THE CENTRAL EFFECTS OF BZP AND TFMPP IN HUMANS: AN INVESTIGATION USING ELECTROENCEPHALOGRAPHY

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ABSTRACT

'Party Pills' containing 1-benzylpiperazine (BZP) and 1-(3-trifluoromethylphenyl)piperazine (TFMPP) were legally available in New Zealand and marketed as safe alternatives to 3,4-methylenedioxymethamphetamine (MDMA) until they were banned in 2008; however, they continue to be available in some parts of the world. BZP and TFMPP are known to stimulate the release and inhibit the reuptake of dopamine, serotonin and noradrenaline in rodents. Studies in humans report that these compounds produce changes in blood pressure, heart rate and subjective feelings comparable to amphetamine and MDMA (also known as 'Ecstasy'). However, there is currently no information available about the acute effects of these drugs on central processing in humans and the extent to which their effects are similar or different to those of better characterised stimulant drugs, such as dexamphetamine. The aim of the work reported in this thesis was to investigate the effects of BZP, TFMPP and the combination of BZP+TFMPP on human neural processing using electroencephalographic techniques and to compare their effects to dexamphetamine (a positive control) and placebo.

Randomised, double blind, placebo-controlled studies using electroencephalography investigated the effects of these compounds on the interhemispheric transfer of information using the Poffenberger task, and efficiency of attention allocation using an auditory oddball task. In addition, reaction time data were collected. Healthy, right-handed males were given an oral dose of either BZP (200 mg), TFMPP (60 mg), a combination of BZP+TFMPP (100/30 mg), dexamphetamine (20 mg), or placebo (lactose) and tested both before and 120 minutes after drug administration.

We measured three variables using the Poffenberger task; absolute N160 latency, interhemispheric transfer time and the mean reaction time pre- and post-drug administration. A mixed factorial repeated measures analysis of variance of absolute N160 latency and contrast analysis revealed that only TFMPP ($F_{(1,77)}$=17.30, $p \leq 0.001$) significantly reduced the absolute N160 latency. Analysis of the interhemispheric transfer time revealed that only TFMPP ($F_{(1,77)}$=5.266, $p \leq 0.02$) significantly reduced the interhemispheric transfer time, while BZP, BZP+TFMPP and dexamphetamine had no effect. Contrast analysis

revealed that both TFMPP ($F_{(1,77)}$=17.30, p≤0.001) and placebo ($F_{(1,77)}$=15.08, p≤0.001) preserved the laterality of information transfer from one hemisphere to the other (i.e. faster Right-to-Left transfer compared to Left-to-Right transfer), whereas this asymmetry was not present in the BZP, BZP+TFMPP and dexamphetamine groups. The reaction time ($F_{(4,91)=}$0.373, p>0.05) was not significantly affected by any of the drug treatments.

Using the auditory oddball paradigm, we collected the P100, P200 and P300 amplitude, latency and mean reaction time data to determine drug effects. A mixed factorial repeated measures analysis of variance of the P300 amplitude revealed a significant Time×Drug effect ($F_{(4,82)}$=2.379, p≤0.05). Contrast analysis revealed that BZP, TFMPP and dexamphetamine significantly reduced the P300 amplitude ($F_{(1,82)}$=9.09, p≤0.004), whereas BZP+TFMPP and placebo had no effect. Neither P300 latency ($F_{(4,82)}$=0.339, p=0.093) nor the mean reaction time ($F_{(4,82)}$=1.274, p=0.960) was affected by any of the drug treatments. In addition, none of P100 amplitude ($F_{(4,82)}$=0.680, p=0.608), P100 latency ($F_{(4,82)}$=0.919, p=0.458) , P200 amplitude ($F_{(4,82)}$=1.430, p=0.234), nor P200 latency ($F_{(4,82)}$=0.460, p=0.765) components were affected following any of the drug treatments.

To conclude, the work described in this thesis has demonstrated that BZP, TFMPP and BZP+TFMPP act centrally to alter neural processing in humans.

I dedicate this thesis to my husband Hee Sung and my daughter Euni,

the best present from God.

Now faith is being sure of

What we hope for and certain of

What we do not see.

Hebrews 11:1

He is like a tree planted by streams of water,

Which yields its fruit in season and

Whose leaf does not wither.

Whatever he does prospers.

Psalms 1:3

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ABBREVIATIONS

[^{3}H]MPP$^+$	DA transporter substrate
5-HT	serotonin
ACh	acetylcholine
ADHD	attention deficit hyperactivity disorder
ANOVA	analysis of variance
ARCI	Addiction Research Centre Inventory
BZP	1-benzylpiperazine
BZP+TFMPP	combination of BZP and TFMPP
CNS	central nervous system
CYP	cytochrome P450
DA	dopamine
DAT	dopamine transporter
EEG	electroencephalography
EPSP	excitatory postsynaptic potential
ERP	event-related potential
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
IPSP	inhibitory postsynaptic potential
kg	kilogram
L	litres
LSD	lysergic acid diethylamide
MDMA	3,4-methylenedioxymethamphetamine
mg	milligram
mL	millilitre
ms	millisecond
n	sample size
NA	noradrenaline
ng	nanogram
nM	nanomole
NMDA	*N*-methyl-*D*-aspartate
POMS	Profile of Mood States
SERT	serotonin transporter
SSRI	selective-serotonin reuptake inhibitor
TFMPP	1-(3-trifluoromethylphenyl)piperazine
T_{max}	time taken to reach peak concentration
VAS	Visual Analogue Scales
VF	visual field

PUBLICATIONS

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CHAPTER ONE

INTRODUCTION

CHAPTER ONE: INTRODUCTION

This thesis examines the effects of 'Party Pill' drugs 1-benzylpiperaine (BZP) and 1-(3-trifluoromethylphenyl)piperazine (TFMPP), both alone and in combination, on neural processing in human participants using electroencephalography (EEG) measures of interhemispheric transfer time (the Poffenberger task) and attention allocation (the P300 oddball task).

The introductory chapter first provides background on the drugs being studied including information about the pharmacology, the results of preclinical and clinical studies, effects on basic physiological function and pharmacokinetics and metabolism. Some of these features are of importance when the experimental design is considered, such as the timing of EEG studies relative to peak blood levels. The EEG techniques used are then described, followed by a rationale for the studies performed in subsequent chapters.

Chapter Two outlines the characteristics of the participant group. Recruitment, demographic and physical characteristics and responses to a lifestyle questionnaire used to balance and/or exclude other possible influences on EEG recordings (such as other drug use) are reported.

