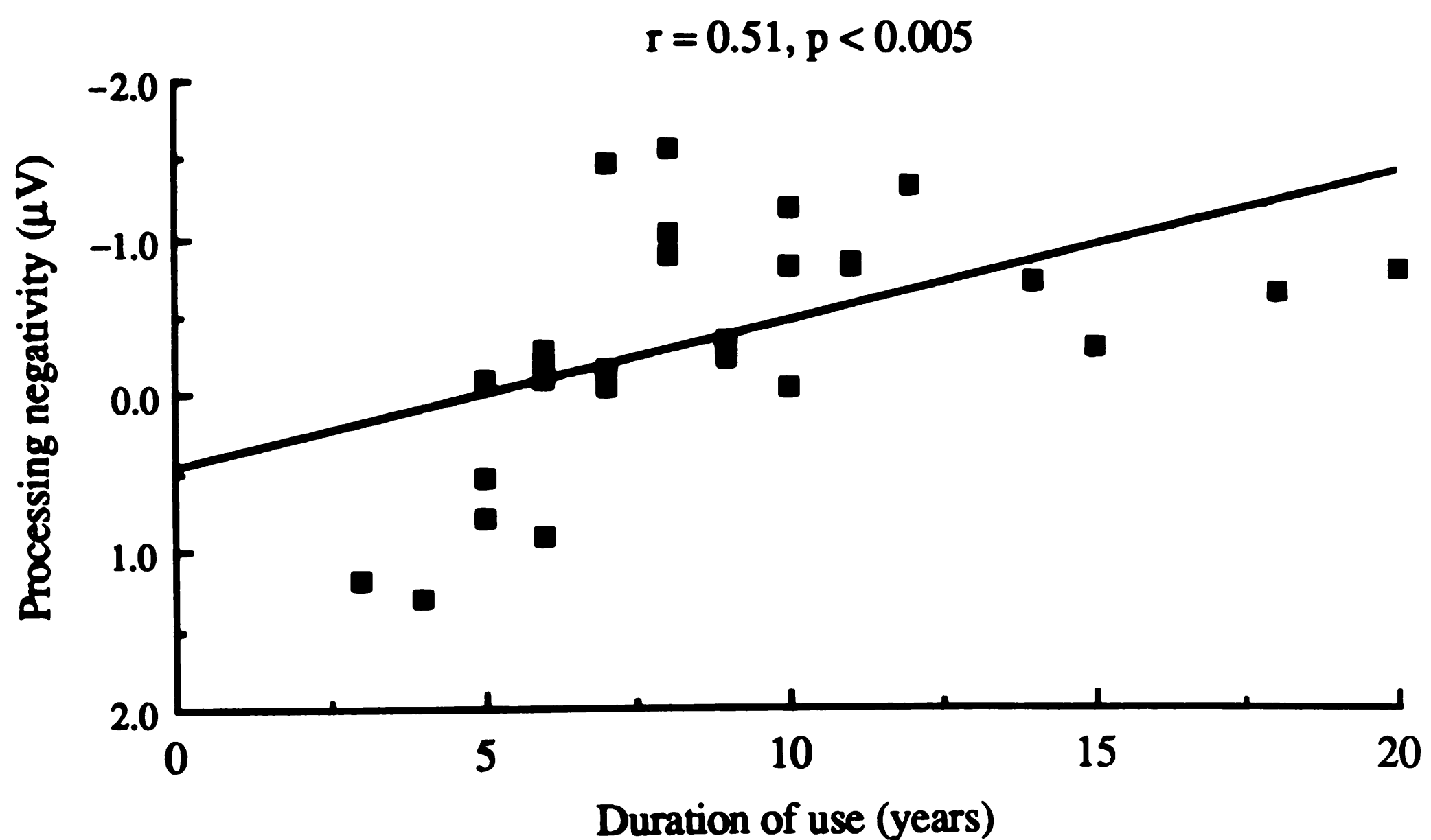
Figure 9.5   Mean amplitude of PN (μV) to pitch irrelevant tones as a function of past duration of cannabis use in the ex-user group.

The relationship between the ex-users past duration of cannabis use and PN was examined further by reducing the sample to only those who had used for up to twelve years (n = 26), for better comparability with the current cannabis users of experiment three (see Chapter 8, Figures 8.10A and B). The results, depicted in Figure 9.6, revealed a far more striking relationship (r = 0.72, p < 0.0001). The relationship between duration of use and age was still significant in this sample (r = 0.69, p < 0.0001), but partial correlational analysis showed that the relationship between past duration of cannabis use and PN to pitch irrelevant tones remained strong after removing the linear effects of age (r = 0.59), whereas there was no relationship between age and PN after removing the effects of duration of cannabis use (r = 0.02).
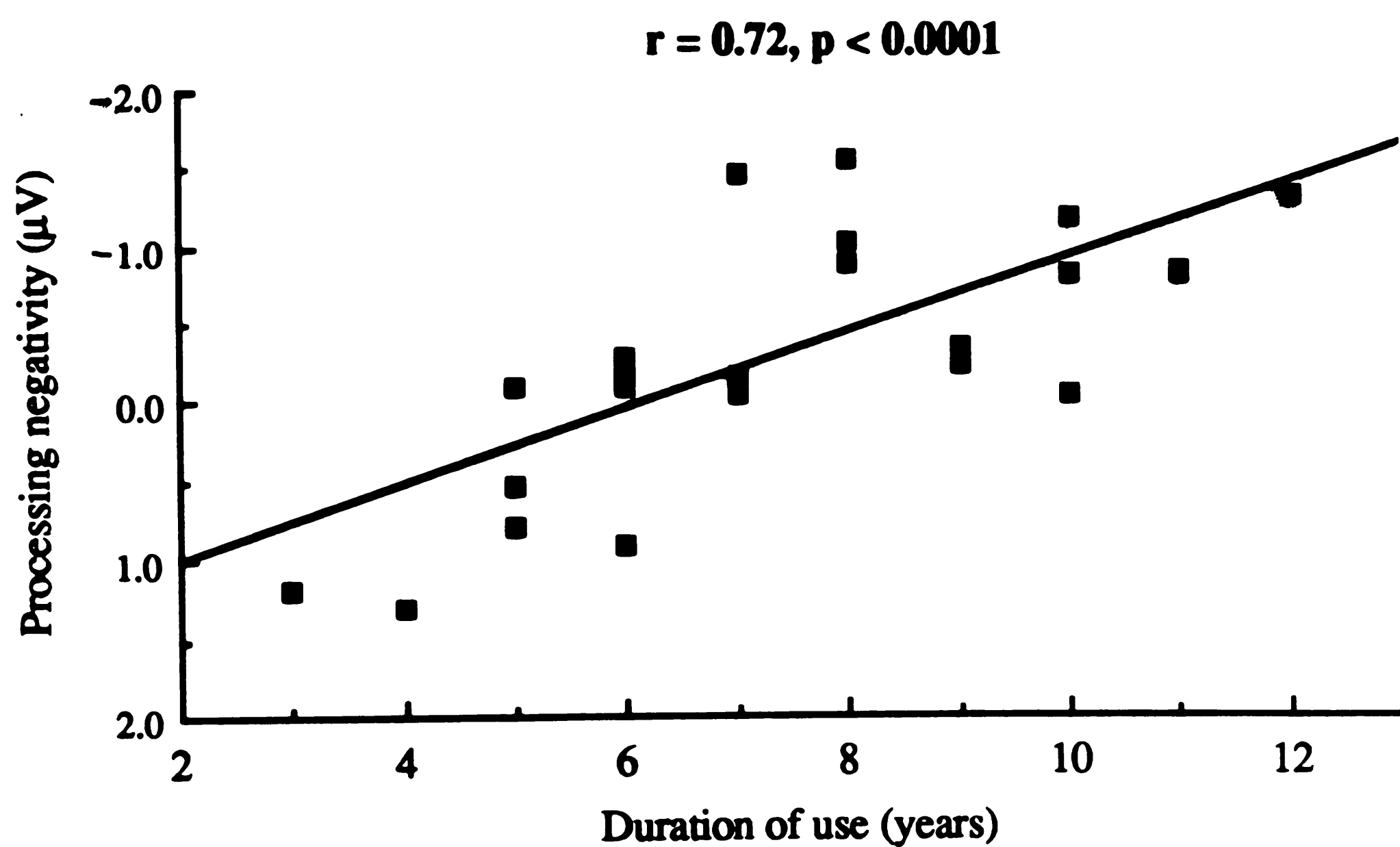
Figure 9.6   Mean amplitude of PN (μV) to pitch irrelevant tones as a function of past duration of cannabis use in a subsample of the ex-user group, those who had used for up to 12 years.

In experiment three, two subjects had used cannabis for 25 and 28 years, while the remainder of the sample had used between 3 and 12 years. When the entire sample had been included in the correlational analysis, a relationship between PN and duration of cannabis use was obscured (r = 0.23). The two very long term users were considered to be outliers and the correlation for the remainder of the sample became highly significant (r = 0.65, p < 0.0001). It was hypothesized that either some kind of tolerance may develop after many years exposure resulting in a nonlinear relationship between duration of use and PN, or else that a linear relationship between duration of use and PN would remain had more subjects using between 12 and 30 years been tested.

In this sample of ex-users the distribution of subjects having used between 3 and 20 years was reasonably even, with 4 out of the 30 subjects having used for more than 12 years. Inclusion of these longer term users also reduced the degree of the relationship between duration of cannabis use and PN. This result reinforces the hypothesis that the relationship appears to be nonlinear, the turning point occurring at some point after having used cannabis for 12 years. This hypothesis was tested by fitting a second order polynomial (BMD-P5R).

As shown in Figure 9.7, the curve appeared to fit the data very well, producing r = 0.73, p < 0.0001, with a remarkable "goodness-of-fit" [F(2,26) = 12.88, p < 0.0001]. The same analysis was then applied to the data of experiment three with similar results (r = 0.64, goodness-of-fit test: F(2,28) = 9.87, p < 0.0006).

The effects of the length of abstinence from cannabis were also explored in a correlational analysis. As shown in Figure 9.8, there was no direct relationship between the length of abstinence and PN to pitch irrelevant tones (r = 0.09). But abstinence cannot be examined in isolation, given the now well established effects of duration of

r = 0.73, p < 0.0001
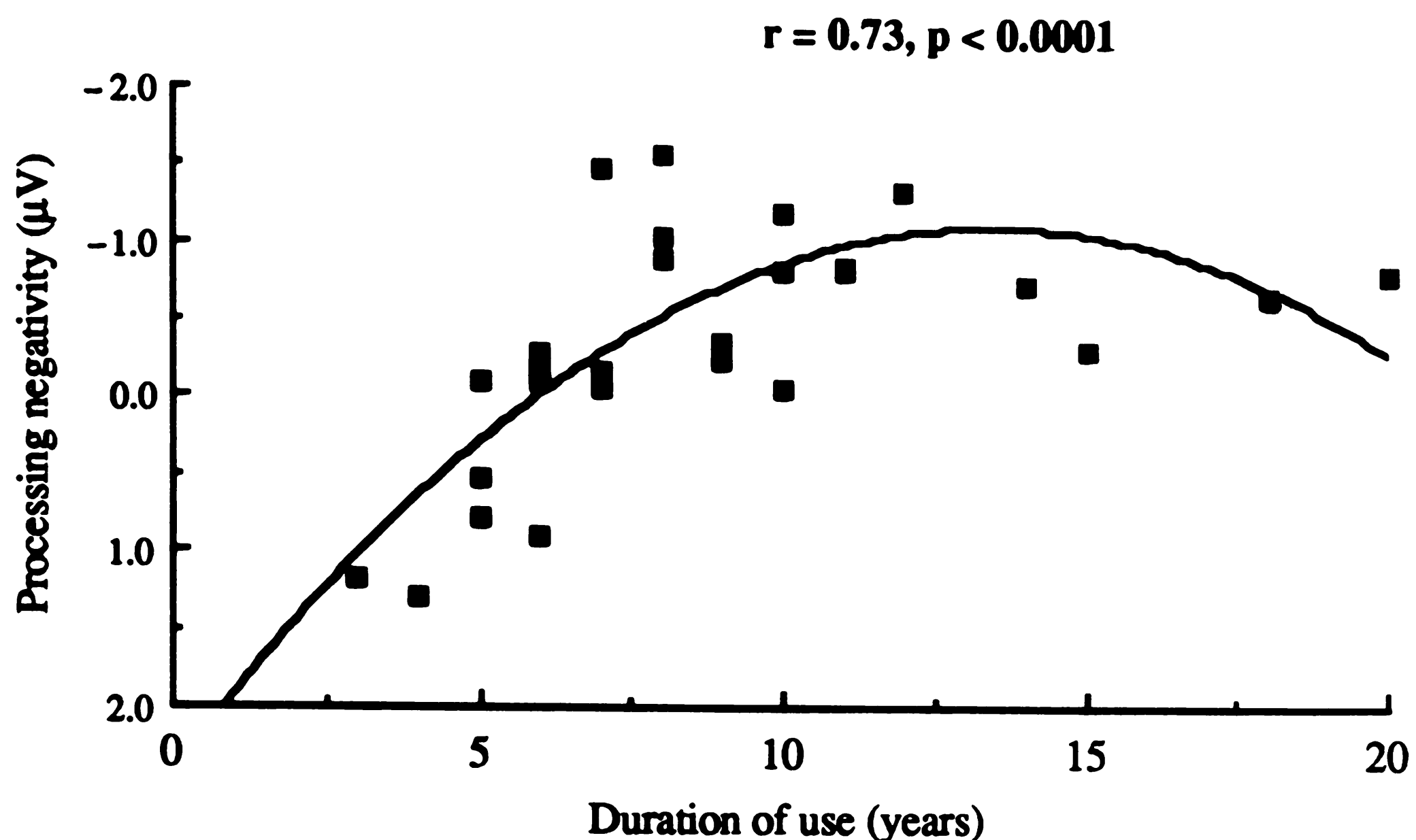
Figure 9.7 Mean amplitude of PN (μV) to pitch irrelevant tones as a two degree polynomial function of past duration of cannabis use in the ex-user group.

use on PN. Nevertheless, removing the linear effects of duration of use in a partial correlational analysis had very little effect on the relationship between abstinence and PN (r = 0.10). Similarly, removing any effect of abstinence did not change the relationship between duration of use and PN (r = 0.51, p < 0.005) for the entire sample.

While there was no relationship between past duration of use and current length of abstinence (r = 0.02), a relationship did exist between age and abstinence (r = 0.36, p < 0.03). Therefore, further partial correlational analyses (linear) were carried out as follows for the entire sample and for that portion of the sample having used for up to 12

years only (n = 26): the relationship between duration of use and PN to pitch irrelevant tones in the attended ear remained after controlling for the effects of both abstinence and age (r = 0.37, p < 0.02; n = 26, r = 0.60, p < 0.0005); there was no relationship between age and PN after removing the effects of duration and abstinence (r = -0.15; n = 26, r = -0.004); and there was no relationship between abstinence and PN after removing the effects of duration and age (r = 0.17; n = 26, r = -0.17). PN was not related to alcohol consumption (r = 0.11).
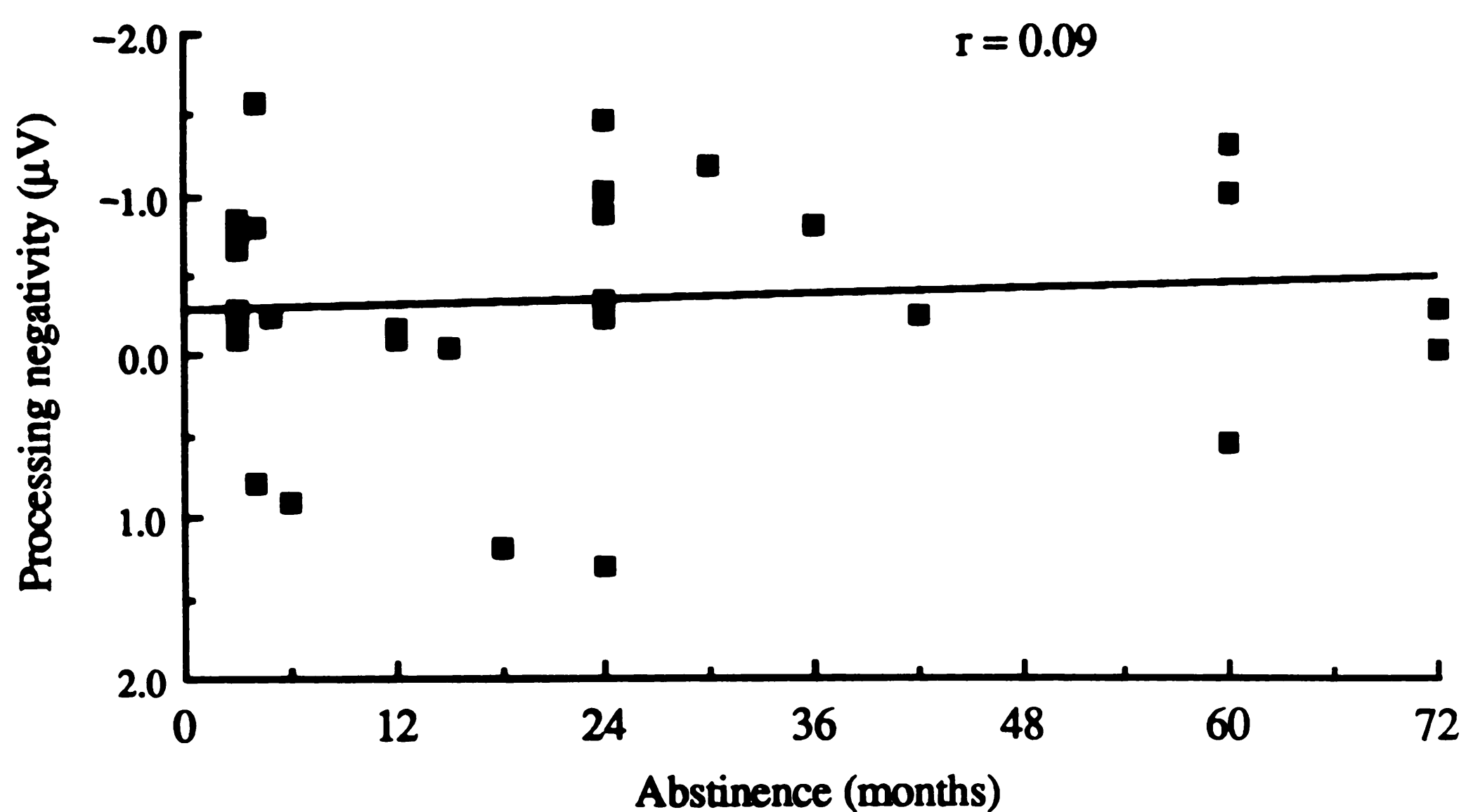
Figure 9.8   Mean amplitude of PN (μV) to pitch irrelevant tones as a function of length of abstinence from cannabis use.