Chapter Three describes the first experimental study comparing the effects of BZP, TFMPP, BZP+TFMPP and dexamphetamine on interhemispheric transfer time using the Poffenberger task. Specifics of the technique of EEG acquisition and data analysis are reported.

In Chapter Four, the second study is reported. This examines the effects of BZP, TFMPP, BZP+TFMPP and dexamphetamine on the P300 wave form, elicited during an oddball task experiment.

Because interpretation of the results involves consideration of the effects of monoaminergic neurotransmitters, alone and in combination, the final chapter (Chapter Five) first presents information on interactions between these neurotransmitters, before moving on to discuss the results of the individual experiments.

1.1. Party Pills

Products containing BZP and/or TFMPP were widely available for recreational use around the world despite their illegal status in some countries. They were collectively known as 'Party Pills' or 'Herbal/Natural Highs' and marketed as a safe alternative to 3,4-methylenedioxymethamphetamine (MDMA) and other amphetamines. Party Pills had trade names such as 'Charge', 'Neuro Blast', 'Pure XTC' and 'Bent', suggesting their ability to cause MDMA- or amphetamine-like effects in users (Figure 1, page 19). It is reported that in 2003, more than 1.5 million capsules of BZP were manufactured for sale in New Zealand (Ministerial Committee on Drug Policy 2007). Furthermore, in 2004 approximately 200,000 doses of Party Pills were sold each month in New Zealand, raising the industry's annual sales to $25 million (Expert Advisory Committee on Drugs 2004). In addition, a conservative industry estimate reported that over 25 million doses of Party Pills were sold in New Zealand between 2000 and 2005 (Wilkins et al. 2006). Under the Misuse of Drugs Act Amendment in 2005, Party Pills containing BZP became 'restricted' which meant they were available for use by those 18 years and over (Ministerial Committee on Drug Policy 2007). However, Party Pills continued to be widely available from dairies, specific Party Pill shops and mobile vendors, in addition to being extensively marketed on the internet until they were reclassified and made illegal in April 2008 (Expert Advisory Committee on Drugs 2004).

A demographic study of the users of Party Pills in New Zealand by Wilkins et al. (2006) reported that they were most commonly consumed by males aged between 18 and 45 for their ability to enhance confidence and mood. Party Pills were also reportedly taken by people in demanding professional jobs and also by single parents looking after children and doing house work, as Party Pills improved concentration and gave them increased levels of energy (Wilkins et al. 2006). The study also reported that Party Pills were often taken with other recreational drugs e.g. alcohol, tobacco/cigarettes, cannabis, MDMA and amphetamines to maximise the drug-taking experience.

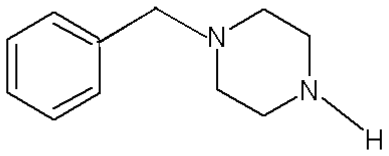
Figure 1. Illustration of trade names and packaging of Party Pills

One of the first references to the use of BZP (Figure 2, page 20) for 'recreational' purposes was reported in 1991 in the book 'PiHKAL' (Shulgin and Shulgin 1991). According to the Drug Enforcement Administration (DEA) of the United States, the first reported misuse of BZP was in California during the mid 1990s. BZP soon became very popular as demonstrated by the "increasing encounters of this substance by law enforcement officials" (Drug Enforcement Administration 2004).

Due to the increasing use of BZP in the USA, it was recommended that BZP was temporarily placed into Schedule I of the Controlled Substance Act in 2002 (Drug Enforcement Administration 2002). During 2004, the DEA recommended permanent placement of BZP in Schedule I of the Controlled Substances Act (Drug Enforcement Administration 2004). Despite this, the use of BZP continues to increase in the USA, as 48

seizures of BZP were reported in 2004 compared to 13,822 in 2009 (Drug Enforcement Administration 2010). In Europe, BZP is subject to control measures and criminal penalties in four Member States – Belgium, Denmark, Greece and Malta (European Monitoring Centre for Drugs and Drug Addiction 2009). In Australia, BZP was placed in Schedule 9 of the Therapeutic Goods Act 1989 (Therapeutic Goods Administration 2006). The New Zealand government reclassified BZP and related piperazines under the Misuse of Drugs Act (1975) in April 2008, placing them in the same class as cannabis.

Figure 2. Chemical structure of 1-benzylpiperazine (C11H16N2)



1.2. BZP

1.2.1. Preclinical studies of BZP

Earlier studies reported that BZP promotes release of newly synthesised dopamine (DA) in a similar manner to amphetamine and methamphetamine, as all three compounds induce contralateral head turning behaviour, a behavioural indicator of DA release (Oberlander et al. 1979). Like MDMA, the DA-releasing properties of BZP are mediated by substrate activity at the DA transporter (DAT), as a low dose of a selective DA uptake blocker, GBR12909, antagonised the effects of BZP. BZP also facilitated the action of DA through extracellular release of [^{3}H]MPP$^+$, a DAT substrate, *in vitro* (Baumann et al. 2002; Baumann et al. 2005). BZP produces an MDMA-like DA release profile as indicated by a rapid and spike-like release, but was found to be three-fold less potent than MDMA. In

addition, a high dose of BZP (10 mg/kg, i.v.) produced an increase in DA release, but was less potent as a serotonin (5-HT) releaser (Baumann et al. 2004; 2005).

BZP also modulates behaviour via the serotonergic system as MDL72,222, a 5-HT_3 antagonist, attenuated the place preference induced by BZP in rats (Meririnne et al. 2006). However, BZP (10 mg/kg/day) produced higher levels of anxiety in adolescent rats (postnatal days: 45-55) as they displayed decreased tendency to explore novel environments, fewer social interactions and a longer latency to emerge from the dark into an illuminated arena compared to saline-treated controls (Aitchison and Hughes 2006). These findings are reminiscent of the long-term effects of MDMA and methamphetamine as adolescent animals treated with these drugs also display an increase in anxiety associated with 5-HT depletion (Clemens et al. 2004; Gurtman et al. 2002).

Tekes et al. (1987) suggested that BZP also possesses central serotonergic properties as BZP induced hyperthermia at a relatively high ambient temperature (28°C) that was reversed by the 5-HT_2 antagonist cyproheptadine. Furthermore, BZP seems to modulate noradrenergic pathways as it inhibited high-affinity uptake of [^{3}H] noradrenaline (NA) both *in vivo* and *in vitro* (Tekes et al. 1987). It also increased the stimulation-evoked release of [^{3}H]NA in the main pulmonary artery of the rabbit. This postsynaptic response was completely inhibited by the preferential α_1-adrenoceptor antagonist prazosin (Magyar et al. 1986). The BZP-potentiated [^{3}H]NA release was also inhibited by α_2-adrenoceptor agonist clonidine, and its inhibition was reversed by yohimbine, a preferential α_2-adrenoceptor antagonist. Therefore, it can be concluded that both serotonergic and noradrenergic pathways are modulated by BZP (Magyar et al. 1986; Szucks et al. 1987).