The results of group multiple comparisons showed PN to pitch relevant tones to be considerably smaller in this group of ex-users than in either current long or short term users or controls. This was an unexpected finding as PN to relevant stimuli was not

affected by cannabis use in the sample of current users of experiment three. In experiment two, early PN to relevant pitch stimuli was reduced in users between 200 and 300 ms only. The measure of PN from 300 to 600 ms in this experiment was for the purpose of comparing ex-cannabis users with groups from experiment three on the processing of pitch irrelevant tones in the attended ear, since no differences between groups in experiment three had occurred outside this range, nor had there been any group differences in PN to pitch relevant tones. In order to further explore the reduction in PN to pitch relevant tones in ex-users, mean amplitude measures over 100 ms intervals were analysed for ERPs to both relevant and irrelevant pitch tones in the attended ear.

When ex-users were compared with current long term users, there was a trend toward greater negativity in the long term users to both relevant and irrelevant pitch tones across almost the entire epoch ($p < 0.10$ for all but one 100 ms range from 200-300 ms). However, differences between groups were significant over three ranges only, from 100-200 ms [$F(1,42) = 4.31$, $p < 0.0440$], 300-400 ms [$F(1,42) = 9.65$, $p < 0.0034$] and between 500 and 600 ms [$F(1,42) = 9.70$, $p < 0.0033$]. The difference between groups in the 100-200 ms range suggests that N1 was smaller in ex-users than current long term users. There were no interactions between stimulus and group, indicating that both PN to relevant and PN to irrelevant pitch tones were larger in current long term users than controls.

In contrast, when ex-users were compared with controls, the only differences between groups appeared as stimulus by group interactions over three ranges: 300-400 ms, $F(1,42) = 7.96$, $p < 0.0073$; 400-500 ms, $F(1,42) = 4.81$, $p < 0.0339$; and 700-800 ms, $F(1,42) = 5.00$, $p < 0.0307$. Multiple comparisons of each group for each stimulus revealed ex-users to have smaller PN to pitch relevant stimuli than controls only in the 300-400 ms range [$F(1,42) = 5.46$, $p < 0.0243$], with nonsignificant trends in the

same direction for the other two ranges, but also nonsignificant trends towards larger PN to pitch irrelevant stimuli in ex-users compared to controls.

Differences between ex-users and short term cannabis users commenced at 300 ms and continued to the end of the epoch. From 300 to 400 ms there was a significant stimulus by group interaction [$F(1,42) = 5.20$, $p < 0.0277$]. From 500 ms onwards, there were significant interactions between stimulus, electrode and group for each 100 ms range [400-500 ms $F(1,42) = 2.93$, $p < 0.0574$; 500-600 ms $F(1,42) = 3.99$, $p < 0.0210$; 600-700 ms $F(1,42) = 3.19$, $p < 0.0422$; 700-800 ms $F(1,42) = 4.28$, $p < 0.0168$; 800-900 ms $F(1,42) = 3.82$, $p < 0.0219$; 900-1000 ms $F(1,42) = 3.57$, $p < 0.0299$]. Group multiple comparisons for each stimulus at each scalp site revealed a multitude of effects.

From 300 to 400 ms, PN to pitch relevant tones was smaller for ex-users than short term users [$F(1,42) = 5.49$, $p < 0.0239$], but groups did not differ in PN to pitch irrelevant tones [$F(1,42) = 0.11$, $p < 0.7385$]. However, from 400-500 ms, ex-users showed significantly larger PN to the pitch irrelevant tones than short term users at all frontal sites, but not at Cz [Fz, $F(1,42) = 10.07$, $p < 0.0028$; Ipsilateral frontal, $F(1,42) = 6.75$, $p < 0.0129$; Contralateral frontal, $F(1,42) = 9.41$, $p < 0.0038$; Cz, $F(1,42) = 2.58$, $p > 0.15$]. These effects are apparent in Figure 9.2 where it can be seen that short term users show a positive shift in the trace for irrelevant pitch stimuli at about 400 ms, while ex-users continue to process pitch irrelevant stimuli for longer, with continued negativity to 600 ms. However, from 500 to 600 ms there is a negative deflection in the irrelevant pitch trace in short term users; there was a resultant lack of significant differences between groups in multiple comparisons for that range. In Figure 9.2 it is clear that both long and short term cannabis users show a double negative peak in the PN to pitch irrelevant tones between 300 and 600 ms, with a positive shift occurring around 400 ms and then a negative deflection again. The ex-cannabis users show no evidence

of such a double peaked negativity, merely a prolonged negativity that appears to be smaller than that seen in current long term users, but larger than that of controls. The finding that, at least within a small range, ex-users showed greater negativity to pitch irrelevant stimuli than short term users but not controls is surprising, but probably reflects large variability in the results of both ex-users and controls. Beyond 600 ms, there were no significant effects from multiple comparisons, but there were trends toward smaller PN to pitch relevant tones in ex-users than short term users, as well as greater negativity to pitch irrelevant tones in ex-users compared to current short term users, at frontal sites continuing to 900 ms. In summary, these results indicate that ex-users showed significantly smaller PN to relevant pitch stimuli than every other group from 300 to 400 ms. From 400 to 500 ms, ex-users appeared to be more similar to current cannabis users in PN to irrelevant pitch stimuli, than to controls.

PN to pitch relevant tones in the ex-user group was also investigated by correlational analysis. An inverse relationship was found to exist between past duration of use and PN to relevant pitch stimuli ($r = -0.43$, $p < 0.0184$), even though no such relationship was found in the current user sample of experiment three ($r = 0.24$). However, the relationship observed here did not remain after controlling for the effects of age and abstinence ($r = 0.02$). Age was also inversely related to PN to pitch relevant tones ($r = -0.39$, $p < 0.0322$), although the association weakened after removing the effects of duration and abstinence ($r = -0.26$, $p > 0.10$). Age and PN to pitch relevant tones were unrelated in the control group ($r = -0.04$). A relationship was not initially apparent between the length of abstinence from cannabis and PN to relevant pitch tones ($r = 0.17$), but increased in strength after removing the effects of duration and age ($r = 0.32$, $p < 0.05$). IQ was unrelated to PN to relevant pitch tones for either ex-users ($r = -0.09$) or controls ($r = 0.16$), and PN was unrelated to alcohol consumption ($r = 0.18$). There were no grounds for suspecting that any of these relationships may be nonlinear.

Finally, the ex-users were compared with the groups of current users in experiment three in their processing of long target tones by analysing the P300 component. The grand average ERPs to long tones from the 28 ex-cannabis users are depicted in Figure 9.9. P300 was measured as the most positive peak between 200 and 1000 ms at parietal scalp sites and was measurable in every subject in the ex-user group (no peak was detected in a number of subjects of experiment three as described in Chapter 8).

The ex-users did not differ from long term cannabis users or controls in the amplitude or latency of the P300 component to targets [Amplitude: ex vs long, group $F(1,38) = 0.67$, $p > 0.41$, electrode by group $F(2,76) = 1.97$, $p > 0.15$; ex vs controls, group $F(1,41) = 0.25$, $p > 0.62$, electrode by group $F(2,82) = 1.33$, $p > 0.26$; Latency: ex vs long, group $F(1,38) = 1.50$, $p > 0.22$, electrode by group $F(2,76) = 1.80$, $p > 0.17$; ex vs controls, group $F(1,41) = 0.07$, $p > 0.78$, electrode by group $F(2,82) = 0.19$, $p > 0.80$]. Ex-users had a significantly smaller P300 component over all parietal scalp sites than short term cannabis users [$F(1,42) = 4.93$, $p < 0.0319$] but they did not differ in latency from short term users [group $F (1,42) = 0.91$, $p > 0.34$; electrode by group $F(2,82) = 1.60$, $p > 0.20$]. The possibility that the sample of controls may have had unrepresentatively small P300 components has been discussed in Chapter 8.

For thoroughness, the ex-users were also compared with the heavy user group of experiment three, since the latter had shown a marked delay in P300 latency. It was hypothesized that the observed delay was only temporary in nature and this was substantiated by a significant difference between ex-users and current heavy cannabis users of experiment three [group $F(1,40) = 5.54$, $p < 0.0236$], and further by the analysis reported above where ex-users did not differ from controls in P300 latency.

EX-CANNABIS USERS
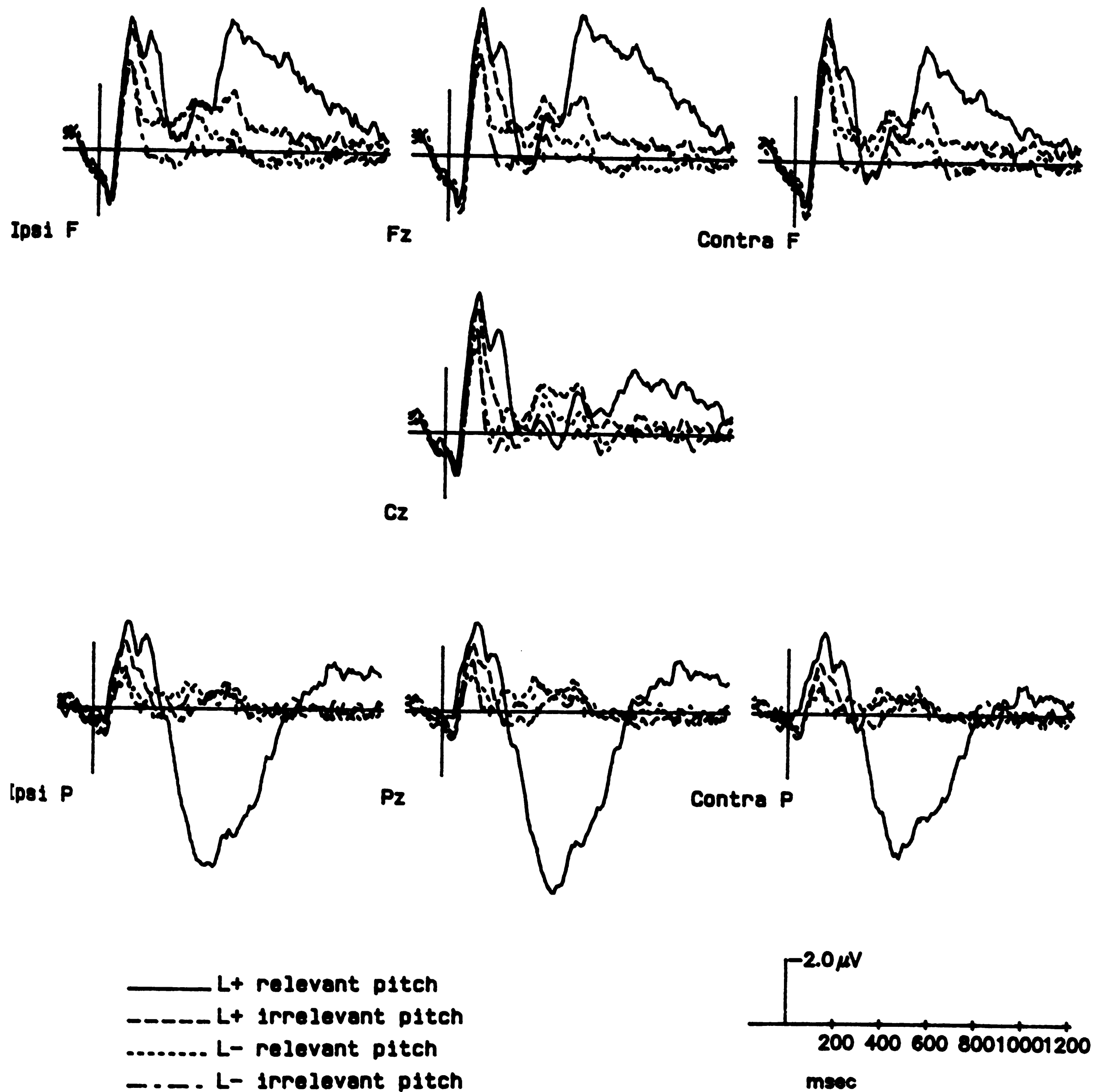
Figure 9.9 Grand average ERPs to long tones recorded from 28 ex-cannabis users depicted at all electrode sites. (L+ and L- refer to attended and unattended location (ear) respectively).

9.1.3 Discussion

A number of factors arising from the statistical analyses of the ERP data from this sample of ex-users imply that the effects of long term exposure to cannabis are similar to those established in the prior two experiments. The strong relationship between PN to pitch irrelevant tones and the past duration of cannabis use of this sample reflects that seen in experiment three with current users. There is no evidence from correlational analysis that the length of abstinence has contributed to a resolution of large PN to pitch irrelevant stimuli. However, it is clear from the ERP plots of Figure 9.1 and the graph of Figure 9.3, and supported by the results of analyses of variance, that PN to the pitch irrelevant tones is smaller in this sample of ex-users than in the current long term users of experiment three. This suggests that the cessation of cannabis use did in fact result in a reduction of the unusually large PN to irrelevant stimuli, even though no analysis was able to identify any relationship between the length of abstinence and the degree of attenuation. It may be argued, therefore, that the attenuation occurs rapidly, possibly within the same period of time that it takes to eliminate stored cannabinoids from the body, about 6 -12 weeks. If this were the case, one would expect to see a dramatic improvement in the ERP signature of the processing of irrelevant information within the first 6-12 weeks following cessation of use, with no further slow or gradual improvements with increasing abstinence as was hypothesised.

Nevertheless, the reduction in PN observed here has not returned the ERP signature to the level of that in nonuser controls. The lack of significance between ex-users and either short term users or controls may be due to the large variability in the ex-cannabis using group. In a report based on preliminary analyses of a subsample of the ex-cannabis users (the first 12 to volunteer for the experiment) (Solowij, in press), the results showed the opposite effect: ex-users did not differ from long term users in PN to

pitch irrelevant tones [$F(1,22) = 0.19$, $p > 0.60$], but differed significantly from both short term users [$F(1,22) = 5.59$, $p < 0.03$] and controls [$F(1,22) = 5.13$, $p < 0.03$]. The reverse of these results with the larger sample emphasises the large variability within the sample of ex-users, and the need to investigate further the possibility that individual differences contribute to an increased susceptibility to cognitive impairment associated with long term cannabis use. Clearly, for a portion of the sample studied here, there was no resolution of the inappropriately large PN to pitch irrelevant stimuli.

In an attempt to investigate possible contributory factors in an exploratory way, the ex-user sample was split at the median according to their PN response to pitch irrelevant stimuli and high responders were compared against low responders on all possible variables pertaining to subject characteristics, eg. age, sex, education, IQ, duration and frequency of cannabis use, alcohol consumption, and a variety of test measures of anxiety and psychopathology as discussed in Chapter 10. The only variable which distinguished between the two groups was duration of cannabis use [11.0 vs. 7.1 years: $F(1,26) = 9.59$, $p < 0.0046$], as would be expected, and there was a trend for the high PN group to be older than the low PN group [29.6 vs. 25.9: $F(1,26) = 3.76$, $p <0.0634$]. Since age itself does not correlate with PN to pitch irrelevant tones, this result could be interpreted to suggest that PN is more likely to resolve with cessation of use in younger subjects.

The finding that PN to relevant pitch stimuli was reduced in the ex-user group was unexpected; such a reduction was not previously found to be associated with the long term use of cannabis. A small reduction in PN to relevant stimuli was seen in the cannabis users of experiment two, but had not replicated in experiment three. In this study, not only did ex-users show smaller PN to relevant pitch stimuli than controls, but also smaller PN than current cannabis users. It may be posited, therefore, that the *cessation* of cannabis use resulted not only in partial resolution of PN to irrelevant pitch

stimuli for the majority of ex-users, but also a reduction in PN to stimuli of relevant pitch. The relationship between PN to pitch relevant tones and length of abstinence implies a slow and gradual improvement with PN becoming increasingly larger over time. This interpretation hinges on the assumption that PN to pitch relevant stimuli in this sample of ex-users was as large prior to their having ceased using cannabis as that seen in all other groups studied in this thesis. With cessation of cannabis use, PN to relevant tones may decrease dramatically, perhaps as a reaction to the withdrawal from cannabis.

Knight and colleagues (1981) reported that patients with dorsolateral frontal lesions showed less attention-related negativity in a simple auditory selective attention task. It is possible that the observed reduction in PN to relevant attended stimuli here reflects some frontal dysfunction. Reduced PN to relevant pitch stimuli has also been demonstrated in schizophrenics (Michie et al, 1990; Ward et al, 1991). These studies found PN to relevant pitch stimuli to be smaller in the early part of the epoch (100-200 ms), but primarily PN was smaller in the later part from 400 - 1000 ms, representing what they termed "late PN". The early PN reduction was correlated with both positive and negative schizophrenic symptom scores. These findings were interpreted as evidence of a number of deficiencies in the information processing strategies of schizophrenics, with an inability to set up an accurate attentional trace and then a failure to maintain it.

While the reduction found in PN to pitch relevant stimuli in the ex-cannabis user sample reported here is not entirely within the same range as that found in schizophrenics, the pattern is similar. It is interesting to speculate upon the possibility that, similar to claims made about the use of cannabis by schizophrenics (eg. Dixon et al, 1990), cannabis users may be "self-medicating". It is possible that cannabis users experience certain psychopathological symptoms which they try to correct by using

cannabis (or else their symptoms lead them to use cannabis). In doing so, they bring their attentional trace, represented by PN to relevant stimuli, up to "normality", perhaps by enhancing attentional mechanisms to all stimuli. This results not only in increased PN to relevant, but also increased PN to complex irrelevant stimuli, and as such does not enhance their ability to *selectively* attend, but merely to attend, to an extent, indiscriminately. When cannabis use is stopped, they return to their predrug level of less efficient attentional processing of relevant information, but also more efficient rejection, or lack of processing, of irrelevant information. Whether or not this is the case, it is interesting to speculate upon these hypotheses.

An alternate explanation may be one based simply upon withdrawal symptomatology: the abrupt, or even weaned, cessation of a psychoactive substance that has been used on a regular basis for many years, may result in disruption of various chemical systems in the brain with resultant impaired cognitive functioning. However, any such withdrawal symptoms should not be expected to endure for a very long time. The mean level of abstinence in the group was around 2 years; any withdrawal-like symptoms should well have dissipated by such time.

Yet another explanation similar to the withdrawal hypothesis may be based on learning theory. It may be that being under the influence of a psychoactive substance for many years, that is, being chronically "stoned", enforces a learned compensation for the effects of the chronic intoxication. In this sense, the cannabis user has to put more resources into attending to complex stimuli. These extra resources may not be distributed in an appropriate manner and hence irrelevant stimuli are also accorded more resources, evident in their increased PN. But this hypothesis cannot explain the reduction in PN to relevant pitch stimuli. Clearly, further research is required to replicate and elucidate these findings. The ideal study would be one that examined the same group of cannabis users before, immediately after stopping cannabis use and at various

times thereafter, but the practice effects of repeated testing sessions would need to be taken into account.

The other interesting finding from this study, which corroborated an hypothesis formed in experiment three, was that of a nonlinear relationship between duration of cannabis use and PN to pitch irrelevant stimuli, as seen in Figure 9.7. In both this sample of ex-users and in the sample of current cannabis users of experiment three, PN to pitch irrelevant tones appeared to increase in a linear manner with duration of cannabis use, up to approximately 12 years of use. Beyond 12 years use, the curve flattens asymptotically, or may even revert to greater positivity with very long duration use. It is not possible to be certain about the nature of the relationship beyond 12 years use given the small number of subjects contributing to that portion of the curve.

It is likely that there is a ceiling beyond which PN would not increase any further, particularly given the fact that PN is a measure of an electrophysiological response reflecting a cognitive process. This suggests that the curve would become asymptotic. However, if further research with more subjects confirmed a positive shift beyond 12 years use, this may reflect a complex interaction between duration of cannabis use and increasing age. Although PN to pitch irrelevant tones appeared to increase with age in the control group of experiment three, others have reported PN to decrease with age in older samples, for example, those above 50 years of age (eg. Karayanidis et al, submitted). This hypothesis of a complex relationship between prolonged cannabis use and increasing age is consistent with other studies examining the interactions between cannabis and the glucocorticoid system of the brain, which suggested that cannabis use may accelerate brain aging (Eldridge et al, 1992; Landfield et al, 1988).

A further possibility to consider is that there may be something particular

associated with use of cannabis beyond 12 years that contributes to this levelling of PN to pitch irrelevant stimuli. For example, if it is considered that the most common age for commencing regular use of cannabis is somewhere between 16 and 20 years of age, after 12 years use, one would be approximately 30 years of age. It is interesting to speculate upon various factors associated with reaching that age, perhaps factors such as maturity and "settling down". There is evidence that most cannabis users discontinue their use in their mid to late twenties (Donnelly and Hall, in press). There may be something qualitatively different about those who continue to use through their thirties and later. Factors such as psychopathology and anxiety, while discussed to some extent in Chapter 10, may be worthy of further research in this regard. It is not known whether any of these factors would have the observed effects on PN.

Perhaps the simplest explanation of the reduction or stability of PN beyond 12 years use may be in the operation of an effect of natural selection: those who do not experience cognitive and other impairments would be those more likely to continue to use. Those who are consciously aware of experiencing problems associated with their use of cannabis are more likely to discontinue their use. Thus, the very long term cannabis users who continue to use through their thirties and into their forties and beyond, may be those for whom cannabis use has either none, or few adverse consequences. This group would be worthy of further investigation, as indeed are the individual differences that might lead to such stratification.

The finding of a relationship between IQ and PN to irrelevant pitch stimuli in the control group but not in users or ex-users is also puzzling. Such a relationship has not previously been reported. It is possible that brighter subjects may find the task relatively easy and may allocate "spare" resources to processing other stimuli within the task purely to maintain some interest in the task, without compromising their performance in

any way. Clearly, for the ex-users of this experiment and all cannabis users studied in previous experiments, large PN to pitch irrelevant stimuli accompanied poorer performance on the task and was therefore interpreted as reflecting an inefficient way of processing information, with unnecessary allocation of attentional resources to pitch irrelevant information. Further, it is important to note that both current cannabis users of experiment three and the ex-users studied here tended to have a lower mean IQ than the controls, but also showed larger PN to pitch irrelevant tones. If the effects were solely due to IQ differences, one would have expected the reverse, ie. cannabis users should have showed smaller PN to pitch irrelevant tones than controls.

A further interpretation of these data may be in terms of a broadening of the attentional "spotlight" (Woods, 1989). It is possible that the use of a particular strategy broadens the attentional spotlight to include stimuli irrelevant to the task but sharing one or more close attributes with the relevant attended stimulus. It may be that the use of such a strategy varies as a function of IQ in the control group, but as a function of cumulative exposure to cannabis in the users. The use of such a strategy could reflect greater cognitive flexibility, which is exercised by bright controls with no resultant impairment in performance. For cannabis users and ex-users, such a cognitive style may be learned from the intoxicating experiences with cannabis, or, may still reflect the changes that occurred in the brain as a result of cumulative exposure to cannabinoids. The altered cognitive style may indeed be a reason for using cannabis; for the experience of noticing more things (or being distractable). Whatever the reason, clearly for cannabis users and ex-users, unlike controls, the broadening of the attentional spotlight is accompanied by poorer performance.

A further finding corroborated in this experiment was that of possibly greater consequences of long term cannabis use in users of low IQ. Although this may appear to be contrary to Soueif's (1976b) hypothesis that performance decrement is more

marked in the best educated subjects, Soueif's hypothesis was formulated on the basis of comparing illiterate, rural subjects with educated urban dwellers. The subjects of this study were well educated, and those of lower IQ still within the high average range of IQ. This suggests, as argued above, that this finding should be interpreted in terms of the better ability of subjects of superior IQ to compensate for the impairing effects of cannabis on cognitive function.

In summary, the results of this experiment suggest that the long term effects of cannabis on the ability to selectively focus attention and reject irrelevant information may *partially* recover with cessation of use for the majority of users (although, a subset of users appeared to show no recovery of function). There was sufficient evidence from this investigation that the past duration of cannabis use continued to have an adverse effect upon electrophysiology and cognition well after discontinuing use. The length of abstinence had no effect upon electrophysiology or performance, and hence there was no gradual improvement over time. This suggests that partial recovery occurs rapidly following cessation of cannabis use. The relationship between cumulative exposure to cannabis and PN to pitch irrelevant tones is robust. In experiment three, this relationship was interpreted as being suggestive of gradual changes occurring in the brain as a result of prolonged exposure to cannabis. The fairly rapid recovery that is suggested to occur here following cessation of use, raises doubt as to the hypothesis that gradual changes occur in the brain, unless the nature of such changes permits rapid recovery. The mechanisms underlying the relationship between PN to irrelevant information and duration of cannabis use require further investigation.

CHAPTER 10

ANXIETY, PSYCHOPATHOLOGY AND THE QUALITATIVE EXPERIENCE OF LONG TERM USE OF CANNABIS

The cannabis users and ex-users studied in each experiment of this thesis completed a number of questionnaires. These assessed levels of anxiety, symptoms of psychopathology and dependence on cannabis, and provided an opportunity for the self-report of any problems associated with long term cannabis use. A qualitative description of the experience of long term cannabis use was obtained through structured and open ended questionnaires. An example of the questionnaires administered is presented in Appendix B, representing the core set of questions asked of the subjects. For each experiment, these may have been modified slightly. For example, for ex-cannabis users the questions were paraphrased to inquire about past experiences and further questions were added which dealt with the experience of giving up and changes perceived by the ex-user as a result of having given up. These questions will be discussed below.

The inclusion of these assessments was important for two reasons: 1) to exclude the possibility that the ERP findings of this thesis might reflect some psychological differences between users and nonusers rather than being the result of cannabis use, with anxiety and psychopathology judged to be the most likely candidates; and 2) to examine the consistency between self-reported symptoms of dependence, subjective effects and cognitive failure, with the results of assessing cognitive functioning by means of ERP measures of selective attention.

This chapter will present the descriptive summaries of the results of all questionnaires administered, provide results of quantitative analyses where appropriate, and discuss the qualitative experience of long term cannabis use. The results from each sample from each experiment will be discussed separately but also combined across studies where appropriate. Correlations between test measures and the ERP results of each study will be presented where appropriate. The ERP measures used in correlational analysis were PN to pitch irrelevant tones measured over 300 to 600 ms at frontal and central sites, and P300 latency measured at the contralateral parietal scalp site. Wherever possible, the results were considered in terms of frequency and duration of cannabis use.

10.1 Anxiety

Many drug using populations have been reported to show higher levels of anxiety than the general population (eg. Grenyer et al, 1992; Meyer, 1986; Ross, Glaser and Germanson, 1988; Rounsaville, 1989; Rounsaville et al, 1991). Also, high anxiety levels are known to influence cognitive test performance in an adverse manner. For example, high levels of anxiety have been shown to reduce both the storage and processing capacity of working memory (Darke, 1988). High anxiety may be reflected in an inability to maintain attentional focus on a particular stimulus or task in the presence of extraneous stimuli. Eysenck (1982; 1988) argued that highly anxious subjects engage in significantly more task-irrelevant processing than their low anxiety counterparts. Task irrelevant thoughts, which are thought to characterise highly test anxious individuals, may be symptomatic of an underlying distractibility to various sources of interference, both internal and external. Therefore, it was considered essential to assess anxiety levels in these cannabis using samples.

The State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch and Lushene, 1970) was selected as the assessment tool since it has been widely used for research purposes, has demonstrated reliability and validity, and provides two measures of anxiety pertinent to the purposes of this assessment. First, it provides a measure of the current state of the individual in terms of the level of transitory anxiety at the time the questionnaire was completed. This enables an assessment of whether subjects may have been anxious as a result of the testing procedure. If it were found that cannabis users' state anxiety was significantly higher than that of controls, it could be conjectured that users were significantly more anxious than controls as a result of the testing procedure and hence may have performed more poorly than controls as a result of this anxiety. Second, a measure of trait anxiety provides an assessment of the general level of background anxiety with which an individual operates in normal life, and their disposition toward being anxiety prone, regardless of the current state of the subject or the testing procedure. This measure enables a comparison of resting levels of anxiety in cannabis using samples versus controls to determine whether users may be generally more anxious than controls. A further measure of trait anxiety, useful for reliability purposes, was provided by the Anxiety subscale of the Symptom Checklist 90-Revised (SCL-90-R) (Deragotis, 1983). Composed of nine subscales, the SCL-90-R was administered as a measure of psychopathology and is discussed further below.

Mean STAI scores for subjects of experiments one, two, three and four are presented in Table 10.1. All scores obtained were comparable to the normative data of undergraduate students (Spielberger, Gorsuch and Lushene, 1970), with the exception perhaps of the control group of experiments one and two whose scores fell within the lower range, at around the 20th percentile for both state and trait measures.

Scores were subjected to an analysis of variance with factors of group and anxiety type (state or trait). For the samples of experiments one and two, there was a significant

Table 10.1 Mean state-trait anxiety scores (and standard deviations) for cannabis users, ex-users and controls.

	N	STATE		TRAIT	
Experiments one and two					
Cannabis users	10	35.20	(7.18)	40.10	(8.37)
Controls	10	27.90	(3.73)	29.60	(6.40)
Experiment three					
Cannabis users overall	32	34.56	(6.48)	36.91	(7.66)
Long term users	16	33.31	(5.45)	38.88	(9.29)
Short term users	16	35.81	(7.32)	34.94	(5.16)
Heavy users	16	37.00	(5.96)	40.44	(7.77)
Light users	16	32.13	(6.21)	33.38	(5.85)
Controls	16	33.94	(9.45)	34.94	(5.27)
Experiment four					
Ex-cannabis users	28	33.54	(6.71)	38.39	(9.53)

main effect of group [$F(1,18) = 12.54$, $p < 0.0023$] and a near significant main effect of anxiety type [$F(1,18) = 4.35$, $p < 0.0515$], but no group by anxiety type interaction [$F(1,18) = 1.02$, $p > 0.32$]. Thus, cannabis users were significantly more anxious than controls on both state and trait levels of anxiety. The near significant main effect of anxiety type indicated that trait levels tended to be higher than state levels for both groups. However, when the groups were analysed separately, state-trait anxiety did not

differ in controls [$F_{(1,9)}$ = 0.52, p > 0.48], but trait levels in cannabis users were significantly higher than their state levels [$F_{(1,9)}$ = 5.36, p < 0.0458]. This indicates that the cannabis users were generally more anxious than controls, but their lower state scores suggest that they were not more anxious than controls as a result of the testing procedure. Due to the relatively small sample size of experiments one and two, any relationships between anxiety and ERP measures were not examined.

The cannabis users of experiment three showed a similar pattern of results to those of experiments one and two, although overall group differences diminished due to the higher scores of the control group. Overall, cannabis users did not differ from controls [$F_{(1,46)}$ = 0.50, p > 0.48], mean levels of state and trait anxiety over both groups did not differ [$F_{(1,46)}$ = 1.75, p > 0.19], and there was no group by anxiety type interaction [$F_{(1,46)}$ = 0.28, p > 0.59]. Similarly groups based on duration of use did not differ overall [$F_{(2,45)}$ = 0.30, p > 0.74] and there was no main effect of anxiety type [$F_{(1,45)}$ = 2.77, p > 0.10], but there was a trend toward a group by anxiety type interaction [$F_{(2,45)}$ = 2.82, p < 0.0702], suggestive of higher trait than state anxiety in both long term users and controls, but nonsignificantly higher state than trait anxiety in short term users. There were no differences between these groups when state and trait anxiety were analysed separately [state: [$F_{(2,45)}$ = 0.47, p > 0.63; trait: [$F_{(2,45)}$ = 1.76, p > 0.18].

A significant group difference emerged when groups were compared on the basis of frequency of use [$F_{(2,45)}$ = 4.98, p < 0.0111]. Group multiple comparisons determined that heavy users had significantly greater anxiety levels overall than both light users [$F_{(1,30)}$ = 13.37, p < 0.0010] and controls [$F_{(1,30)}$ = 4.20, p < 0.0492]. Light users did not differ from controls [$F_{(1,30)}$ = 0.65, p > 0.42]. There was no main effect of anxiety type [$F_{(1,45)}$ = 0.1201] and no group by anxiety type interaction [$F_{(2,45)}$ = 0.42, p > 0.66]. However, analyses of state and trait anxiety separately confirmed that the group differences were significant only for trait anxiety [$F_{(2,45)}$ = 5.39, p <

0.0079], whereas groups did not differ in terms of state anxiety [$F_{(2,45)}$ = 1.79, p > 0.17].

The ex-cannabis users of experiment four were compared to long and short term users and controls of experiment three. The ex-users did not differ from any group on either state or trait anxiety scores [state: ex vs long $F_{(1,43)}$ = 0.01, p > 0.91; ex vs short $F_{(1,43)}$ = 1.10, p > 0.30; ex vs controls $F_{(1,43)}$ = 0.03, p > 0.87; trait: ex vs long $F_{(1,43)}$ = 0.03, p > 0.87; ex vs short $F_{(1,43)}$ = 1.79, p > 0.18; ex vs controls $F_{(1,30)}$ = 1.78, p > 0.18].

These results were corroborated by analysis of the anxiety subscale of the SCL-90-R (see below), where heavy users scored significantly higher than both light users [$F_{(1,30)}$ = 8.04, p > 0.0081] and controls [$F_{(1,30)}$ = 5.56, p < 0.0251], and light users did not differ from controls [$F_{(1,30)}$ = 0.48, p >0.49]. Overall, cannabis users did not score significantly higher than controls [$F_{(1,46)}$ = 1.09, p > 0.30] and groups did not differ on the basis of duration of use [$F_{(2,45)}$ = 0.70, p > 0.50].

Correlational analyses found no relationship to exist between duration of cannabis use in the current users of experiment three and either state (r = -0.12) or trait anxiety (r = -0.12) as measured by the STAI. Similarly, past duration of cannabis use in the ex-user sample did not correlate with state (r = -0.22) or trait anxiety (r = -0.145). However, as might be expected on the basis of the results reported above, the frequency of cannabis use in current users was significantly related to trait anxiety (r = 0.44, p < 0.01), but not state anxiety (r = 0.29). A similar relationship was evident in the sample of ex-users (trait: r = 0.31, p < 0.05; state: r = 0.17). Interestingly, while state and trait anxiety were highly correlated in the control group (r = 0.78, p < 0.0001) and in the ex-user group (r = 0.55, p < 0.005), the relationship was nonexistent in current cannabis users (r = 0.19). This finding is difficult to interpret but may reflect either

inconsistencies in self-reported anxiety levels in cannabis users, or a different mode of operation of anxiety in cannabis using populations. The latter hypothesis is given credence by the some of the differential relationships found between anxiety levels and performance measures for cannabis using and nonusing groups, as reported below.