Studies have shown that the behavioural profile of BZP resembles psychostimulants, producing hyperactivity and stereotypy in animals. In mice, BZP (30 mg/kg, i.v.) doubled locomotor activity while a higher dose (100 mg/kg; i.v.) induced hyperlocomotion (Yarosh et al. 2007). BZP also induces methamphetamine- and MDMA-like dose-dependent ambulation and stereotypical behaviours such as intense grooming, head-bobbing and repetitive sniffing (Baumann et al. 2005; Brennan et al. 2007; Negus et al. 2009). Baumann et al. (2005) reported BZP (10 mg/kg; i.v.) induced greater locomotion than MDMA (3

mg/kg; i.v.), suggesting that BZP induces amphetamine-like stimulation in rats via an increase in extracellular DA release.

Primate studies have also demonstrated that BZP possesses discriminative stimulus and reinstatement properties. BZP induced reinstatement of self-administration previously maintained by amphetamine in rhesus monkeys (McClung et al. 2010), and fully substituted for amphetamine in monkeys trained to self-administer cocaine (Fantegrossi et al. 2005; Negus et al. 2009).

In summary, the present findings suggest that the complex pharmacological and behavioural profile of BZP is under the influence of the dopaminergic, serotonergic and noradrenergic systems.

1.2.2. Clinical studies of BZP

1.2.2.1. Effects of BZP on mood ratings

Only two early studies of BZP in humans were available until recently (Bye et al. 1973; Campbell et al. 1973). Bye et al. (1973) compared the effects of BZP (25-100 mg; oral) to dexamphetamine (1-7.5 mg; oral) in healthy volunteers and found that both compounds significantly improved performance in a finger tapping task. In addition, performance in a prolonged signal detection test was significantly improved following a low dose of BZP (20 mg) or dexamphetamine (2.5 mg) compared to placebo. Furthermore, BZP significantly increased the ratings of 'alert', 'elated', 'quick-witted', 'stimulated' and 'talkative'. On the other hand, Campbell et al. (1973) compared the effects of BZP (100 mg; oral) and dexamphetamine (10 mg; oral) in former dexamphetamine addicts. The subjective mood ratings measured by the psychiatric rating scale and questionnaires revealed that both BZP and dexamphetamine produced time-dependent increases in excitation, amphetamine-like effects, drug liking, drug effect and willingness to take the drug again. In particular, the participants were unable to distinguish BZP from dexamphetamine, suggesting BZP produces dexamphetamine-like changes in humans.

Although both studies provide useful information about the stimulant-like effects of BZP in humans, there are some methodological flaws. Firstly, the simple mood questionnaires used in both studies were not tested for objective validity and relied on the subjective opinions of the observers. In particular, Campbell et al. (1973) based their analysis on questions such as “Are there any special effects?” and “Do you think the subject liked the drug?”. Consequently, the authors reported no significant differences in the subjective mood ratings. Using validated subjective mood rating scales such as the Addiction Research Centre Inventory (ARCI), the Profile of Mood State (POMS) and the Visual Analogue Scales (VAS) would have provided more accurate details about the effects of BZP in comparison to dexamphetamine. Secondly, the former amphetamine addicts in the Campbell et al. (1973) study were still under psychiatric care and reported a history of substance abuse with amphetamine, barbiturates, lysergic acid diethylamide (LSD) and cannabis. Repeated exposure to methamphetamine and MDMA are linked to modifications in dopaminergic neurotransmission leading to potentiated stimulant-produced behaviour (Brennan et al. 2007). Therefore it is possible that the former addicts displayed a more sensitised response to BZP, hence being unable to distinguish BZP from dexamphetamine. Nonetheless, these two studies were the first to report stimulant-like effects of BZP in humans.

Since the report of the stimulant-like properties of BZP in humans by Bye et al. (1973) and Campbell et al. (1973), there have been no further studies investigating its effects on BZP on mood until recently. In a study conducted by Lin et al. (2009), the effects of BZP (200 mg; oral) on mood were measured in healthy volunteers using the ARCI, POMS and VAS. BZP produced significant changes in the ARCI scales as indicated by increased euphoria, dysphoria and amphetamine-like effects. BZP also significantly affected five of seven POMS scales: decreased depression/dejection, fatigue/inertia, confusion/bewilderment, increased vigour/activity and total mood disturbance. In addition, BZP was associated with increased positive effects such as drug effect, good drug effect, drug liking, ‘stimulated’, ‘high’, ‘talkative’, ‘self-confident’ and ‘social’, and negative effects such as bad drug effect as measured by the VAS scales. This study demonstrates that the stimulant-like effects of BZP are similar to other amphetamines and therefore are likely to be mediated by the same dopaminergic and serotonergic pathways.

1.2.2.2. Effects on blood pressure, heart rate and body temperature

BZP also produced stimulant-like physiological effects in humans i.e. increased blood pressure and tachycardia (Bye et al. 1973; Campbell et al. 1973; Lin et al. 2009). These changes are likely to be induced by increased levels of circulating NA in the body. In addition, BZP produced pupil dilation (mydriasis; Campbell et al. 1973). Other α_2-adrenoceptor agonists such as cocaine and amphetamine also induce mydriasis, increase blood pressure and tachycardia by influencing central adrenergic function (Klemfuss and Adler 1986; Koss 1980).

Interestingly, Lin et al. (2009) reported BZP (200 mg; oral) reduced body temperature. This is in contrast to research by Campbell et al. (1973) where BZP induced signs of flushing and sweating. In rats, BZP causes hyperthermia at an ambient temperature of 28°C (Tekes et al. 1987). Similarly, both methamphetamine and MDMA administration induce 5-HT-mediated hyperthermia in animals (Farfel and Seiden 1995a; b). However, it is known that the amphetamine-induced effects on body temperature are dependent on the ambient temperature, as low ambient temperature (e.g. 10°C or lower) induces hypothermia, whereas high ambient temperature (e.g. 22-23°C) induces hyperthermia (Bowyer et al. 1992; Cryan et al. 2000). In light of this evidence, Lin et al. (2009) argued that an ambient temperature of 22°C may not be sufficient to cause BZP-induced hyperthermia in humans, and that a higher BZP dose in combination with an increase in physical activity and/or high ambient temperature may increase body temperature. Regardless of the discrepancies between human and animal research, the findings highlight that BZP behaves similarly to other amphetamine-based stimulants and is likely to produce either hypo- or hyperthermia depending on ambient temperature.