An unexpected finding was that both measures of anxiety were inversely related to PN to pitch irrelevant tones in the control group (state: $r = -0.56$, $p < 0.005$; trait: $r = -0.49$, $p < 0.01$). Thus, PN to pitch irrelevant tones was smaller with higher levels of anxiety. This finding suggests that increased anxiety may have actually improved the ability to focus attention by tuning in to the relevant stimuli and rejecting irrelevant stimuli more efficiently. This is contrary to Eysenck's hypothesis that highly anxious subjects engage in significantly more task-irrelevant processing, however, it may be that there is an optimum level of anxiety which boosts performance, beyond which performance deteriorates. That is, it is reasonable to assume that a certain amount of anxiety generated by motivation to do well on any given task and not reflect badly upon the self, would be useful and advantageous as opposed to a lack of concern with ones performance (similar to the Yerkes-Dodson law). If anxiety levels were to exceed these hypothetical optimal levels, this might result in significant processing of task-irrelevant thoughts and stimuli. There is no reason to suspect that the levels of anxiety measured in any group of this series of studies was excessive and as such would not be expected to affect their performance. Thus, the finding of large PN to pitch irrelevant tones in long term cannabis users cannot be explained by increased anxiety levels. In fact, users also showed a marginally significant inverse relationship between PN to pitch irrelevant tones and state anxiety ($r = -0.33$, $p < 0.05$) but no relationship with trait anxiety ($r = 0.02$), and PN in ex-users showed no relationship with either state ($r = -0.21$) or trait ($r = -0.05$) levels of anxiety. The reduced PN to pitch relevant tones in the ex-users could not be explained by anxiety levels either as there was no relationship with either state ($r = 0.17$) or trait ($r = 0.16$) anxiety.

P300 latency, which increased as a function of frequency of cannabis use in current users, was also found not to be significantly related to levels of state anxiety ($r = 0.10$), and a nonsignificant trend toward longer latency P300 with greater trait anxiety ($r = 0.25$) disappeared after controlling for the effect of frequency of cannabis use ($r = 0.06$). In controls there was a trend toward a reduction in P300 latency with increasing levels of state anxiety ($r = -0.34$, $p > 0.05$) but no relationship with trait anxiety ($r = 0.02$). P300 amplitude did not vary as a function of anxiety in any group (range $r = -0.23$ to 0.12).

Reaction time in the current cannabis users increased as a function of state anxiety ($r = 0.40$, $p < 0.05$) but not trait anxiety ($r = 0.26$), whereas for ex-users and controls there were trends in the opposite direction (ex: state $r = -0.23$, trait $r = -0.21$; controls: $r = -0.26$, trait $r = -0.35$). There was no relationship between anxiety and number of correct detections in the cannabis users (state: $r = 0.01$; trait: $r = -0.16$) or ex-users (state: $r = 0.04$; trait: $r = -0.16$), although for controls there was a trend toward poorer performance with increasing anxiety (state: $r = -0.32$; trait: $r = -0.31$). The most striking difference between groups was in the relationship between anxiety and the number of errors of commission (false alarms). Neither state nor trait anxiety correlated with false alarm rate in the cannabis users (state: $r = 0.08$; trait: $r = -0.01$) or ex-users (state: $r = 0.04$; trait: $r = -0.07$), but in controls the number of false alarms increased dramatically as a function of state anxiety ($r = 0.76$, $p < 0.0001$), and to a lesser degree with trait anxiety ($r = 0.58$, $p < 0.01$). These results suggest that anxiety may operate in different ways in cannabis users and controls. Nevertheless, the finding that the false alarm rate is correlated with state anxiety in controls but not in ex-users or current users lends credence to the ERP interpretation that there is a carry-over effect of long term past use of cannabis.

The results of these investigations suggest that cannabis users were not more anxious than controls as a result of the testing procedure. Therefore, the differences found between groups on measures of test performance and efficiency of information processing, are more likely to reflect the effects of long term cannabis use and not be due

to higher levels of anxiety in the cannabis users. However, the results do suggest that cannabis users may have generally higher resting levels of trait anxiety than controls, particularly if they are frequent or heavy users of cannabis. It is possible that individuals with high anxiety choose to use cannabis to "self-medicate". The other possibility is that heavy cannabis use might lead to the development of greater anxiety; to what extent this may occur is difficult to determine without prospective studies. Some support for this hypothesis was provided by the ex-cannabis users' descriptions of increasing paranoia and anxiety with prolonged heavy use, as prime factors for ceasing cannabis use (see below).

10.2 Psychopathology

Many studies have also established that drug using populations show significantly more signs and symptoms of psychopathology than seen in the general population (eg. Anthony and Helzer, 1991; Darke et al, 1992; Meyer, 1986; Ross, Glaser and Germanson, 1988; Rounsaville, 1989; Rounsaville et al, 1991; Swift et al, 1990). There has been extensive debate over the possible causal significance of this psychopathology: does an underlying psychopathology induce a person to seek out and use drugs, either as an attempt to self-medicate the symptoms of the pathology, or is drug use itself a symptom? Some claim there is sufficient evidence that cannabis use is causal in the development of psychotic disorders. Hall, Solowij and Lemon (in press) reviewed the literature pertinent to this issue and found little support for the hypothesis that cannabis use can cause either an acute or a chronic functional psychosis which persists beyond the period of intoxication. There is suggestive evidence that heavy use may produce an acute toxic psychosis and that long term use may precipitate a latent psychosis in vulnerable individuals, but the estimated attributable risk is small. Others have argued

that drug use is merely an expression of deviance without any negative connotation, and that deviant persons are more likely to show deviant scores in measures of psychiatric symptomatology (eg. Mugford and Cohen, 1989). Regardless of the true causality, psychopathology was considered worthy of investigation, and given that various psychiatric groups are known to have different ERP signatures to the normal population, it was deemed essential to determine the relationship between cannabis use, psychopathology and the ERP effects found in this course of study.

The Symptom Checklist 90-R (SCL-90-R) (Derogatis, 1983) was selected to assess psychopathology in cannabis users and controls in the studies reported here. This is a 90 item checklist of symptoms that the subject rates on a five point scale ranging from "not at all" (0) to "extremely" (4), to indicate the level of distress caused by each symptom within the past week. The 90 symptoms are subdivided into nine categories of primary symptom dimensions: 1) Somatization; 2) Obsessive-Compulsiveness; 3) Interpersonal Sensitivity; 4) Depression; 5) Anxiety; 6) Hostility; 7) Phobic Anxiety; 8) Paranoid Ideation; 9) Psychoticism. In addition, three global measures of psychopathology indexing distress are calculated: the Global Symptom Index (GSI), the Positive Symptom Distress Index (PSDI) and the Positive Symptom Total (PST). The GSI is the mean value of all 90 raw scores, the PSDI is the average value of all items scored from 1 to 4, and the PST is the total number of items scored between 1 and 4. Although there have been numerous studies that demonstrate adequate reliability and validity for the SCL-90-R, there has been criticism that the subscales are not well differentiated and that its primary value may be as a measure of global symptomatology (Riskind et al, 1987). The test manual itself recommends the GSI as the most meaningful overall measure of global symptom distress (Derogatis, 1983). It states that the GSI is the single best indicator of depth of disorder or psychopathological distress, as it combines information on the number of symptoms and the intensity of perceived distress.

Mean scores for cannabis users, ex-users and controls of experiments three and four are presented in Table 10.2. When cannabis users overall were compared with controls, they differed significantly only on one subscale, that of hostility [$F(1,46)$ = 4.77, $p < 0.0341$], with cannabis users scoring significantly higher than controls. There were trends toward higher scores in cannabis users on a number of other subscales: Paranoid Ideation [$F(1,46)$ = 3.58, $p < 0.0646$], Phobic Anxiety [$F(1,46)$ = 2.89, $p < 0.0957$], and Psychoticism [$F(1,46)$ = 2.86, $p < 0.0975$]. Cannabis users had a significantly greater Positive Symptom Total (PST) than controls [$F(1,46)$ = 5.13, $p < 0.0283$], indicating that users reported experiencing distress on a greater number of symptoms overall than did controls. There were trends toward a higher total score [$F(1,46)$ = 3.18, $p < 0.0811$], and a higher Global Severity Index (GSI) [$F(1,46)$ = 3.20, $p < 0.0803$] in cannabis users than in controls. The normative data provided in the test manual gave a score of 0.31 (SD = 0.31) on the GSI for an adult population, or 0.76 (SD = 0.54) for adolescents. It is clear that the sample of controls of the studies reported in this thesis were very close to the normal adult GSI score, whereas cannabis users scores fell between the scores for adults and adolescents. This may be a reflection of delayed maturation in the cannabis users.

When groups were compared on the basis of duration or frequency of cannabis use, there were few differences between long term users, short term users and controls, but heavy frequency use resulted in higher scores on many subscales and global measures of distress. Comparison of heavy users, light users and controls resulted in significant group differences on the following measures: Total score [$F(2,45)$ = 5.95, $p < 0.0051$], Depression [$F(2,45)$= 4.36, $p < 0.0186$], Anxiety [$F(2,45)$ = 5.43, $p < 0.0077$], Hostility [$F(2,45)$ = 7.08, $p < 0.0021$], Psychoticism [$F(2,45)$ = 4.33, $p < 0.0191$], GSI [$F(2,45)$ = 5.96, $p < 0.0051$], and PST [$F(2,45)$ = 5.87, $p < 0.0054$].

Table 10.2. Mean scores (and standard deviations) from subscales of the SCL-90-R for cannabis users, ex-users and controls.

	Cannabis users overall	Long term users	Short term users	Heavy users	Light users	Ex-cannabis users	Controls
TOTAL	48.06	47.38	48.75	63.00	33.13	58.29	30.75
	(33.49)	*(38.32)*	*(29.12)*	*(38.06)*	*(19.83)*	*(38.46)*	*(27.64)*
SOM	0.457	0.376	0.537	0.527	0.386	0.476	0.444
	(0.396)	*(0.225)*	*(0.509)*	*(0.512)*	*(0.227)*	*(0.432)*	*(0.577)*
O-C	0.753	0.688	0.819	0.906	0.600	1.018	0.563
	(0.483)	*(0.429)*	*(0.538)*	*(0.537)*	*(0.380)*	*(0.653)*	*(0.486)*
IPS	0.732	0.826	0.639	0.916	0.548	0.845	0.443
	(0.624)	*(0.818)*	*(0.340)*	*(0.777)*	*(0.358)*	*(0.555)*	*(0.569)*
DEP	0.646	0.678	0.614	0.875	0.418	0.767	0.428
	(0.646)	*(0.714)*	*(0.369)*	*(0.675)*	*(0.284)*	*(0.565)*	*(0.464)*
ANX	0.378	0.344	0.413	0.550	0.206	0.582	0.269
	(0.380)	*(0.403)*	*(0.365)*	*(0.408)*	*(0.262)*	*(0.640)*	*(0.247)*
HOS	0.594	0.636	0.552	0.833	0.355	0.530	0.261
	(0.566)	*(0.667)*	*(0.462)*	*(0.650)*	*(0.343)*	*(0.499)*	*(0.311)*
PHOB	0.218	0.231	0.204	0.303	0.133	0.260	0.053
	(0.372)	*(0.442)*	*(0.299)*	*(0.448)*	*(0.263)*	*(0.383)*	*(0.146)*
PAR	0.558	0.501	0.614	0.667	0.448	0.691	0.271
	(0.527)	*(0.533)*	*(0.532)*	*(0.640)*	*(0.374)*	*(0.517)*	*(0.416)*
PSY	0.381	0.388	0.375	0.544	0.219	0.432	0.169
	(0.453)	*(0.480)*	*(0.440)*	*(0.462)*	*(0.394)*	*(0.477)*	*(0.303)*
GSI	0.535	0.526	0.543	0.701	0.369	0.647	0.342
	(0.372)	*(0.426)*	*(0.323)*	*(0.422)*	*(0.222)*	*(0.428)*	*(0.307)*
PSDI	1.458	1.449	1.468	1.579	1.337	1.487	1.363
	(0.332)	*(0.378)*	*(0.290)*	*(0.334)*	*(0.290)*	*(0.359)*	*(0.393)*
PST	31.00	29.69	32.31	37.44	24.56	36.11	20.19
	(16.25)	*(16.44)*	*(16.49)*	*(16.73)*	*(13.33)*	*(19.44)*	*(14.13)*

TOT = Total score; SOM = Somatization; O-C = Obsessive-Compulsiveness; IPS = Interpersonal Sensitivity; DEP = Depression; ANX = Anxiety; HOS = Hostility; PHOB = Phobic Anxiety; PAR = Paranoid Ideation; PSY = Psychoticism; GSI = Global Symptom Index; PSDI = Positive Symptom Distress Index; PST = Positive Symptom Total.

Group multiple comparisons indicated that for every measure above, heavy users scored significantly higher than light users and controls, while the latter two groups did not differ. Trends toward greater distress reported by heavy cannabis users were also apparent for Obsessive-Compulsiveness [$F(2,45) = 2.55$, $p < 0.0890$], Interpersonal Sensitivity [$F(2,45) = 2.81$, $p < 0.0710$], Phobic Anxiety [$F(2,45) = 2.67$, $p < 0.0801$], Paranoid Ideation [$F(2,45) = 2.61$, $p < 0.0846$] and on the global measure of PSDI [$F(2,45) = 2.43$, $p < 0.0992$]. Thus, the subscale of Somatization was the only measure where there was no tendency toward an effect of frequency of cannabis use. The only indication of some effect due to duration of use appeared as trends toward group differences for Hostility [$F(2,45) = 2.46$, $p < 0.0972$] and the PST [$F(2,45) = 2.63$, $p < 0.0829$].

The cannabis users of experiments one and two showed similar results to the heavy users of experiment three. They differed significantly (or marginally) from their nonuser controls on every measure except Somatization. The control group of experiments one and two, however, may have been somewhat atypical: not only did they fall within a low percentile with their STAI scores (as reported above), but their SCL-90-R scores were lower than those of the control group of experiment three. Caution must be observed when analysing and interpreting data from small samples. For this reason, correlational analyses between SCL-90-R scores and ERP and performance measures were not conducted for experiments one and two.

Ex-cannabis users did not differ significantly from long term or short term current cannabis users on any measure from the SCL-90-R. There was a trend toward higher scores for ex-users than long term users on Obsessive-Compulsiveness [$F(1,42) = 3.27$, $p < 0.0776$]. In contrast, when ex-users were compared with controls, they differed significantly (or near to significantly) on every measure except Somatization and the

PSDI: Total score [F(1,42) = 6.31, p < 0.0160], Obsessive-Compulsiveness [F(1,42) = 5.90, p < 0.0195], Interpersonal Sensitivity [F(1,42) = 5.24, p < 0.0271], Depression [F(1,42) = 4.14, p < 0.0481], Anxiety [F(1,42) = 3.51, p < 0.0681], Hostility [F(1,42) = 3.78, p < 0.0585], Phobic Anxiety [F(1,42) = 4.29, p < 0.0445], Paranoid Ideation [F(1,42) = 7.67, p < 0.0083], Psychoticism [F(1,42) = 3.95, p < 0.0535], GSI [F(1,42) = 6.26, p < 0.0163], and PST [F(1,42) = 8.21, p < 0.0065].

The higher scores for ex-users compared to controls may be interpreted in a number of ways. It is possible that their long term use of cannabis resulted in an increase in the kind of symptoms assessed by the SCL-90-R. Most of the measures on the SCL-90-R appear to be affected by frequency of cannabis use and the ex-user group had used cannabis heavily in the past. While current heavy users scored significantly higher on most SCL-90-R measures compared to both light users and controls, frequency of use did not correlate significantly with the GSI in current cannabis users (r = 0.27) nor in ex-users (r = 0.24). Nor did a relationship exist between GSI and duration of cannabis use in current users (r = -0.20) or ex-users (r = -0.15). Nevertheless, it may be that the sample of ex-cannabis users represent those more vulnerable to the harmful effects of cannabis and this is precisely the reason why they ceased their use of cannabis. Another possible interpretation is that the ex-users had used cannabis to self-medicate underlying psychopathological symptoms which have resurfaced since the cessation of use. However, given the self-reports of the ex-users experiences with cannabis, this explanation seems unlikely and also the duration of abstinence in the ex-users did not correlate significantly with the GSI (r = 0.22).

PN to pitch irrelevant tones was unrelated to the GSI in any group (current users: r = -0.19; ex-users r = -0.05; controls r = -0.09). P300 latency did not vary as a function of GSI in current cannabis users (r = -0.05) or ex-users (r = 0.29), although a striking

inverse relationship was found to exist in the control group (r = -0.73, p < 0.001).

Thus, in controls only, it appeared that the greater the global symptoms of distress, the

earlier P300 occurred. This was initially considered puzzling, possibly reflecting a

spurious association due to small sample size (N =15 controls for this analysis).

However, a search of the literature on P300 latency and psychiatric symptomatology

found one recent report of shorter latency P300 in obsessive compulsive patients (Towey

et al, 1990), which was suggested to be the result of hyperactive perceptual systems.

The nonuser controls studied here scored more highly on obsessive-compulsiveness than

the normative sample published in the test manual (mean 0.39, SD = 0.45). In fact, the

controls scored higher on obsessive-compulsiveness than on any other subscale, but in

most instances so did the cannabis user groups. This suggests that once again there are

underlying differences in the *modus operandi* of cannabis users and controls.

In the current cannabis user group, the relationship between their frequency of

cannabis use and P300 latency (r = 0.50) was only strengthened by removing any effects

of GSI (r = 0.69). GSI was unrelated to any of the performance measures from

cannabis users (RT: r = 0.11; hit rate: r = -0.12; false alarm rate: r = 0.15), whereas in

controls there were nonsignificant trends toward a lower hit rate (r = -0.43, p > 0.09)

and greater false alarm rate (r = 0.35) with increasing GSI, but no relationship with

reaction time (r = -0.20).

10.3 Cannabis dependence

The Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) (American

Psychiatric Association, 1987) defines cannabis dependence as daily or almost daily use

of the substance, while cannabis abuse is defined as episodic use with evidence of

maladaptive behaviour, such as driving whilst intoxicated. Both develop over a
substantial period of time with repeated use; typically it is the frequency of use that
increases over time, rather than the absolute amount, often with concomitant loss of
pleasurable effects and an increase in dysphoric effects. It is stated that impairment in
social and occupational functioning, and the development of physical disorders, are less
than those typically seen with other psychoactive substances. By these criteria, most of
the cannabis users participating in the studies reported here could be labelled "cannabis
dependent" or "cannabis abusers".