1.2.2.3. Pharmacokinetics and metabolism of BZP

In vitro studies carried out using human liver microsomes reported that BZP inhibited the metabolism of dextromethorphan, ethinyloestradiol and caffeine (Antia et al. 2009c; Murphy et al. 2009). These compounds are thought to be substrates of CYP 450 isoenzymes

i.e. CYP2D6, CYP3A4 and CYP1A2 respectively. The CYP2D6 enzyme deficiency shows genetic variability as 7% of Caucasians and about 1% of Asians are classified as poor metabolisers. On the other hand, the rest of the population are classified as either ultrarapid/extensive/intermediate or normal metabolisers and show variable enzymatic activity due to more than 70 allelic variants identified (Bertilsson et al. 2002). Drugs subject to CYP2D6 metabolism include antidepressants such as nortriptyline, amitriptyline and fluoxetine, and antipsychotics such as haloperidol, risperidone and perphenazine. In addition, a number of β-adrenoceptor blockers and antiarrhythmic drugs are also subject to CYP2D6-dependent metabolism (Bertilsson et al. 2002). Consequently, polymorphic variation of the expression of CYP2D6 leads to individual differences in drug metabolism with subsequent variability in plasma drug concentration i.e. too low a concentration can result in sub-therapeutic effects and too high a concentration can result in unwanted adverse effects. As BZP is a CYP2D6 substrate, it is possible that extensive metabolisers need to consume larger amounts of BZP to experience stimulation, whereas poor metabolisers are more likely to experience drug-induced side effects. These findings are reflected in a report where some users were able to consume as many as 8-10 Party Pills at one time, compared to a mean number of 2.6 Party Pills usually taken on a typical occasion (Wilkins et al. 2006). In addition, Party Pill users are more likely to experience adverse effects when BZP is consumed in combination with other drugs subject to CYP2D6 metabolism due to competitive enzyme inhibition. For example, MDMA is also metabolised by CYP2D6 and several hospital admissions have been linked to the concomitant use of MDMA and BZP (Balmelli et al. 2001; European Monitoring Centre for Drugs and Drug Addiction 2009; Wikstrom et al. 2004).

In fasting humans, an oral dose of BZP (200 mg), reached a maximum plasma concentration of 262 ng/ml, 75 minutes post-dose. The half-life of BZP is 5.5 hours and BZP plasma concentration drops below the limit of quantification 24 hours after ingestion. Although studies using rat urine suggested several metabolites of BZP, human urinary analysis detected only an N-sulphate conjugate of BZP and an O-sulphate conjugate of its hydroxylated metabolites, 4-OH-BZP and 3-OH-BZP (Antia et al. 2009b). Furthermore, although Tsutsumi et al. (2006) reported identification of glucuronide conjugates of BZP in

rat urine, Antia et al. (2009b) reported no detection of BZP glucuronides in urine or plasma samples of humans. See Table 1 for a summary of the current findings relating to BZP.

Table 1. Summary of current findings relating to BZP

Preclinical evidence (Baumann et al. 2004)	**BZP**
Neurotransmitters involved	DA, 5-HT, NA
Neurotransmitter transporters involved	DA/5-HT transporter
Behavioural changes	hyperactivity, stereotypy, self-administration
Clinical evidence (Lin et al. 2009)	
1. Mood ratings	
ARCI	
Euphoria	↑
Dysphoria	↑
Amphetamine-like effects	↑
POMS	
Tension/anxiety	-
Depression/dejection	↓
Fatigue/inertia	↓
Confusion/bewilderment	↓
Vigour/activity	↑
Total mood disturbance	↑
VAS	
Drug effect	↑
Good drug effect	↑
Drug liking	↑
Stimulated	↑
High	↑
Anxious	↑
Talkative	↑
Self-confident	↑
Social	↑

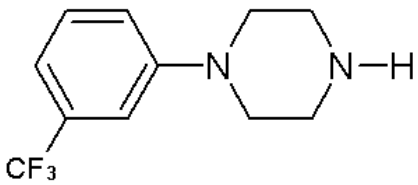
2. Physiological measures	
Blood pressure	↑
Heart rate	↑
Body temperature	dependent on ambient temperature
3. Pharmacokinetic parameters (Antia et al. 2009b)	
Peak plasma concentration	262 ng/ml at 75 minutes
Absorption half-life	6.2 minutes
Apparent clearance	58.3 L/h
Half-life	5.5 hours
Time taken to reach limit of quantification	24 hours (< 15 ng/mL)
Metabolites	4-OH-BZP/ 3-OH-BZP

1.3. TFMPP

1.3.1. Background

TFMPP (Figure 3) is also a major component of many Party Pills, but it is rarely consumed alone and generally combined with BZP. Due to the increasing misuse of TFMPP in the USA, it was temporarily placed in Schedule I of the Controlled Substances Act during 2002 (Drug Enforcement Administration 2002); however, it was later controversially removed from the Schedule in 2004 due to a lack of evidence for potential harm (FDA 2009). Consequently, TFMPP remains uncontrolled in the USA. TFMPP is now a controlled substance in Denmark, Sweden and the UK, however, it is not controlled in the Netherlands (European Monitoring Centre for Drugs and Drug Addiction 2009). In Australia, TFMPP was placed in Schedule 9 of the Therapeutic Goods Act 1989 (Therapeutic Goods Administration 2006). In New Zealand, TFMPP is subject to the same legislative restrictions as BZP and other piperazine derivatives under the Misuse of Drugs Act (1975).

Figure 3. Chemical structure of 1-(3-trifluoromethylphenyl)piperazine ($C_{11}H_{13}F_3N_2$)



1.3.2. Preclinical studies of TFMPP

In contrast to BZP, TFMPP affects mainly the serotonergic pathways and exhibits varying affinity for most 5-HT receptor subtypes. Therefore, TFMPP has been used in a number of studies as a probe for 5-HT activity. It has been reported that TFMPP releases endogenous stores of 5-HT and is a weak inhibitor of 5-HT uptake (Fuller et al. 1981; Pettibone and Williams 1984). Receptor binding studies report that TFMPP is a non-

selective 5-HT receptor agonist with preferential affinity for 5-HT_{1B} receptors (McKenney and Glennon 1986). Binding studies have reported that TFMPP also displays substantial affinity for 5-HT_{1A}, 5-HT_{2C} and slightly less affinity for 5-HT_{1D} receptors (Schoeffter and Hoyer 1989). Rodent studies have reported that acute administration of TFMPP (10 mg/kg; i.p.) reduced overall brain synthesis of 5-HT in the dorsal and median raphé (Tohyama et al. 2002). Furthermore, animals trained to discriminate TFMPP from saline generalised to fenfluramine and mCPP, both selective for 5-HT_{1B} receptors, suggesting that the stimulus properties of TFMPP are mediated via 5-HT_{1B} receptors (McKenney and Glennon 1986).

Currently, no evidence has been presented about the effects of TFMPP on 5-HT_4 receptors and limited evidence suggests that TFMPP displays a moderate affinity for other 5-HT receptor subtypes such as 5-$HT_{5/6/7}$ (Table 2; Kohen et al. 1996; Plassat et al. 1992; Shen et al. 1993).

Table 2. Relative potencies of TFMPP at 5-HT receptor subtypes

Site	Actions as reported in the literature	Potency	References
5-HT_{1A}	Weak partial agonist	K_i=288 nM	(Schoeffter and Hoyer 1989)
5-HT_{1B}	Weak partial agonist	K_i=27 nM	(Titeler et al. 1987)
5-HT_{1D}	Weak partial agonist	K_i=282 nM	(Schoeffter and Hoyer 1989)
5-HT_{2A}	Weak partial agonist	K_i=62 nM	(Hoyer and Schoeffter 1988)
5-HT_{2C}	Weak partial agonist	K_i=288 nM	(Hoyer and Schoeffter 1988)
5-HT_3	Minimal affinity	K_i=2373 nM	(Cloez-Tayarani et al. 1992; Robertson et al. 1992)
5-HT_4	No evidence has been presented for TFMPP and 5-HT_4 receptors		
5-HT_5	Low affinity	K_i=2511.99 nM	(Plassat et al. 1992)
5-HT_6	Moderate affinity	K_i=430 nM	(Kohen et al. 1996)
5-HT_7	Moderate affinity	K_i=532/236 nM	(Shen et al. 1993)

Recently, Baumann et al. (2005) reported that TFMPP is an effective releaser of [^{3}H]5-HT from synaptosomes *in vitro*. The [^{3}H]5-HT-releasing capacity of TFMPP was significantly antagonised by the 5-HT reuptake inhibitor fluoxetine, suggesting that *in vitro* release of TFMPP is mediated by substrate activity at 5-HT transporters (SERT). In rat synaptosomes, the EC_{50} of TFMPP was 121±17 nM compared 58±6 nM for MDMA, indicating that TFMPP is less potent than MDMA with respect to stimulating [^{3}H]5-HT release *in vitro* (Baumann et al. 2005). In addition, TFMPP elicited an MDMA-like 5-HT release in the rat nucleus accumbens *in vivo*; however, it had no effect on dialysate DA content (Baumann et al. 2005).

Animal behavioural studies suggest that TFMPP, as a result of its non-selective release of 5-HT, modulates a number of 5-HT receptor subtypes to elicit a range of behaviours. For example, TFMPP is reported to produce hypophagia and hypolocomotion via activation of hypothalamic 5-HT_{1B} and, to a lesser extent, 5-HT_{2C} receptors (Aulakh et al. 1989; Hutson et al. 1988; Kennett and Curzon 1988; Titeler et al. 1987). Additional reports also confirmed that TFMPP produced dose-dependent hypolocomotor activity in rats and rhesus monkeys mediated by activation of 5-HT_{2C} receptors (Fantegrossi et al. 2005; Frances 1988; Kennett and Curzon 1988; Lucki 1992). In addition, TFMPP (10 mg/kg, i.p.) induced hyperthermia in in rats at a high ambient temperature of 28°C (Klodziska and Chojnacka-Wojcik 1992).

Although TFMPP has affinity for 5-HT_{1A} receptors, evidence suggests they are not directly involved in mediating the stimulus effects of TFMPP. Rats trained to discriminate TFMPP from saline did not generalise to buspirone or 8-OH-DPAT (Cunningham and Appel 1986; Glennon et al. 1989; Herndon et al. 1992). Furthermore, 1-(2-methoxyphenol)-4-[4-(2-phthalimido)butyl]-piperaine (NAN-190), a selective 5-HT_{1A} agonist, failed to substitute or antagonise the TFMPP stimulus which argues against the involvement of 5-HT_{1A} receptors in TFMPP-induced stimulus.

Rats trained to discriminate MDMA and fenfluramine showed full generalisation to a TFMPP cue while LSD produced intermediate results (Cunningham and Appel 1986; Fantegrossi et al. 2004; Schechter 1988; Yarosh et al. 2007). Furthermore, rhesus monkeys trained to self-administer cocaine did not generalise to TFMPP, suggesting that TFMPP

predominantly activates 5-HT receptors whereas cocaine predominantly activates DA receptors (Fantegrossi et al. 2005). Although TFMPP was not self-administered by rhesus monkeys, it produced MDMA-like stimulus effects in rats, demonstrating that TFMPP induces different behaviours across species (Fantegrossi et al. 2005; Fantegrossi et al. 2004). In summary, TFMPP produces fenfluramine- and MDMA-like behaviours by activating a range of 5-HT receptor subtypes.

1.3.3. Clinical studies of TFMPP

1.3.3.1. Effects of TFMPP on mood ratings, blood pressure, heart rate and body temperature

There has only been one clinical trial describing the effects of TFMPP in humans (Jan et al. 2010). The authors found that TFMPP (60 mg; oral) has moderate stimulant-like effects in humans. For example, TFMPP produced an increase in euphoria scores compared with placebo within the ARCI scales. In addition, TFMPP produced an increase in the VAS measures such as drug liking, stimulated and high compared with placebo. On the other hand, TFMPP also produced an increase in dysphoria scores within the ARCI scales, as well as an increase in effects on the tension/anxiety and confusion/bewilderment scales compared with placebo. Moreover, TFMPP also produced fenfluramine-like effects, resulting in increased feelings of paranoia and decreased self-confidence in the VAS measures (Jan et al. 2010). The authors concluded that while TFMPP produced amphetamine-like subjective effects (i.e. stimulated, tension/anxiety and high), it also produced subjective effects more commonly associated with serotonergic agents such as mCPP, fenfluramine and LSD (i.e. dysphoria, confusion/bewilderment). Furthermore, the findings from Jan et al. (2010) provide the support for the claims that TFMPP produces MDMA-like effects in humans as MDMA has also been reported to induce both amphetamine-like (i.e. euphoria, drug liking, high, stimulated) and LSD-like (i.e. dysphoria, confusion) effects in humans (Cami et al. 2000).