Despite these DSM-III-R definitions, there has been debate over the years about
the existence of a dependence syndrome, with claims that the concept remains poorly
defined and its existence questionable. Hall, Solowij and Lemon (in press) reviewed the
literature pertaining to evidence for the existence of cannabis dependence and concluded
that the syndrome as defined by DSM-III-R probably does exist in chronic heavy users
and that the general diagnostic criteria for psychoactive substance abuse disorders
provided by DSM-III-R are probably appropriate. Nevertheless, unlike alcohol and
other drugs such as opiates, for which many scales and assessment tools for dependence
have been formulated, there is no internationally accepted measure of dependence on
cannabis. One scale developed by Hannifin (1987), named the Cannabis Abuse Severity
Screening Test (CASST), was piloted but has not been widely applied. As a short scale
consisting of eleven yes/no questions each worth one point (see Appendix B), this
provided for the purposes of this study an assessment of "cannabis dependence" that
was quick to administer, with a maximum score of 11. The questions were paraphrased
retrospectively for the ex-users of experiment four. The CASST was only added to the
experimental protocol for experiments three and four. Hence, no data is available for the
small sample of cannabis users of experiments one and two, although six of the ten users
claimed to have felt dependent on cannabis.

Mean scores on the CASST for each of the cannabis using groups of experiment three and the ex-users of experiment four are presented in Table 10.3. The ex-users scored significantly higher than either the current long term [$F(1,42) = 4.55$, $p < 0.0388$] or short term users [$F(1,42) = 12.69$, $p < 0.0009$]. Ex-users did not differ from current heavy users [$F(1,42) = 1.93$, $p > 0.17$] but scored significantly higher than light users [$F(1,42) = 19.45$, $p > 0.0001$]. Of the current user groups, long term users did not differ from short term users [$F(1,30) = 1.24$, $p > 0.27$] and heavy users scored significantly higher than light users [$F(1,30) = 9.56$, $p < 0.0043$].

Table 10.3 Mean "cannabis dependence" scores (and standard deviations) from the CASST for cannabis user groups and ex-users.

Long term users	Short term users	Heavy users	Light users	Ex-users
4.44	3.50	5.13	2.81	6.14
(2.63)	(2.10)	(2.00)	(2.23)	(2.51)

These results reinforce the concept of cannabis dependence, as measured by the CASST, as being related to frequency of use. This was supported also by a significant correlation between CASST scores and frequency of cannabis use ($r = 0.51$, $p < 0.005$) in the current user group, whereas there was no relationship between CASST score and duration of cannabis use ($r = -0.21$). Interestingly, CASST scores did not correlate with monthly alcohol consumption ($r = 0.02$), suggesting a dissociation between dependence on alcohol and cannabis. However, caution with such interpretations is warranted since eight of the eleven questions of the CASST are specific to cannabis, and also it is not well established that the CASST is indeed measuring "dependence". Only two questions

specifically address frequency of use, whereas the other items address possible problems associated with cannabis use.

The CASST did not correlate with past reported frequency of use in the ex-user group (r = 0.10), but tended toward a stronger inverse relationship with their past duration of use (r = -0.27). It is possible that ex-users overreport symptoms of dependence as a justification for giving up and as a source of motivation to remain abstinent and not give in to their perceived "addiction". Similarly, current long term users may be less likely to report symptoms of dependence, perhaps to justify their continued use of the drug, than those who have successfully given up.

Perhaps for the ex-users, the perception of cannabis related problems was unrelated to their frequency of use, but was related to use in general. Thus, for many ex-users the idea of cutting down was not feasible, and they saw a "cold turkey" approach as the only way of succeeding in "beating the addiction". Indeed, one ex-user reported regular weekly attendance at both Narcotics Anonymous and Alcoholics Anonymous meetings since his cessation of cannabis use two years ago. This particular subject claimed never to have used any other drugs on a regular basis, nor to have ever had a problem with his alcohol consumption. He complained of feeling embarrassed at the meetings if others found out that his problem drug was cannabis and not narcotics or alcohol, and tried to conceal this fact whenever possible. He lamented the lack of support groups for "cannabis dependent" individuals and had felt a need himself to resort to the above organisations for assistance. This came in the way of constant reinforcement of the notion of addiction, which for him was a method of justifying and coping with abstinence.

Ex-users' self-reports of dependence and definitions of the concept of dependence, have already been discussed in Chapter 9 (60% of the sample claimed to have felt

dependent on cannabis). The remaining 40% of the sample of ex-users denied ever having felt dependent on cannabis, but nevertheless scored between 3 - 9 on the CASST with a mean score of 5.17. In the sample of current users of experiment three, the figures were reversed, with 40% reported having felt dependent and 60% claiming never to have felt dependent. The CASST scores of the latter group were lower than in the ex-users who had denied feeling dependent, ranging from 0 - 6 with a mean of 2.84. Some clarified this denial of dependence by stating that they had experienced a strong desire to smoke cannabis, but not a need to. Some said they had felt strong cravings but would not label this as dependence, whereas for others the experience of strong cravings or even just the frequent desire to get "high" defined the concept of dependence. Dependence was seen as primarily emotional and psychological, not physical, with descriptions of cannabis being an integral part of daily life, a crutch used to assist in the completion of routine activities, a habitual cure for boredom and stress, an escape from depression. A number of subjects described dependence on the ritualistic cues associated with the actual smoking of cannabis, and the enormous amounts of time and energy involved in going out to "score" and the feelings of stress and "hanging out" (strong craving) when unable to obtain any cannabis.

Withdrawal symptoms were described by 14 of the ex-cannabis users, the remainder claiming not to have experienced any, or reporting that these could be minimised by gradual cutting down as opposed to sudden "cold turkey" cessation of use. The types of symptoms experienced included both physical and psychological effects: headaches, insomnia, palpitations, flushes, tingles and shakiness, weight loss, sweating, tension, depression, nightmares and strong cravings. Most reported that these symptoms diminished within a few weeks of cessation of use.

Correlational analyses between CASST scores and performance measures on the selective attention task found marginally significant longer reaction times and a smaller

number of correct detections as a function of CASST score in the ex-cannabis user group (RT: r = 0.34; hit rate: r = -0.32, p = 0.05), but these effects were not apparent in current users (RT: r = 0.11; hit rate: r = -0.13). Errors of commission did not correlate with CASST score in either sample (current users: r = 0.19; ex-users: r = 0.21). CASST scores were unrelated to PN to pitch irrelevant tones in current users (r = 0.03) or ex-users (r = -0.02), and no relationship was apparent with P300 latency (users: r = 0.03; ex-users: r = 0.11). None of these relationships were altered by controlling for the effects of frequency of cannabis use.

10.4. Cognitive failures ?

The Cognitive Failures Questionnaire (CFQ) was developed by Broadbent (et al, 1982) in the hope of providing a scale sensitive to mild cognitive dysfunction and in particular as an index of everyday absent-mindedness and failures of attention. The scale consists of 25 questions about minor mistakes in everyday functioning, for which subjects indicate frequency of occurrence on a five point scale: very often, quite often, occasionally, very rarely, never. Examples of the types of questions in the scale include: Do you read something and find you haven't been thinking about it and must read it again?; Do you fail to notice signposts on the road?; Do you forget why you went from one part of the house to the other? Do you start doing one thing at home and get distracted into doing something else (unintentionally)?. While these minor "cognitive failures" are experienced by us all from time to time, clinical and anecdotal evidence suggests that cannabis users seem to complain of their occurrence more frequently. It is often such complaints that incline users to believe that their memory is impaired (see section 10.5 below).

Although the CFQ has not been widely applied in research, it was considered

worthy of including in this investigation for a number of reasons aside from the frequency of self-report in cannabis users. On the surface, the minor mistakes appear to reflect problems with both memory and attention, the two most frequently reported cognitive deficits associated with cannabis use (see Chapter 5). However, the questionnaire is thought to specifically provide a measure of everyday failures of selective attention, since scores do not predict performance on memory tasks, but are thought to predict the efficiency of selective attention (Broadbent et al, 1982). One explanation for cognitive failures is that they occur when processing requirements exceed the amount of general processing capacity postulated to be available. Broadbent, Broadbent and Jones (1986) demonstrated that subjects with low CFQ scores were less susceptible to interference and showed more efficient selection of targets. Tipper and Baylis (1987) investigated individual differences in selective attention and found that high CFQ scorers had longer reaction times to targets in the presence of distractors. Only the more efficient selectors, those scoring low on the CFQ, also showed an enhanced ability to inhibit distractors in another experiment, showing strong evidence of negative priming. The questionnaire has not been administered to cannabis users. From the ERP results of this series of studies, which indicated a difficulty in inhibiting irrelevant information in long term cannabis users, together with previous reports of attentional problems, distractibility and intrusion errors, it was hypothesised that cannabis users would score more highly on the CFQ than controls. The relationships between CFQ scores, cannabis use and ERP measures were also examined.

Mean CFQ scores are depicted in Table 10.4. Cannabis users of experiments one and two did not differ from their control group [$F(1,18) = 0.22$, $p > 0.64$]. The remainder of this section will focus on users and controls of experiment three, and the ex-users of experiment four. Data was missing from six current cannabis users of experiment three: 4 long term users (2 heavy and 2 light) and 2 short term users (one each heavy and light). Cannabis users did not differ from controls overall [$F(1,40) =$

0.82, p > 0.37] and groups did not differ on the basis of duration of use [F(2,39) =

1.14, p > 0.32]. There was a marginally significant effect of frequency of use [F(2,39)

= 3.14, p < 0.0544] and group multiple comparisons revealed heavy cannabis users to

score significantly higher than light users [F(1,24) = 9.36, p < 0.0054], with a trend

toward higher scores than controls [F(1,27) = 3.18, p > 0.08] and no difference

between light users and controls [F(1,27) = 0.15, p > 0.70]. Ex-users did not differ

from controls [F(1,42) = 0.28, p > 0.60], nor from current long [F(1,38) = 0.19, p >

0.66] or short term users [F(1,30) = 0.60, p> 0.44].

Table 10.4 Mean CFQ scores (and standard deviations) for cannabis users, ex-users and controls.

Experiments one and two

Cannabis users	Controls
37.50	35.30
(13.20)	(6.70)

Experiments three and four

Cannabis users overall	Long term users	Short term users	Heavy users	Light users	Ex-cannabis users	Controls
39.12	36.42	41.23	43.69	34.54	38.29	36.06
(8.81)	(7.99)	(9.10)	(9.05)	(5.87)	(13.69)	(13.07)

Correlational analyses showed CFQ scores to be significantly related to frequency

of cannabis use in the current users (r = 0.50, p < 0.005), but not in the ex-users (r = -0.10). There was a trend toward an inverse relationship between CFQ and duration of use in current users (r = -0.31), with a weaker trend in the same direction in ex-users (r = -0.20). The lack of a relationship with past frequency of use in ex-users is not surprising since any effect due to frequency of use would not be expected to endure with abstinence from the drug, as opposed to effects due to cumulative exposure to cannabis which may linger well beyond the period of active cannabis use (as discussed in Chapter 8). The trend toward a relationship in the unexpected direction between CFQ score and duration of cannabis use, may be explained by the interpretation that those who continue to use cannabis on a long term basis may be those who experience the least cognitive dysfunction associated with their use of cannabis, while those who experience problems discontinue their use earlier (as discussed in Chapter 9). However, given the findings throughout this thesis of poorer inhibition of irrelevant stimuli increasing as a function of duration of cannabis use, CFQ scores, if they indeed reflect mechanisms of selective attention, should have correlated with duration of cannabis use as well. In fact, CFQ scores did not correlate with PN to pitch irrelevant tones in any group (users: r = 0.00; ex-users: r = 0.12; controls: r = -0.21). Nor were there any significant relationships between CFQ scores and P300 latency (users: r = 0.29; ex-users: r = 0.13; controls: r = -0.31).

There was a trend toward a correlation between CFQ score and the percent of false alarms on the selective attention task in the current cannabis user sample of experiment three (r = 0.33, p < 0.09]. No such trend was apparent in the control group (r = 0.19), nor in the ex-users (r = -0.11), and there was no relationship between CFQ score and any other performance measure in any group. Similarly, Broadbent et al (1982), did not find performance in a wide range of cognitive tasks to be associated with levels of cognitive failures.

Martin and Jones (1983) suggested that "there appears to be no evidence that the generation of cognitive failures in everyday life is related to inefficient performance in laboratory tasks that require the focussing of attention upon a single channel of information (as opposed to its distribution over more than one channel)". They went on to say that "cognitive failures are likely to be the consequence not of fluctuations in an otherwise satisfactory level of performance of individual tasks, but rather the consequence of attempting to perform adequately two or more tasks whose joint requirements ... may interact to temporarily exceed the resources available" (p. 187). This implies that the incidence of cognitive failures would be higher when processing is performed in parallel than in a serial manner, and particularly in multiple tasks. As proposed by Kahneman (1973), only if the combined processing demands of the tasks exceed the limited capacity available, is performance on one or the other or both tasks impaired. CFQ scores may therefore correlate with scores on divided attention tasks, but not selective attention tasks. Thus, the failure to detect a relationship between CFQ scores and either PN or duration of cannabis use, may be because the CFQ measures different mechanisms of attention and cognition, or is related more to tasks that exceed resource capacity.

10.5. The qualitative experience of long term cannabis use: effects and problems by self-report

It has often been assumed that because cannabis does not evince a well defined physical dependence and is not lethal, extensive use by adults must by definition be less problematic than that of alcohol and most other drugs (Roffman and George, 1988). Unfortunately, there has been little systematic effort to assess and understand chronic or problematic cannabis use. The literature devoted to the assessment of cannabis users and

the perceived effects of cannabis use has been scant, and there have been no standardized

instruments for research purposes. The questionnaires administered to the cannabis

users studied in this thesis were designed in an attempt to incorporate suggestions for

consistency in the assessment of self-reported problems and effects. Thus, ideas and

items were adapted from Roffman and George's (1988) discussion of cannabis abuse

assessment, Rittenhouse's (1979) pool of questionnaire items developed to tap users

perceptions concerning the effects of marijuana use on their lives, and Huba, Bentler and

Newcomb's (1981) examples of questionnaire items for both positive and negative

marijuana consequences. The final questionnaire items selected are presented in

Appendix B.

The purpose of this assessment was to provide an opportunity for cannabis users

to self-report perceived effects and problems associated with their use. It was hoped to

ascertain to what extent users themselves are aware of the types of cognitive deficits

generally attributed to the chronic use of cannabis (see Chapter 5), and the deficits in

selective attention detected in the research of this thesis.

First of all, why do people like to smoke cannabis ? The most frequent reasons

given by the users across all experiments fell into two categories: therapeutic / self-

medicating reasons (eg. in order to relax, relieve stress or boredom, elevate mood,

escape depression or the reality of the outside world, enhance appetite, help sleep, dispel

aggression, and for its analgesic effects in curing headaches, stomach aches, nausea

etc.); and general pleasurable effects (eg. for fun, mental stimulation, creativity,

enhancement of the senses, enhanced enjoyment of music and films, alteration of

perception and consciousness, sociability). Some noteworthy reasons provided by one

or two subjects were that they like to smoke in order to cure the cravings, to feel normal

again, and because they genuinely like the actual ritual of smoking cannabis.

In response to a short checklist of perceived acute effects of cannabis, 70% of current users reported their ability to relax was enhanced by the use of cannabis (47% of ex-users agreed). Just over two thirds of the sample of users reported enhanced sexual experience under acute intoxication (corroborated by 53% of ex-users). Although many reported using cannabis to enhance creativity and the flow of ideas, one third of the sample reported diminished ability to think clearly under the influence of cannabis (43% of ex-users) and 48% reported variation in the acute effect of cannabis sometimes enhancing, sometimes diminishing the ability to think clearly (50% of ex-users). While many acknowledged an impaired ability to drive a motor vehicle while under the influence of cannabis (47% of users and 50% of ex-users), a substantial proportion believed cannabis to sometimes enhance and sometimes diminish their driving ability (35% of users, 23% of ex-users). The small number of subjects who believed that cannabis consistently improved their driving performance were offset by the small number of subjects who claimed never to drive while under the influence of cannabis.

The things that subjects reported disliking most about cannabis were primarily its cost, its illegal status, the lack of availability, the development of tolerance and cannabis's addictive qualities, the development of paranoia, lethargy, depression and tiredness, loss of motivation, and the detrimental effects on memory, concentration, study and communication. Some subjects claimed there was nothing they disliked about cannabis.

In response to an open ended question about any problems associated with the use of cannabis, memory and in particular short term memory, was the most frequently reported problem, nominated by approximately 50% of the sample. This was closely followed by problems with concentration, and third in order of frequency was a loss of motivation and general lethargy. Depression and paranoia were reported by a small percentage of the samples studied, and a few reported the addictive qualities of cannabis

as problematic. One third of the current user sample claimed never to have experienced any problems associated with their use of cannabis. Some subjects claimed to be aware of problems with memory and concentration during only the acute phase of intoxication. In general, few of the current users believed there to be any persistent adverse effects on cognition, but some were concerned that they themselves may not perceive or be aware of the deficits.

These general results were also apparent in current cannabis users' responses to a checklist of the perceived consequences of use. The percentages reporting impairment on a variety of items in a checklist are presented in Table 10.5, listed in rank order for current users. The item judged by the largest proportion of users and ex-users combined as a long term consequence of cannabis use was that of impaired memory. Interestingly, the abilities to think clearly and concentrate on complex tasks were judged as being impaired by slightly more ex-users than judged memory to be impaired. Thus, the rank order of perceived impairments was slightly different in the ex-cannabis user group, and impairment was perceived by a vastly larger percent of the sample in ex-users compared to current users. Reasons for this have already been discussed with regard to dependence (see section 10.3 above) and it is not surprising that those who choose to cease their use of cannabis would be those who experience greater problems with their use. Otherwise, there would be no good reason to stop.