TFMPP did not cause significant changes in systolic/diastolic blood pressure, heart rate or body temperature (unpublished observation, Russell, B. R.). However, animal

studies suggest that TFMPP dose-dependently elicits body temperature changes and locomotor activity, therefore a careful dose-response study in humans would allow further characterisation of these effects.

1.3.3.2. Pharmacokinetics and metabolism of TFMPP

In fasting humans, TFMPP (60 mg; oral) reaches a maximum plasma concentration of 24 ng/mL, 90 minutes post-dose (Antia et al. 2010). TFMPP displayed a time delay of 30 minutes before being detected in human urine and plasma. The concentration of TFMPP dropped below the limit of quantification after 24 hours (Antia et al. 2010). Antia et al. (2010) reported that only one TFMPP metabolite, 4-OH-TFMPP was detected in humans. The authors tentatively identified a glucuronide conjugate of TFMPP and speculated that TFMPP also undergoes hydroxylation.

Human liver microsome studies report that TFMPP is metabolised by CYP 450 isoenzyme CYP2D6, CYP3A4 and CYP1A2 (Antia et al. 2009d), and is therefore subject to CYP 450 isoenzyme polymorphism (Bertilsson et al. 2002). See Table 3 (page 33) for a summary of the current findings relating to TFMPP.

Table 3. Summary of current findings relating to TFMPP

Preclinical evidence (Baumann et al. 2004)	TFMPP
Neurotransmitters involved	5-HT
Neurotransmitter transporters involved	5-HT transporter
Behavioural changes	hypolocomotor, hypophagia, head twitch
Clinical evidence (Jan et al. 2010)	
1. Mood ratings	
ARCI	
Dysphoria	↑
amphetamine-like effects	↑
POMS	
Tension/anxiety	↑
Confusion/bewilderment	↑
VAS	
Drug liking	↑
Stimulated	↑
High	↑
2. Physiological measures	
Blood pressure	-
Heart rate	-
Body temperature	-
3. Pharmacokinetic parameters (Antia et al. 2010)	
Peak plasma concentration	24 ng/ml at 90 minutes
Absorption half-life	24.6 minutes
Apparent clearance	384.24 L/h
Half-life	2 and 6 hours
Time taken to reach limit of quantification	24 hours (< 5 ng/mL)
Metabolite	4-OH-TFMPP

1.4. The combination of BZP and TFMPP (BZP+TFMPP)

1.4.1. Background

Party Pills consisted of BZP and TFMPP because the combination was thought to produce more profound MDMA-like mood changes. Preparations with a higher BZP content compared to TFMPP had trade names such as 'Hammered', 'The Grunter', 'Inferno' and 'Jet' suggesting their amphetamine-like effects, whereas preparations with higher TFMPP content had trade names such as 'Bent', 'Charge' and 'D-lite' suggest MDMA-like effects (see Table 4).

One study has suggested that when BZP and TFMPP were given together, they produced more pronounced effects in animals (suggesting drug-drug synergism), compared to when they were given separately (Baumann et al. 2004). The following section will examine current information available for the pharmacodynamic and behavioural effects and the metabolism of the combination of BZP+TFMPP.

Table 4. Stated amounts of BZP and TFMPP in Party Pills

Name	BZP (mg)	TFMPP (mg)
Hammered	**200**	100
The Grunter	**200**	25
Inferno	**180**	100
Jet	**170**	20
Bent	60	**250**
Charge	75	**200**
D-lite	75	**170**

1.4.2. Preclinical studies of BZP+TFMPP

In vivo studies of the rat nucleus accumbens report that MDMA increased levels of dialysate DA and 5-HT. In contrast BZP induced preferential release of DA over 5-HT (to a lesser extent at a higher concentration for the latter), whilst TFMPP selectively increased 5-HT release (Baumann et al. 2004). BZP and TFMPP, when administered separately, were at least three-fold less potent than MDMA in DA- and 5-HT-releasing potency. However, the combination of BZP+TFMPP produced a dramatic increase in extracellular levels of DA and 5-HT. The releasing potency of BZP+TFMPP (3mg/kg of each drug) on dialysate DA and 5-HT emulated the effects produced by low-dose MDMA (1 mg/kg). The effects of the combination on DA release were far greater (1286% increase) than the summed effects of BZP (402% increase) and TFMPP (129% increase). Interestingly, the combination (10 mg/kg) produced a smaller increase in 5-HT release (872%) compared to MDMA (3 mg/kg, 1445%), but a four-fold greater increase in DA levels (285%), suggesting the combination has synergistic effects on DA transmission. See Table 5 for summary of effects of MDMA, BZP and TFMPP and BZP+TFMPP on transporter-mediated release of the 5-HT transporter substrate [^{3}H]5-HT and DA transporter substrate [^{3}H]MPP$^+$ *in vitro*.

Table 5. Summary of the potency of MDMA, BZP, TFMPP and the combination of BZP and TFMPP to release preloaded [^{3}H]MPP$^+$ and [^{3}H]5-HT from rat synaptosomes in vitro (Baumann et al. 2005)

	[^{3}H]MPP$^+$	[^{3}H]5-HT
MDMA	Dose-dependent efflux EC_{50} = 119±8 nM	Dose-dependent efflux EC_{50} = 58±6 nM
BZP	Dose-dependent efflux EC_{50} = 175±13 nM	**Inactive at [10 µM]**
TFMPP	**Inactive at [10 µM]**	Dose-dependent efflux EC_{50} = 121±17 nM
BZP+TFMPP	BZP did not influence the 5-HT-releasing potency of TFMPP, and TFMPP did not influence the MPP$^+$-releasing potency of BZP	

Baumann et al. (2005) reported that although the combination of BZP+TFMPP produced an increase of extracellular DA and 5-HT *in vivo*, it did not produce significant locomotor activity in comparison to MDMA. In fact, BZP+TFMPP was less reinforcing than BZP alone in rhesus monkeys that were trained to discriminate amphetamine from saline (Fantegrossi et al. 2005). The discrepancies between biological and physiological activities may be explained by antagonism between TFMPP and BZP. Selective 5-HT_{2A} antagonists and selective 5-HT_{2C} agonists have been shown to reduce amphetamine/cocaine-induced hyperactivity and stimulation (Filip and Cunningham 2003; Grottick et al. 2000; Moser et al. 1996; O'Neill et al. 1999). Therefore, it is possible that TFMPP inhibits the motor-stimulant properties of BZP via partial agonist/antagonist activity at 5-HT_{2A} receptors together with full agonist activity at 5-HT_{2C} receptors (Baumann et al. 2005).

The combination of BZP+TFMPP produced less dose-appropriate responding in rhesus monkeys (Fantegrossi et al. 2005). The findings are reminiscent of the serotonergic modulation of the reinforcing effects of cocaine. Facilitation of the serotonergic system has been reported to reduce the reinforcing properties of cocaine in rats (Richardson and Roberts 1991) and rhesus monkeys (Kleven and Woolverton 1993), and modulate the specific behavioural and reinforcing effects of cocaine in squirrel monkeys (Czoty et al. 2002; Howell and Byrd 1995). TFMPP may act as a behavioural antagonist of the reinforcing effects of BZP. Other studies suggest that TFMPP reduces firing rates of DA neurons in the ventral tegmental area leading to a decrease DA levels within the nucleus accumbens (Di Matteo et al. 2000; Prisco et al. 1994). In addition, activation of 5-HT_{2C} receptors is said to suppress activity within the mesolimbic DA system (Di Matteo et al. 2001). These effects may reduce the reinforcing effects of BZP, leading to reduced self-administration when BZP and TFMPP are administered in combination.

In vitro metabolism studies of the BZP+TFMPP combination reported that they are substrates of CYP2D6, CYP1A2, CYP3A4 and CYP2C9 (Antia et al. 2009c; Staack et al. 2002; Tsutsumi et al. 2006). As these enzymes are involved in the metabolism of an extensive range of drugs such as antidepressants, antipsychotics and amphetamines, BZP/TFMPP are likely to interact with these drugs (Bertilsson et al. 2002). In addition, because BZP and TFMPP are substrates of the same CYP 450 enzymes, co-administration is likely to result in

reduced metabolism of one or both of these compounds and increase their respective plasma concentrations.

1.4.3. Clinical studies of BZP+TFMPP

1.4.3.1. Effects of BZP+TFMPP on mood ratings, blood pressure, heart rate and body temperature

As stated above, recreational drug users have taken BZP and TFMPP in combination for their ability to elicit MDMA-like subjective effects. A recent clinical trial reported that the combination of BZP+TFMPP (100/30 mg, respectively), even at 50% of the base dose (200, 60 mg, respectively), significantly increased their stimulant-like effects as reported by increases in amphetamine-like effects and dysphoria rating scales used within the ARCI. The authors deliberately used 50% of the base dose due to reported drug-drug synergism in rodents (Baumann et al. 2005). The combination also significantly increased the vigour/activity scale within the POMS, and increased a number of VAS scales i.e. 'drug effect', 'good drug effect', 'drug liking', 'stimulated' and 'self-confident' (Lin et al. 2011). These results suggest that when BZP and TFMPP are taken together at these doses, they produce dexamphetamine- and MDMA-like effects.

Despite the reported synergism of the combination of BZP+TFMPP in animals (Baumann et al. 2004; 2005), human studies suggest that this combination is less reinforcing than when BZP was taken separately. When BZP (200mg; oral) was given alone, it produced pronounced effects on subjective mood rating scales, specifically it significantly changed three of five ARCI scales, five of seven POMS scales and 10 of 20 VAS scales, all of which indicated that BZP induces amphetamine-like effects (Lin et al. 2009). Similarly, TFMPP (60 mg; oral) significantly changed two of five ARCI scales, one of seven POMS scales and 2 of 20 VAS scales (Jan et al. 2010). However, when the combination of BZP+TFMPP (100/30 mg, respectively) was given changes in two of five ARCI scales, one of seven POMS scales and 5 of 20 VAS scales were seen (Lin et al. 2011). The subjective mood ratings suggest that BZP (200 mg; oral) produced the most significant changes, followed by the combination of BZP+TFMPP (100/30mg, respectively) while TFMPP produced the least changes. The

discrepancies observed in neurochemical synergism between rodents and humans can be attributed to the fact that Baumann et al. (2004; 2005) administered a high dose of BZP+TFMPP (10 mg/kg of each compound) in rats, translating to 700 mg of each compound in a 70 kg human. Therefore, the chemical synergism observed is likely due to the relatively higher doses of BZP+TFMPP administered to animals or their competitive inhibition of their metabolism by CYP2D6 resulting in higher plasma levels.

BZP+TFMPP significantly increased blood pressure and heart rate (Lin et al. 2011), similarly to BZP (200 mg; oral) and other stimulants such as cocaine and MDMA in humans (Higgins et al. 1993; Lin et al. 2009; Vollenweider et al. 1998). These effects are reportedly mediated by NA acting on postsynaptic α_1- and α_2-adrenoceptors (Kanagy 2005); however, the combination at this dose did not significantly affect body temperature.

1.4.3.2. Pharmacokinetics and metabolism of BZP/TFMPP

When an oral dose of BZP and TFMPP (100/30 mg, respectively) was given to humans, apparent changes in the metabolism of BZP and TFMPP were observed compared to when they were administered individually (Antia et al. 2009a). BZP in the presence of TFMPP reached a peak plasma concentration of 295 ng/ml 60 minutes post-dose. The absorption half-life was reported to be 6 minutes and the BZP concentration dropped below the limit of quantification after 24 hours. Only one metabolite of BZP i.e. 4-OH-BZP, was detected in human urine samples, suggesting that the metabolism of BZP was altered in presence of TFMPP. In addition, some pharmacokinetics properties of TFMPP were altered, as the lag time taken for absorption was reduced from 30 to 0 minutes. See Table 6 for a summary of the current findings relating to BZP+TFMPP.