When cannabis is used regularly over a prolonged period of time, a state of chronic intoxication is believed to develop (Lundqvist and Ericsson, 1991). This state of chronic intoxication is characterised by "cloudy", "foggy" or "muddy" thought processes as described by users themselves. It is likely, therefore, that during such a state of continued use, the user is unable to perceive the long term consequences of his or her use. As argued by Lundqvist (personal communication), this is because the user has

Table 10.5 Percent reporting impairment as a long term consequence of cannabis use and the percent of ex-users reporting improvement following cessation of use.

	Current users	Ex-users	Percent improved
Memory	52	77	70
Physical health	50	53	94
General level of energy	36	70	76
Ability to think clearly	29	80	79
Ability to concentrate on			
complex tasks	26	80	75
Work performance and studies	24	70	95
Ability to cope and solve			
life's problems	21	60	89
Ability to communicate	14	57	88
Relations with employers/seniors	14	43	69
General confidence	14	60	83
General co-ordination	12	40	92
Excitement and enthusiasm			
for life	5	43	54

nothing to compare against, has no drug-free reference point. The "normal" state of being becomes the state of chronic intoxication and hence the user can only contrast the state of being acutely intoxicated with that of being chronically intoxicated, but cannot be aware of the differences between chronic intoxication and drug-free "normality". This

is particularly because the chronic state of intoxication develops gradually over time. According to this hypothesis, when the use of cannabis is stopped and the accumulated cannabinoids given sufficient time to flush out of the body, the ex-user will notice differences between the new drug-free state and the past state of functioning as a cannabis user and will be more aware of the effects that cannabis use was having upon their general state of functioning. Such an explanation is also consistent with the reports of ex-users versus current users in this study.

Clearly, from Table 10.5, the majority of those who reported experiencing long term consequences of cannabis use, also reported an improvement upon cessation of use. Perhaps the area most resilient to improvement was that of excitement and enthusiasm for life, possibly reflecting difficulties with general motivation. While most report improvement on each item, it is nevertheless of concern that some do not. For example, 30% of those who perceived impaired memory function reported that it had not improved following cessation of cannabis use. Similar figures can be seen for concentration, energy levels, clear thinking and relations with seniors.

This thesis established subtle impairments in focussing attention and rejecting irrelevant information as being associated with the long term use of cannabis. It is possible that such specific processes and mechanisms involved in selective attention are not amenable to conscious awareness by users themselves. On the other hand, it is possible as argued above, that current long term users may be unable to perceive such deficits, but ex-users certainly reported difficulties in concentration on complex tasks. The finding that the ability to reject irrelevant information partially resolves upon cessation of use is in accord with the report of 70% of ex-users of an improvement in the general functions associated with performance on such a task. However, it is difficult to ascertain to what extent the recovery is partial, and to what extent the apparent partial recovery may be due to the 30% of subjects who claim not to have improved functioning

after stopping cannabis use.

It is likely that numerous individual differences in response to cannabis lurk beneath the findings of this thesis. A variety of variables were examined to explore possible individual differences. The age at which cannabis was first tried was similar across all samples studied, generally around 15 (SD = 2.3), and the age at which regular use commenced was around 17 (SD = 3.0). It is possible that the younger the age at which cannabis use is commenced, the more severe long term consequences will be experienced. However, neither age first tried nor earliest age of regular use correlated with PN to pitch irrelevant tones (r = 0.02 and r = 0.08 respectively).

The types of cannabis preparation nominated as usually smoked by users were heads and hashish, both far more potent than leaf material. Thus, regular users specifically sought to purchase stronger varieties. On a scale from 0 to 10 representing potency, users rated the strength of what they usually smoked as about 7.5, and on a scale from 0 to 10 representing degree of intoxication, the usual mean level reached was reported to be 6.6. These cannabis users were smoking to this level of intoxication, highly potent forms of cannabis at quantities of between 15 to 300 mg per day, 3 days per week on average. A combination of high potency, large quantity, heavy frequency, long duration use may interact with other factors specific to the individual, and may contribute to the exacerbation of long term adverse consequences. It is beyond the scope of this thesis to examine further possibilities or propose more hypotheses in this regard, but this is an important area for future research.

To summarise the findings of this chapter, there is no reason to suspect that the ERP and performance differences between cannabis users and controls were related to greater levels of anxiety or psychopathology, and the self-reported cognitive consequences of long term use are mostly in accord with those found in this thesis.

CHAPTER 11

GENERAL DISCUSSION AND CONCLUSIONS

11.1 Summary and discussion of the findings of this thesis

The event-related potential studies presented in this thesis have provided evidence for long-lasting functional brain impairment and subtle cognitive deficits in chronic cannabis users in the unintoxicated state. Partial resolution of these impairments was demonstrated following the cessation of cannabis use.

This series of studies was conducted in an attempt to isolate the types of cognitive dysfunction associated with the long term use of cannabis. Specific stages of information processing were examined, with a focus on attentional mechanisms. Miller and Branconnier (1983) noted that many of the observed memory deficits in cannabis users may occur because cannabinoids disinhibit septal-hippocampal inputs to the reticular activating system resulting in failure to habituate to irrelevant stimuli. Accordingly, this thesis assessed the integrity of attentional processes in long term cannabis users using a combination of performance and brain event-related potential measures, which together can provide insight into the nature of attentional dysfunction. Event-related potential (ERP) measures are sensitive markers of covert cognitive processes underlying overt behaviour; the amplitude and latency of various ERP components have been shown to reflect various stages of information processing.

The general protocol for this course of research was to examine the ERP indices of cognitive functioning in a group of cannabis users compared with a group of nonusers performing a complex task of auditory selective attention. In each experiment cannabis users were matched on age, sex and years of education with a group of nonuser controls who had either never used or had limited experience with cannabis. NART scores (Nelson, 1984) were used as an estimate of premorbid IQ, and both IQ and monthly alcohol consumption were used as covariates in the analyses. Strict exclusion criteria were applied to any subjects with a history of head injury, neurological or psychiatric illness, significant or recent use of other drugs, or high levels of alcohol consumption. Subjects were instructed to abstain from cannabis and alcohol for 24 hours prior to testing and two urine samples were analysed to ensure that subjects were not intoxicated at the time of testing.

The first study of this thesis examined a small and heterogeneous group of long term cannabis users, who had used cannabis for approximately 11 years (range 3-20 years) at the level of 5 days per week (range twice/week to daily use). They participated in two experiments. The first examined the ERP response in a simple auditory discrimination "oddball" task. The results showed evidence of electrophysiological and information processing differences between cannabis users and controls: these were suggestive of delayed stimulus evaluation processes, dysfunctional stimulus evaluation strategies, and functional differences in the frontal regions of the brain in cannabis users compared to controls. Manipulation of task difficulty gave credence to the hypothesis that differences between users and controls are more likely to be detected in more complex and demanding tasks.

In the second experiment (and the remainder of the studies in this thesis), subjects completed a complex multidimensional auditory selective attention task in which random sequences of tones varying in location, pitch and duration were delivered through

headphones. They were instructed to attend to a particular ear and pitch, and respond with a button press to the infrequent long duration tones. This procedure enabled an examination of the brain's response to tones when attended and unattended.

Cannabis users performed significantly more poorly than controls, with fewer correct detections, more errors (false alarms) and slightly longer reaction times. Analysis of the ERP measures showed that cannabis users had reduced P300 amplitudes compared to controls, reflecting dysfunction in the allocation of attentional resources and stimulus evaluation strategies. The most striking difference between groups was in the large processing negativity to stimuli of irrelevant pitch seen in cannabis users but not controls, indicative of unnecessary pitch processing by cannabis users and thus an inability to filter out complex irrelevant information. Cannabis users continued to process stimuli of irrelevant pitch, while controls were able to reject this irrelevant information from further processing at an early stage. These results were interpreted as suggesting that long term use of cannabis may impair the ability to efficiently focus attention and reject irrelevant information.

The third experiment replicated and extended these findings with a larger sample of cannabis users and controls, examining the effects of frequency and duration of cannabis use. Thirty two cannabis users recruited from the general community, were split at the median on both frequency (light: ≤ twice/week vs heavy: ≥ 3 times/week) and duration (short: 3-4 years vs long: ≥ 5 years) of cannabis use. Equal numbers of heavy and light cannabis users contributed to the long and short duration user groups and vice versa. The mean number of years of use for the long duration users was about 10, and about 3 years for short duration users (overall range 3 to 28 years). The mean frequency of use was 18 days per month for the heavy group and 6 for the light group (range: once/month to daily use). Subjects were matched to a group of nonuser controls (N=16) and a similar methodology to that of experiment two was employed.

Once again, cannabis users performance was worse than that of controls, with the greatest impairment observed in the heavy user group. The ERP results indicated that different attentional processes were differentially affected by frequency and duration of cannabis use. The long duration user group showed significantly larger processing negativity (PN) to pitch irrelevant stimuli than did short duration users and controls, while the latter two groups did not differ. There were no differences in PN between groups defined on the basis of frequency of cannabis use. A significant correlation between PN and duration of cannabis use indicated that the ability to focus attention and filter out irrelevant information was progressively impaired with the number of years of use, but was unrelated to frequency of use. Frequency of use affected the speed of information processing, reflected in a delay in P300 latency in the heavy user group compared to light users and controls. P300 latency reflects the time taken to evaluate a stimulus. There was a significant correlation between P300 latency and increasing frequency of use, but P300 latency was unaffected by duration of use.

These results were interpreted to reflect different mechanisms of short-lasting and long-lasting action of cannabinoids. The slowing of information processing in the brain, evidenced by a delayed P300 component, was interpreted as a function of a chronic build up of cannabinoids resulting in a state of semi-intoxication where cannabis users may perform as though they are acutely intoxicated even when they are not. Hence as a residual effect, it was hypothesised that the delay would be eliminated by decreasing frequency of use and thus eliminating the build up of cannabinoids from the body. The progressive impairment in focussing attention and rejecting irrelevant information, evidenced by inappropriately large PN to complex irrelevant stimuli and being related to cumulative exposure to cannabis, was interpreted as reflecting long term gradual changes, possibly occurring at the cannabinoid receptor site.

Experiment four assessed the extent of reversibility of the impairment observed as large PN to pitch irrelevant stimuli in experiments two and three, in a sample of long term cannabis users who had ceased using between 3 months and 6 years prior to testing. All had used cannabis for more than 5 years prior to cessation, with a mean duration of past use of 9 years (range 5 to 20 years). This group was compared with the current long and short duration cannabis users and controls of experiment three. It was hypothesised that the excessively large PN to irrelevant stimuli would gradually resolve as a function of prolonged abstinence from cannabis.

The results of this study were complex: there was partial recovery of function but also continual evidence of an effect of past duration of cannabis use. The ex-cannabis users still performed more poorly than controls on the selective attention task and did not differ from current users. PN to pitch irrelevant tones still appeared large in the ex-user group, although ex-users did not differ significantly from controls or short term users, and showed smaller PN than current long term cannabis users. Nevertheless, there was a highly significant relationship between PN to pitch irrelevant tones and the ex-users past duration of cannabis use, of the same order as that found in experiment three with current users. PN did not correlate with the duration of abstinence. These results were interpreted to suggest that large PN to irrelevant information partially resolves soon after the cessation of cannabis use, with no evidence of further improvement with prolonged abstinence. It appears that past cumulative exposure to cannabis continues to affect the processing of irrelevant information, and further there was evidence that the cessation of use may have affected the processing of relevant stimuli as well. A number of hypotheses were proposed to account for this unexpected finding. There was considerable variability in the sample of ex-users; for a portion of the sample there was no resolution of the inappropriately large PN to pitch irrelevant stimuli. These results emphasise the need to explore the possibility that individual differences contribute to an increased susceptibility to cognitive impairment associated with long term cannabis use.

This research provides a substantial advance in terms of rigour of methodology, specificity of assessment techniques and sensitivity of the measures used to investigate cognitive functioning in long term cannabis users. The results provide further evidence of subtle impairments in specific stages of cognitive functioning which are related both to attention, and also to memory function (even though memory function was not directly assessed). These studies have demonstrated the relative insensitivity of performance measures to cannabinoid effects, emphasising the need to use more sensitive measures to examine otherwise inaccessible, covert cognitive processes.

11.2   Discussion of the findings and implications for future research

The demonstration of differential impairments due to frequency and duration of use are important in terms of distinguishing residual from more long-lasting or chronic impairments as a function of long term use of cannabis. However, the mechanisms involved in such differential impairments remain obscure. If a given effect is strongly correlated with cumulative exposure to cannabis, this implies progressive impairment that reflects gradual long term changes in brain function; it is therefore puzzling that such an effect would resolve fairly rapidly upon cessation of use, even if not entirely. This pattern of results suggests that there should be an interaction between frequency and duration of use, yet nowhere in this thesis was such an interaction observed. Effects due to frequency and duration of use were entirely separable. Future research should address these issues and elucidate the mechanisms involved.

Of course, the possibility that the dysfunction in information processing observed here could be due to some factor other than cumulative exposure to cannabis, cannot be eliminated. It is hard to imagine what such a factor might be, since it would have to

correlate highly with duration of cannabis use. The obvious candidate, age, was examined in specific analyses conducted to disentangle the relationship between duration of cannabis use and age. The results indicated that age did not correlate with PN to pitch irrelevant stimuli, although the study with ex-users suggested that recovery of function may occur more readily in younger subjects. Impairments appeared to be greater in cannabis users and ex-users of lower IQ. Since the cut off below which impairments were manifest was a Full Scale IQ of 119-121, the latter finding might indicate that only subjects of high average to superior intelligence are able to compensate for the detrimental effects of long term cannabis use.

Another possible candidate in explaining the results obtained could be personality. It is possible that those who are prone to using cannabis for a prolonged period may possess particular characteristics associated with a different style of information processing. Against this hypothesis is the fact that no personality typologies have been shown to affect ERP components and selective attentional processing in the way demonstrated in long term cannabis users in this thesis. While anxiety and certain aspects of psychopathology may be related to heavy frequency use of cannabis, none of these variables correlated with duration of cannabis use nor with PN to pitch irrelevant tones. Nevertheless, the possibility of differing cognitive styles does exist (Peter Nelson, personal communication). The phenomenological experience of acute intoxication has been shown to vary as a function of personality characteristics (eg. Musty, 1988), and cannabis use has been shown to be significantly associated with psychological distress in highly introspective individuals (Zablocki et al, 1991). Future research might attempt to better characterise such influences.

One psychological variable that was not assessed was motivation. It could be argued that cannabis users may have been less motivated than controls to do well on the selective attention task, and that any differences found between groups could have been

due to these motivational differences. While levels of motivation were not assessed in this course of studies, it is worthy to note that participants were observed to fall into two broad categories. One group of users was of the opinion that they had smoked cannabis for many years and they believed that it had no severe long term consequences. As such, they almost challenged the experimenter to perform whatever test they like and they would "prove" that cannabis had no long term adverse effect. Some participants, particularly those who belonged to the organisation NORML, were actively involved in lobbying for legalisation. The other broad category of participants were those who were genuinely interested in contributing to scientific knowledge regarding their drug of choice, and/or were concerned that their use of cannabis had adversely affected their cognitive functioning. Some hoped that their involvement in this research might provide them with a personal assessment. Not all subjects belonged to one of these categories, but in general terms the categories describe a majority of participants. In each case, the motivating factor to participate in this research was one that suggests both categories of subjects were motivated to do well. It could be argued that even those who were motivated more by payment for subject participation, rather than any personal or political concerns about cannabis, would nevertheless be unlikely to perform in such a way as to jeopardise the future availability of their drug of choice by providing evidence that cannabis may indeed be harmful.

Some might wish to argue that the ERP findings of this thesis do not necessarily indicate a cognitive deficit, merely a difference. This hypothesis is not sustained by the performance data which indicate generally slower reaction times, lower correct hit rates and a greater number of errors of commission in cannabis users and ex-users compared to controls. Thus, the ERP pattern must be interpreted as reflecting a less efficient mode of information processing. Nor is the hypothesis sustained by the fact that the large PN to irrelevant pitch stimuli was partially reversible after abstinence.

As discussed in Chapter 9, it may be that cannabis acts to broaden the attentional "spotlight" to include irrelevant stimuli that share some of the attributes of the relevant attended stimuli (Woods, 1989). Whether it is a direct neurophysiological effect of cannabinoids or whether it reflects the adoption of different strategies in performing the task, influenced by the intoxicating effects of cannabis, is a question for future research. Even if the large PN to pitch irrelevant tones is a consequence of a strategy difference between groups, it is still a less than optimal strategy to use for the cannabis users. The processing of irrelevant information, reflecting perhaps a wider distribution of attentional resources, need not necessarily be disruptive; it does not appear to be detrimental in high IQ nonuser controls. If the large PN to irrelevant pitch stimuli reflects the adoption of the same strategy in both users and controls, it is a strategy which impairs performance in the case of users and ex-users, but not in controls. It is possible also that cannabis use camouflages the relationships between electrophysiological measures and intellectual functioning and personality; this hypothesis would explain the contrasting direction of correlations between ERP measures and the numerous other variables tested throughout this thesis, and particularly in Chapter 10; the direction of the relationships, even when not significant, were consistent between cannabis users and ex-users, but usually in the reverse direction to those found in controls.

There is good theory to support a neurophysiological mechanism for the broadening of the attentional spotlight. Woods (1989) proposed that neurons in higher-order sensory association cortex have large receptive fields and that their selective priming would result in a broad attentional spotlight. Further, he suggested that attentional selection may begin in higher order association cortex and proceed, when necessary to narrow the focus of attention, backward "through a reafferent modulation of lower-order sensory cortex and koniocortex, to modulate neurons with narrower receptive fields" (Woods, 1989, p.202). It is possible that cannabinoid receptors reside along the pathways involved in the narrowing of the attentional spotlight, and that

cumulative exposure to cannabinoids disrupts these mechanisms. These hypotheses are highly speculative, but nevertheless worthy of further research.

The results of this thesis are also in accord with the EEG findings of Struve and colleagues (eg. 1993) and the neuropsychological test results of Leavitt and colleagues (1991; 1992; 1993), discussed in Chapter 5. While the alterations in EEG observed by Struve et al are difficult to interpret, they were nevertheless progressive with the duration of cannabis use, as were the neuropsychological impairments. The interpretation of the ERP data in this thesis is entirely consistent with Leavitt's conclusions from neuropsychological test results that:

1) while basic attentional processes appear to be intact, long term cannabis users are less efficient when performing complex cognitive tasks or attempting to resist distraction;

2) long term users' ability to efficiently process information declines more rapidly under a moderate cognitive load compared with short duration users or controls; and

3) long term users show increased susceptibility to interference, consistent with difficulty in resisting distraction.

Struve's group suggested that the quantitative EEG changes they observed in association with increases in cumulative exposure to cannabis may reflect organic change. In Chapter 8 of this thesis it was suggested that there may be gradual changes occurring in the brain, possibly at the cannabinoid receptor site. The precise nature of such changes is beyond the scope of this thesis, although one mechanism known to occur with long term exposure to a number of drugs is that of receptor down-regulation. Animal research has not demonstrated this phenomenon to be irreversible (see Chapter 4). The results of the study of ex-cannabis users (Chapter 9) lend further support to the hypothesis that any long term changes associated with chronic cannabis use are likely to be reversible, although perhaps not entirely reversible or at least not for everyone.

Rather than proposing a mechanism for gradual changes to occur in the brain (as they may not at all, given the rapid partial recovery suggested by the ex-users' data) , what was proposed instead in Chapter 8 was the involvement of anandamide. Naturally, as an endogenous cannabinoid-like substance in the brain, anandamide would be involved in the interactions between ingested cannabinoids, and the cannabinoid receptors and pathways. But what this thesis proposes is that anandamide may itself play a role in the modulation of attention. As a newly discovered neurotransmitter, there is much speculation about its role in the nervous system.

The distribution of receptors in the brain, as discussed in Chapter 2, provides clues as to the various functions in which anandamide may be involved. It is likely that it plays some role in movement or motor control (Mechoulam, 1993), and as proposed here, in the modulation of attention. The cerebellum in particular, traditionally viewed as being responsible for motor control, has recently been shown to play a role in selective attention, and particularly in switching attention (Akshoomoff and Courchesne, 1992). The globus pallidus and anterior cingulate cortex, both rich in cannabinoid receptors, have been shown to respectively be activated under selective and divided attention (Corbetta et al, 1991). Just as there are times when it is essential to focus attention and concentrate solely on the task at hand, there are other times when it is important to be able to divide attention and monitor a number of sources of information (eg. in the work of flight controllers or in driving a motor vehicle). It is not unreasonable to presume that the switching of attentional requirements may be regulated by neurotransmitter systems, and that anandamide may well perform such a function. It is possible that ingestion of cannabinoids over a long term period displaces or modifies the normal functioning of anandamide, resulting in dysfunction in attentional processes with wider distribution of resources over irrelevant sources of information, as opposed to the selective and focussed attention required in tasks such as that utilised in the course of studies

comprising this thesis.

With increasing evidence that impairments associated with long term use of cannabis may reflect dysfunction of the frontal lobes, further measures of strategy formation, self-monitoring and cognitive flexibility might be included in future research and the data examined in relation to ERP indices of selective attention and to levels of cannabis use. Until such research is conducted, the evidence that attentional processing is progressively impaired as a function of cumulative exposure to cannabis remains convincing, although the mechanism behind such a relationship has not been elucidated.

11.3 Implications for long term cannabis users

It must be emphasised that the findings of this thesis do not imply that cannabis causes "brain damage". There is no evidence in humans that chronic cannabis use leads to structural brain damage. Further, the weight of evidence suggests that the long term use of cannabis does not result in any severe or grossly debilitating impairment of cognitive function. Nonetheless, there is sufficient clinical and experimental evidence, including the findings of this thesis, which suggests that long term use of cannabis leads to cognitive impairments that are more subtle in nature. Impairments appear to be specific to various aspects of attention, memory, and the organization and integration of complex information. While these impairments may be subtle, they could potentially affect functioning in daily life. The evidence suggests that increasing duration of use leads to progressively greater impairment. To what extent such impairment recovers with abstinence is uncertain, although the evidence from this thesis suggests that there is at least partial recovery.

Attention underlies many cognitive functions. The ability to focus attention, ignore

irrelevant stimuli and efficiently process complex information is essential in the execution of many everyday tasks. The consequences of the attentional impairments observed may be apparent in high levels of distractibility, for example when driving, operating complex machinery, learning in the classroom situation, and may interfere with memory function. The typical age range of most intense cannabis use occurs between 15 and 25 years; precisely the age during which educational and intellectual achievements are at their most crucial stage, and emotional and maturational development is coming to fruition.

Use of cannabis 3 times per week or more frequently, probably results in a state of chronic intoxication due to the accumulation of cannabinoids. This would result in a general slowing of information processing with sluggish mental performance in a variety of tasks. Not only would scholastic aptitude be adversely affected by such a state, but also the integration of thoughts and experiences so crucial to personal development may be disrupted. Continued use at or above these levels may lead to the experience of high levels of anxiety, and greater signs and symptoms of psychological distress or overt psychopathological symptomatology, such as paranoid ideation, depression and hostility.

If the use of cannabis is prolonged, for more than three years for example, the user may incur gradual long term changes in brain function. In particular, the ability to focus attention and ignore irrelevant information may be progressively impaired. Some users may become aware of this impairment, primarily in the form of memory problems, others may be aware of general decline in cognitive abilities but unable to specify where the problem lies, while others may be totally unaware of any such impairment. Nevertheless, it is likely that their general level of performance abilities will be below that of their optimum level of functioning.

If the user continues to use cannabis for many years and then decides to cut down or cease using, it is likely that their mental proficiency will improve somewhat, and probably noticeably so, but not entirely. Partial impairment in attentional processes is likely to remain, regardless of the duration of abstinence. However, as with all of the above implications, these predictions are not hard and fast. There clearly are individual differences in response to cannabis; certain individuals may be more predisposed to adverse cognitive consequences and there has been insufficient research devoted to examining such predispositions. The research of this thesis suggests that younger users may be more likely to improve upon abstinence, and users of lower IQ may also be more vulnerable to adverse cognitive consequences.

In general, the message to cannabis users is one of common sense, applicable to almost all substances: experimental use or use in moderation is unlikely to lead to problems in most individuals, but prolonged or excessive use can result in adverse physical, psychological and cognitive consequences. Users should be advised that use of three times per week or more often for even a short period of time, or use of five years or more at the level of even once per month, may each lead to compromised ability to function to their full mental capacity, and could possibly result in lasting impairments. It is important to present such information to the user in an informed and realistic manner to avoid the misperception of yet more sensationalised anti-drug propaganda.

Until better measures have been developed to investigate the subtleties of dysfunction produced by chronic cannabis use, cannabis may be viewed as posing a lower level threat to cognitive function than other psychoactive substances such as alcohol. Nevertheless, the fact remains that in spite of its illegal status, use of cannabis is widespread. We therefore have a continuing responsibility to minimise drug-related harm by identifying potential risks, subtle though they may be, and communicating the necessary information to the community.

11.4   General discussion and conclusion

Previous reviewers have generally concluded that there is insufficient evidence to conclude that cannabis produces any long term cognitive deficits (eg. Wert and Raulin, 1986a; 1986b). This is probably a reasonable conclusion when gross deficits are considered. However, the findings of this thesis, together with other recent, more methodologically rigorous research, provide evidence for complex but subtle cognitive impairments which appear to increase with duration of cannabis use. There is evidence that impairment on some neuropsychological tests may become apparent only after 10 to 15 years of use (Leavitt et al, 1993). But as demonstrated in this thesis, very sensitive measures of brain function are capable of detecting specific impairments after 5 years of use and users of only 3-4 years showed early signs of impairment.

Impairments appear to be specific to higher cognitive functions, which include the organization and integration of complex information involving various mechanisms of attention and memory processes. The similarity between the kinds of subtle impairments associated with long term cannabis use and with frontal lobe dysfunction is becoming more apparent (eg. short term memory deficits, increased susceptibility to interference, lack of impairment on general tests of intelligence or IQ). Frontal lobe function is difficult to measure as indicated by the fact that patients with known frontal lobe lesions do not differ from controls on a variety of neuropsychological tests (Stuss, 1991). Thus, the difficulty of assessing frontal lobe functions is not unique to research into the long term effects of cannabis.

One of the functions of the frontal lobes is the temporal organization of behaviour, a key process in efficient memory function, self-awareness and planning. The frontal

lobe hypothesis of impairments due to long term use of cannabis is consistent with the

altered perception of time demonstrated in cannabis users (eg. Webb et al, 1992; 1993)

and with cerebral blood flow studies which demonstrate greatest alterations in the region

of the frontal lobes (Mathew and Wilson, 1992). The studies reported in this thesis also

found electrophysiological evidence of altered brain functioning in the region of the

frontal lobes. The ability to selectively attend to one source of information while actively

rejecting another is also a function attributed to the frontal lobes. The frontal lobes are

important in organising, manipulating and integrating a variety of information, and in

structuring and segregating events in memory. Further research incorporating better

measures of frontal lobe function in long term cannabis users is clearly indicated.

The equivocal results of previous studies of cognitive functioning in long term

cannabis users appear to be due primarily to poor methodology and insensitive test

measures. Wert and Raulin (1986b) had rejected the possibility that tests used

previously were not sensitive enough to detect impairments, on the grounds that the

same tests had demonstrated impairment in alcoholics and heavy social drinkers.

However, the cognitive deficits produced by chronic alcohol consumption may be very

different to those produced by cannabis. The mechanisms of action of the two

substances are different with cannabis acting on its own specific receptor. As

demonstrated in experiment three, the attentional impairment evidenced by increased PN

to irrelevant stimuli in long term cannabis users was not related to their alcohol

consumption. Thus not only have tests used previously not been sensitive enough, they

have probably not been specific enough to detect impairments peculiar to cannabis.

Furthermore, tests may have been selected inappropriately because they were

previously shown to be affected by acute intoxication, when the consequences of chronic

use may be very different. Block and colleagues (Block, Farinpour and Braverman,

1992; Block and Ghoneim, in press) showed reasonable, albeit imperfect agreement

between acute and chronic effects of cannabis on cognition and the authors emphasized that such effects can be markedly different. The patterns of cognitive deficit associated with long term cannabis use have still not been entirely characterised. A priority for future research would be the identification of mechanisms of impairment with greater specificity, perhaps by making direct comparisons with the acute effects of cannabis and the long term effects of alcohol and a variety of other substances.

The research described in this thesis has aimed at identifying specific cannabis effects by using strict exclusion criteria and matching control groups on numerous variables to ensure that any deficits observed are attributable to cannabis. Nevertheless, interactions between the effects of long term cannabis use concurrently with other substances need to be further explored, particularly since many regular cannabis users also use alcohol and other substances to a greater degree than the rest of the population, and the cumulative effects of polydrug use may be additive. Further, subjects have tended to be excluded if they have had a history of childhood illness, learning disabilities, brain trauma or other neurological or psychiatric illness. The effects of long term cannabis use on such individuals may be worthy of further investigation, especially as evidence suggests that such individuals are more likely to use cannabis (Hall, Solowij and Lemon, 1994).

When comparisons are made between groups of users versus non users, differences may not always reach statistical significance due to large individual variability, particularly when small sample sizes are used. Carlin (1986) proposed that "studies that rely upon analysis of central tendency are likely to overlook impairment by averaging away the differences among subjects who have very different patterns of disability". Individual differences in vulnerability to the acute effects of cannabis are well recognised and are likely to be a factor in determining susceptibility to a variety of cognitive dysfunctions associated with prolonged use of cannabis.

Cognitive deficits may not be an inevitable consequence of cannabis use. The long term effects of cannabis on healthy individuals may differ from those in individuals with co-existing mental illness or pre-existing cognitive impairments. As a clinical example, cannabis may trigger psychotic episodes in those already predisposed to psychiatric disturbances. On the other hand, some individuals appear to function normally even in high ranking professions despite their long term use. To what extent their mental proficiency would improve further if possible subtle cognitive deficits were resolved by discontinuing cannabis use is unknown. Wert and Raulin (1986b) suggested that some individuals may adapt and overcome some forms of cognitive impairment by a process of relearning: "it is well known that a chronic or slow-developing lesion will often be masked by the adaptation of the patient to the deficits produced by the lesion".

There has been very little research designed specifically to identify individual differences, predispositions or susceptibilities to the adverse effects of cannabis. A predisposition may be due to structural, biochemical or psychological factors, or as Wert and Raulin suggested, to lack of the "cerebral reserve that most of us call on when we experience mild cerebral damage", for example, after a night of heavy drinking. They propose that "that functional reserve can mask very real cerebral damage". Wert and Raulin suggested that prospective studies are the ideal way to identify those subjects who show real impairment in functioning by comparing pre- and post- cannabis performance scores. However, even in a retrospective design it is possible to retrospectively compare the characteristics of subjects who show impairment with those who do not, thereby identifying possible risk factors. Insufficient consideration has been given to gender, age, IQ and personality differences in the long term consequences of cannabis use. Gender differences may be important given that such differences have become apparent in differential responses to alcohol.

Virtually all of the studies investigating cognitive functioning in long term cannabis users have been retrospective studies of naturally occurring groups (users vs. nonusers). Although the matching of control groups has become more stringent, and attempts to obtain estimates of premorbid functioning have increased, prospective studies where each subject is used as his/her own control would eliminate the possibility of cannabis users having demonstrated poorer performance before commencing their use of cannabis. A longitudinal study in which several cohorts at risk for drug abuse are followed over time would certainly be an excellent, if expensive, approach to assessing the detrimental effects of long term cannabis use on cognition and behaviour. Recommendations that prospective studies be carried out using measures of greater sensitivity and specificity have been made in almost every review of the topic since the early 1970s. Unfortunately, actual research has been slow to adopt this design and incorporate such measures.

Carlin (1986) has suggested as an alternate approach, namely, that a "meta-analysis" be conducted of the studies to date. Such an analysis would "estimate effect size in order to cumulate research findings across studies", perhaps allowing the apparently conflicting findings of the studies to be a reconciled. The adequacy of control groups, entry criteria, health factors and other possible contaminating variables could be coded and entered into the analysis. He states that "an overall determination can be made of the extent of the relationship between consumption of a substance and measures of impairment which is relatively independent of traditional statistical significance". Such an analysis would be of particular importance if the impact of the drug on neuropsychological function is modest, as is likely to be the case with cannabis. A modest or even small effect size may have major public health implications. To date, no such research has been applied to the cannabis literature, perhaps because of the limited number of studies, and the absence of similar methodology and outcome measures may preclude the application of a meta-analytic approach. Nevertheless, the substantial

advances have been made in recent years justify the continuation of retrospective studies.

Future research should adhere to rigorous methodology. This should include the use of the best available techniques of detecting the presence of cannabinoids in the body to provide greater precision in the investigation of the influence of length of abstinence on performance. This would permit a distinction to be made between those impairments which are residual, and likely to resolve with abstinence over time, from those of a more enduring or chronic nature, which would be associated with the duration of use. The research of this thesis has identified cognitive impairments that are associated with cumulative exposure to cannabis and has demonstrated evidence of partial reversibility of these impairments with cessation of use. It is therefore a priority to investigate further the recovery of function following cessation of cannabis use.

There is clearly a need to examine the time course of improvement in cognitive functioning and its association with the elimination of accumulated cannabinoids from the body. Subjects should be monitored before and for up to 3 months after stopping regular, long term cannabis use. A strong association would provide evidence that cognitive impairments are due to the chronic state of intoxication produced by accumulated cannabinoids. If the association proved to be weak, the possibility of more lasting changes in brain function should be explored further.

The existence of a naturally occurring cannabinoid in the human brain (anandamide) signifies that this substance plays some role in our normal functioning. It has been suggested that anandamide may play a role in movement or motor control (Mechoulam, 1993), or as suggested in this thesis, in the modulation of attention. However, the neurotransmitters and peptides that govern our behaviour are finely balanced and any major surplus or depletion generally results in dysfunction. With long term use of cannabis, prolonged or continual binding to the cannabinoid receptor may

alter its properties. There is a need to elucidate these physiological mechanisms and the interactions between ingested cannabis, anandamide and the cannabinoid receptor.

The parameters of drug use require careful scrutiny in terms of evaluating how much cannabis must be smoked and for how long before impairments are manifest in what kinds of individuals. One of the problems in assessing the cannabis literature is the arbitrariness with which various groups of users have been described as "heavy", "moderate" or "light", "long term", or "short term". Is a light user someone who uses once, twice or ten times per month? Is a heavy user one who uses daily or at least 10 times per day?

The use of very sensitive measures of cognitive function, such as event-related potential measures, is important for the detection of early signs of impairment which may permit a harm minimisation approach to be applied to cannabis use. With further research, it may be possible to specify levels of cannabis use that are "safe", "hazardous" and "harmful" levels from the perspective of cognitive impairment. These could be used in health education in the same way similar guidelines have been used in advising people about safe levels of alcohol consumption.

Given the growing prevalence of cannabis use, and proposals to reduce legal restrictions on cannabis use, it is essential that research into cognitive functioning of long term cannabis users continues. According to American survey data (Deahl, 1991), more than 29 million people in the United States may be using cannabis, and more than 7 million of these use on a daily basis. While there is some controversy surrounding the issue, it seems likely that the potency of cannabis has increased over the years as more potent strains have been developed for the black market. Increased THC potency combined with decreased age of onset of use may result in the longer term in more marked cognitive impairments in larger numbers of individuals.

While it may be true that "real and substantial inconsistencies in the literature have been magnified by those who tend to cite selected pieces of evidence in support of their own ideological beliefs" (Fehr and Kalant, 1983, p. 501), it is essential that "any new evidence implicating cannabis with persistent harmful effects is subject to critical scrutiny and careful replication if accusations of prejudice and moral bias are to be avoided" (Deahl, 1991). It appears that the onus of proof is on researchers to prove impairment rather than on the proponents of cannabis use to prove safety. In the case of cognitive impairments in young people, "safe until proven unsafe" may be a dangerous stance to take since cannabis, like all psychoactive substances could never be labelled entirely "safe". The evidence that cannabis impairs cognitive functioning whilst intoxicated and that cannabis smoke is damaging to the respiratory tract, for that matter (eg. Tashkin, 1993) cannot be refuted, and there is now sufficient evidence for some long term cognitive effects. Further research examining the consequences of its use in comparison to other substances is clearly warranted. The dissemination of research findings in a realistic and less sensational manner would provide users with the ability to make an informed decision about whether or not to use the drug, and if they use, how much and how often to use.

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APPENDIX A

COGNITIVE FUNCTIONING IN LONG TERM CANNABIS USERS
CONSENT FORM

Thankyou for volunteering to participate in this project. This experiment is being conducted t the National Drug and Alcohol Research Centre which is part of the University of New Soutl Wales. We are interested in examining the way that the brain processes information and whether long term use of cannabis has any effect on these processes. We are particularly interested in attention and memory function.

The experimental session will take approximately 3 hours. You will be required to complete several questionnaires before proceeding with the experimental computerised tasks. One task involves responding to tones presented through headphones. While you are doing the task, w will record the electrical activity of the brain. This involves wearing an elasticised cap with electrodes sewn into it. The procedure is neither painful nor stressful. All procedures will be fully explained to you. If you have any questions, feel free to ask.

The experiment requires that you consume no cannabis (marijuana), alcohol or non-prescription drugs for 24 hours prior to the session. We also require you to bring in a urine sample from the night before testing and we will take another from you today. These samples will be tested for the presence of cannabis and any other drugs. If you have complied with these requirements, please read and sign the following statement. Note that only the researchers who are directly involved in this study will have access to the data. All informatic you provide will be treated as strictly confidential and you will not be personally identifiable i any way. You may expect no personal benefit from the study. However, the information gained from the study might be useful in helping to better understand the effects of cannabis.

I acknowledge that I have read the above statement which explains the nature and object of th investigation to my satisfaction. I have been given the opportunity to ask any questions. My participation in this study is entirely voluntary and I may withdraw from the study at any tim My decision whether or not to participate will not prejudice my future relations with the University in any way. I understand that I will be paid the sum of $30 which is to cover the costs of travel to and from the National Drug and Alcohol Research Centre.

You are making a decision whether or not to participate. Your signature indicates that you ha decided to participate having read the information provided above.

Name: _____ Age: _____

Signature: _____ Date: _____

Signature of Investigator: _____

APPENDIX B

SCREENING AND DRUG USE QUESTIONNAIRE

NAME: _____

DATE OF BIRTH: _____

GENERAL HEALTH & EDUCATION

1. Are you on any prescription medication or receiving treatment for any medical condition?
   _____

2. Have you ever been hospitalised for any condition?

   _____

3. Have you ever had any of the following:

   Serious illnesses _____

   Fits, convulsions or epileptic seizures _____

   Serious head injuries or periods of unconsciousness
   _____

4. Have you ever been in treatment for drug or alcohol problems?
   _____

5. Have you ever consulted a psychologist, psychiatrist or counselor or undergone therapy for any reason?
   _____

6. Is there any psychiatric illness in your family?
   _____

7. What is the highest level of education that you have completed or are currently completing?
   _____

8. What is your usual occupation? _____

9. Have you ever had any musical training? What kind? _____

Now I would like to ask you some questions about your drug and alcohol use.

ALCOHOL

1. Do you drink alcohol? _____

2. On how many days would you drink alcohol in a typical week?

    _____

3. On a day when you drink, how many drinks would you have (per occasion)?

    _____

4. How long have you been drinking at that level? _____

5. Has there ever been a period in your life when you drank much more heavily?

    _____

    _____

6. When did you have your last drink of alcohol? How much did you drink?

    _____

7. How much did you drink last week? (go through each day of the week). Was this
a   typical week in terms of drinking habits?

    _____

    _____

Selection criteria: Males: Preferably no more than 42 drinks / week on average
Females: Preferably no more than 28 drinks / week on average
(No significant history of heavy consumption of alcohol, never been in treatment
for alcohol dependence)

OTHER DRUGS

Do you or have you ever used any of the following substances?
If so, how frequently, and when was the last time you used each particular substance.

DRUG	QUANTITY / FREQUENCY	LAST USE
Tobacco		
Amphetamines		
Cocaine		
Barbiturates (downers)		
Tranquilizers		
LSD, Mushrooms, Ecstasy		
Opiates (heroin, methadone)		
Inhalents (amyl, aerosols)		
Anything else?		

Have you ever had any problems associated with the use of any of these drugs?
eg. been arrested, involved in a car accident, felt you were dependent, etc.

_____

_____

Selection criteria: Reject anyone with a history of use ≥ 1 / month or use in the month prior to testing.

(CONTROLS ONLY)

1.   Have you ever tried marijuana? _____

2.   Have you ever used marijuana on a regular basis?

    _____

3.   When was the last time you used marijuana?

    _____

4.   How many times have you had marijuana in total, over what time period?

    _____

Selection criteria: Reject anyone who has used cannabis recently or more often than once/year.

(USERS ONLY)

Now I'd like to ask you some detailed questions about your use of cannabis.

1.   How old were you when you first tried marijuana? _____

2.   How old were you when you first started using regularly? _____

3.   How often are you currently smoking marijuana? eg.many days would you smoke marijuana in a typical month?

    _____

4.   What do you usually smoke? ie, leaf, heads, hash? _____

5.   How would you rate the strength of the marijuana you usually smoke on a scale from 0 (mild) to 10 (strong)? _____

6.   Do you mix your marijuana with tobacco? _____

7.   Do you smoke joints, bongs or pipes? _____

8.   How many would you smoke in a typical session? _____

9.   On a day when you are smoking marijuana, how many sessions would you have?

    _____

10. On a scale from 0 to 10, where 0 = totally straight, and 10 = the most stoned you've ever been, what level of intoxication do you usually like to reach?_____

11. How long have you been smoking at this level? _____

12. Has your pattern of use changed over time?_____

13. Has there ever been a period in your life when you smoked much more heavily?

14. Have you ever used on a daily basis? When was the last time you were using on a daily basis and how long for?

15. Altogether, if you added up every month that you have ever used DAILY, for about how much of your life would you estimate that you have used daily or almost daily? eg. < 3 months, 3-9 months, 1 year, 2-3 years, 5-9 years, >10 years.

16. Have you ever felt dependent on cannabis? How would you define that?

17. Have you ever had any problems associated with your use of cannabis? (eg. arrests, problems with concentration or memory, etc, anything)

18. In the last three years, what is the longest period you've gone without marijuana?

19. When did you have your last smoke? How much did you smoke at that time?

20. How much did you smoke last week? Was this a typical week in terms of marijuana use? (If not last week, think back to the last time you smoked)

EFFECTS OF CANNABIS

1. Sometimes the effects you experience when you take drugs are the ones you want; sometimes they are not. Sometimes drugs improve things for you; sometimes they make matters worse. This section asks about the short-term effects you get just after smoking marijuana. Tick one answer for each question.

The SHORT-TERM or immediate effects of marijuana on your:

	Usually made better	Usually made worse	Sometimes better sometimes worse	Usually no effect
Ability to think clearly	_____	_____	_____	_____
Excitement and enthusiasm for life	_____	_____	_____	_____
Enjoyment of sex	_____	_____	_____	_____
Ability to relax	_____	_____	_____	_____
Driving ability	_____	_____	_____	_____

2. Using marijuana sometimes leads to changes in people's lives. For each question listed below, indicate whether you think marijuana has improved, impaired or had no effect on your life. What we are asking about here are long term effects, not the effects you experience just after taking the drug.

The LONG-TERM effect of marijuana on your:

	Improved	Impaired	No effect
Ability to think clearly	_____	_____	_____
Ability to cope and solve life's problems	_____	_____	_____
Physical health	_____	_____	_____
General self confidence	_____	_____	_____
Ability to concentrate on complex tasks	_____	_____	_____
Work performance (studies)	_____	_____	_____
Ability to communicate	_____	_____	_____
Relations with employers / seniors	_____	_____	_____
Memory	_____	_____	_____
General co-ordination	_____	_____	_____
General level of energy	_____	_____	_____
Excitement and enthusiasm for life	_____	_____	_____

3. Why do you like to smoke marijuana?

4. What do you dislike about marijuana?

5. Have you ever made a conscious decision to stop smoking? If so, for what reasons, and how long did you give up for? Why did you start again?

CASST (Hannifin, 1987)

1. Have people close to you complained about your cannabis use?	Y / N
2. Do you have problems with short term memory?	Y / N
3. Have you ever experienced paranoid episodes following cannabis use?	Y / N
4. Do you find it difficult to get through a day without a joint?	Y / N
5. Do you lack the energy to get things done in the way you used to?	Y / N
6. Do you ever worry about the effects of your cannabis use?	Y / N
7. Do you have more difficulty in understanding new information? (eg. difficulty in studying)	Y / N
8. Have you ever unsuccessfully attempted to cut down or stop your cannabis use?	Y / N
9. Do you like to get stoned in the morning?	Y / N
10. Are you spending more and more time stoned?	Y / N
11. Do you experience cravings, headaches, irritability or difficulty in concentration when you cut down or cease cannabis use?	Y / N

APPENDIX C

Publications arising from this thesis

Solowij, N., Michie, P.T. & Fox, A.M. (in press) Differential impairments of selective attention due to frequency and duration of cannabis use. *Biological Psychiatry*.

Solowij, N. (in press) Cannabis and cognitive functioning. In Hannifin, J. (Ed) *Cannabis and Health: The Experts Comment*. Palmerston North, New Zealand: Dunmore Press

Solowij, N., Michie, P.T. & Fox, A.M. (1993) Frequency and duration of cannabis use differentially affect brain function in a selective attention task. *International Journal of Neuroscience*, 71, 129-130.

Solowij, N. (in press) The effects of chronic cannabis use on cognitive functioning. In Oliphant, D.A. and Mattick, R.P. (Eds) *Correlates and Consequences of Excessive Drug Use*. National Drug and Alcohol Research Centre Monograph No. 19, University of New South Wales.

Solowij, N., Michie, P.T. & Fox, A.M. (1991) Effects of long term cannabis use on selective attention: An event-related potential study. *Pharmacology, Biochemistry and Behavior*, 40 (3), 683-688.

Solowij, N., Michie, P.T. & Fox, A.M. (1990) *The Effects of Long-Term Cannabis Use on Cognitive Functioning: An event-related potential study*. National Drug and Alcohol Research Centre Occasional Paper No.15.

Hall, W. & Solowij, N. (in press) Cannabis and health: The literature. In Hannifin, J. (Ed) *Cannabis and Health: The Experts Comment*. Dunmore Press: Palmerston North, New Zealand.

Hall, W., Solowij, N. & Lemon, J. (1994) *The health and psychological consequences of cannabis use*. Report prepared for the Australian National Task Force on Cannabis.

APPENDIX D

Conference presentations arising from this thesis

Solowij, N., Michie, P.T. & Fox, A.M. (1993) ERP indices of selective attention in ex-cannabis users. Paper presented at the 3rd Australasian Psychophysiology Conference, Newport, Sydney, December 3-5.

Solowij, N. (1993) Long term cognitive effects of chronic cannabis use. Keynote address at *Cannabis and Health in New Zealand*, Wellington, New Zealand, October 4-6.

Solowij, N. (1993) Cognitive and behavioural effects of cannabis. Invited paper at *Cannabis and Health in New Zealand*, Wellington, New Zealand, October 4-6.

Solowij, N., Michie, P.T. & Fox, A.M. (1993) Differential impairments of selective attention due to frequency and duration of cannabis use. Paper presented at the *International Cannabis Research Society Annual Meeting*, satellite to the *College on Problems of Drug Dependency (CPDD) Annual Conference*, Toronto, Canada, June 11-17.

Solowij, N. (1992) Effects of chronic cannabis use on cognitive functioning. Invited paper presented at *The Fifth Anniversary Annual Symposium of the National Drug and Alcohol Research Centre*, University of New South Wales, 6 December.

Solowij, N., Michie, P.T. & Fox, A.M. (1992) Frequency and duration of cannabis use differentially affect brain function in a selective attention task. Paper presented at the *10th International Australasian Winter Conference on Brain Research (AWCBR)*, Queenstown, New Zealand, 16-21 August.

Solowij, N. (1992) An update on cognitive functioning in long term cannabis users. Paper presented at the *National Event-Related Potential Workshop*, Macquarie University, 31 July and at the National Drug and Alcohol Research Centre, University of New South Wales, 13 August.

Solowij, N., Michie, P.T. & Fox, A.M. (1990) Effects of long term cannabis use on cognitive functioning: An event-related potential study. Paper presented at *Marijuana '90*, Kolympari, Crete, 9-13 July, a satellite symposium to the International Pharmacology Conference.

Solowij, N., Michie, P.T. & Fox, A.M. (1990) Effects of long term cannabis use on selective attention. Paper presented at the *National Event-Related Potential Workshop*, Prince of Wales Hospital, Sydney, 7 December.

Solowij, N., Prescott, J. & Michie, P.T. (1990) Cognitive functioning in long term cannabis users. Poster presented at the *5th International Conference on Treatment of Addictive Behaviours (ICTAB-5)*, University of Sydney, 4-9 February.

APPENDIX E

Other publications and conference presentations during the term of candidature

Publications

Solowij, N. (1993) Ecstasy (3,4-methylenedioxymethamphetamine). *Current Opinion in Psychiatry*, 6, 411-416.

Solowij, N., Hall, W. & Lee, N. (1992) Recreational MDMA use in Sydney: a profile of 'Ecstasy' users and their experiences with the drug. *British Journal of Addiction*, 87, 1161-1172.

Solowij, N. & Lee, N. (1991) *A Survey of Ecstasy Users in Sydney*. Drug and Alcohol Directorate Report Series B91/1, NSW Health Department.

Solowij, N., Michie, P.T., Crawford, J.M. & Glue, L.C. (1990) Auditory ERPs during auditory attention and a visual control task: Effects of visual task difficulty. In Brunia, C.H.M., Gaillard, A.W.K. & Kok, A. (Eds) *Psychophysiological Brain Research*. Vol. 1, Tilburg University Press, 217-220.

Grenyer, B.F. & Solowij, N. (Eds) (1989) *Cognitive-Behavioural Approaches to the Treatment of Drug and Alcohol Problems*. National Drug and Alcohol Research Centre, Monograph No 7, University of New South Wales.

Michie, P.T., Solowij, N., Crawford, J.M. & Glue, L.C. (1993) The effects of between-source discriminability on attended and unattended auditory ERPs. *Psychophysiology*, 30, 205-220.

Michie, P.T., Solowij, N., Crawford, J.M. & Glue, L.C. (1990) Auditory ERPs during auditory attention and a visual control task: Effects of auditory task difficulty. In Brunia, C.H.M., Gaillard, A.W.K. & Kok, A. (Eds) *Psychophysiological Brain Research*. Vol. 1, Tilburg University Press, 208-211.

Fox, A.M., Coltheart, M., Solowij, N., Michie, P.T. and Fox, G.A. (submitted) Dissociable cognitive impairments in excessive drinkers.

Fox, A.M., Michie, P.T., Coltheart, M. & Solowij, N. (submitted) Memory functioning in social drinkers: A study of event-related potentials.

Fox, A.M., Michie, P.T., Coltheart, M. & Solowij, N. (1991) *Alcohol consumption and memory: An event-related potential study*. National Drug and Alcohol Research Centre Occasional Paper No. 26.

Fox, A.M., Michie, P.T., Coltheart, M. & Solowij, N. (1991) *An event-related potential study of memory functioning: Effects of alcohol*. National Drug and Alcohol Research Centre Technical Report No. 12.

Michie, P.T., Coltheart, M., Kellenbach, M., Terry, L. & Solowij, N. (in press) Neighbourhood size effects on words and nonwords: Behavioural and ERP indices. *Biological Psychology*, (Proceedings of the Australasian Society for Psychophysiological Research Conference, Nelson Bay, December 1992).

Conference presentations

Solowij, N., Michie, P.T., Crawford, J.M. & Glue, L.C. (1989) Auditory ERPs during auditory attention and a visual control task: Effects of visual task difficulty. Poster presented at the *9th International Conference on Event-Related Potentials of the Brain (EPIC IX)*, Noordwijk, The Netherlands, 28 May - 3 June.

Michie, P.T., Solowij, N. & Fox, A.M. (1992) Event-related potential indices of visual selective attention of category vs location. Paper presented at the *5th International*

Conference on Cognitive Neurosciences (ICON X), Jerusalem, Israel, 14-19 June.

Michie, P.T., Solowij, N. & Fox, A.M. (1991) Event-related potential indices of attention to spatial location vs category of stimuli. Paper presented at the *Inaugural Australasian Psychophysiology Conference*, University of Sydney, 10-12 December.

Michie, P.T., Solowij, N., Crawford, J.M. & Glue, L.C. (1989) Auditory ERPs during auditory attention and a visual control task: Effects of auditory task difficulty. Poster presented at the *9th International Conference on Event-Related Potentials of the Brain (EPIC IX)*, Noordwijk, The Netherlands, 28 May - 3 June.

Michie, P.T., LePage, E., Solowij, N., Terry, L., Haller, M. & Belcredi, M. (1993) Evoked otoacoustic emissions (EOAEs): Are they sensitive to attention? Paper presented at the 3rd Australasian Psychophysiology Conference, Newport, Sydney, December 3-5.

Punter, S., Michie, P.T., Solowij, N. & Haller, M. (1993) Differential effects of intermodal and intramodal attention tasks on ignore mismatch negativity (MMN). Paper presented at the 3rd Australasian Psychophysiology Conference, Newport, Sydney, December 3-5.

Michie, P.T., Coltheart, M., Kellenbach, M., Terry, L. & Solowij, N. (1992) Neighbourhood size effects on words and nonwords: Behavioural and ERP indices. Paper presented at the *Australasian Psychophysiology Conference*, Nelson Bay, 6 December.