Table 6. Summary of current findings relating to BZP+TFMPP (100 mg + 30 mg)

Preclinical evidence **(Baumann et al. 2004)**	**BZP**	**TFMPP**	**BZP+TFMPP**
Neurotransmitters involved	DA, 5-HT, NA	5-HT	5-HT, DA
Neurotransmitter transporters involved	DA/5-HT transporters	5-HT transporter	DA/5-HT transporters
Behavioural changes	hyperactivity, stereotypy, self-administration	hypolocomotor, hypophagia, head twitch	less stimulating than BZP alone
Clinical evidence **(Lin et al. 2009)**			
1. Mood ratings			
ARCI			
Euphoria	↑		
Dysphoria	↑	↑	↑
Amphetamine-like effects	↑	↑	↑
POMS			
Tension/anxiety		↑	
Depression/dejection	↓		
Fatigue/inertia	↓		
Confusion/bewilderment	↓	↑	
Vigour/activity	↑		↑
Total mood disturbance	↑		
VAS			
Drug effect	↑		↑
Good drug effect	↑		↑
Drug liking	↑	↑	↑
Stimulated	↑	↑	↑
High	↑	↑	
Anxious	↑		
Talkative	↑		
Self-confident	↑		↑
Social	↑		
2. Physiological measures			
Blood pressure	↑	-	↑
Heart rate	↑	-	↑

Body temperature	dependent on ambient temperature	-	-	
3. Pharmacokinetic parameters (Antia et al. 2009b)			BZP	TFMPP
Peak plasma concentration	262 ng/ml at 75 min	24 ng/ml at 90 min	295 ng/ml at 60 min	28 ng/ml at 75 min
Absorption half-life	6.2 minutes	24.6 minutes	6 minutes	13.3 minutes
Apparent clearance	58.3 L/h	384.24 L/h	NA	NA
Half-life	5.5 h	2 and 6 h	2.3 h	4.3 h
Time taken to reach limit of quantification	24 h (< 15 ng/mL)	24 h (<5 ng/mL)	24 h	24 h
Metabolites	4-OH-BZP/ 3-OH-BZP	4-OH-TFMPP	4-OH-BZP	-

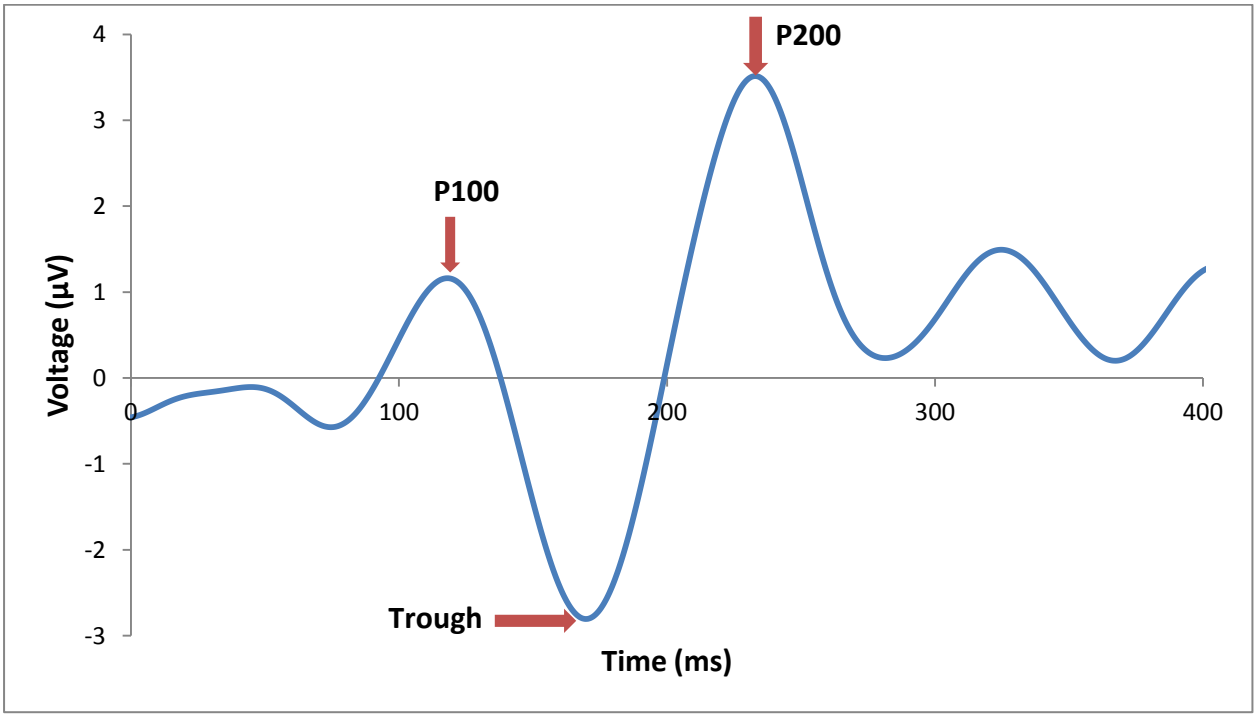
1.5. Electroencephalography and event-related potentials

The electrical activity of the brain, either the on-going activity or changes in activity related to a given sensory or motor event (i.e. the event-related potentials or ERPs) can be measured by electroencephalography (EEG) and allows us to study brain function. ERPs provide information about the electrical activity of the brain and allow for the analysis of dynamic activities such as global brain functions (e.g. sleep, arousal), cognitive processes (e.g. perception, motor preparation) and higher cognitive functions (Lopez da Silva 2004). ERPs have excellent temporal resolution, in the magnitude of milliseconds, and allow precise analysis of the timing of neurophysiological activity. Hence, it is possible to gather information about the electrical activity of the brain related to a given sensory or motor event. In addition, ERPs can be measured non-invasively and are very sensitive to a range of experimental manipulations. Donchin and Coles (1988) reported that electrophysiological patterns in response to cognitive tasks and events were consistent across subjects and repetitions, supporting the hypothesis that recorded ERPs can be valuable tools for research about human neural processing and cognition (Donchin and Coles 1988).

Advances in the analysis of ERPs and our increasing knowledge of the anatomical structures and cellular processes underlying ERPs allow us to bridge the gap between ERPs and their basic neurophysiology. ERPs result from intracortical currents produced by excitatory and inhibitory postsynaptic potentials (EPSPs, IPSPs), which are essentially mediated by the release of neurotransmitters (Frodl-Bauch et al. 1999; Lopez da Silva 2004). Therefore, it has been suggested that ERPs reflect the postsynaptic effects of neurotransmitters such as glutamate and gamma-aminobutyric acid (GABA) and the indirect modulating effects of neuromodulators such as acetylcholine, NA, DA or 5-HT. Therefore, changes in ERPs can be used as indicators for disturbances in these neurochemical systems within the central nervous system (CNS). In this thesis, we have utilised interhemispheric transfer time and the P300 ERP to investigate the central effects of BZP, TFMPP and their combination. The following section will provide an overview of how research in psychopharmacology has utilised the interhemispheric transfer time and P300 ERP as tools to explore drug-induced changes in the CNS.

In ERP studies, the participant is repeatedly stimulated using sensory (i.e. visual or aural) stimuli while EEG is continuously recorded. The electrophysiological activity is synchronised with the exact time point of stimulus presentation and the ERP data are extracted from the background noise signal by averaging the single responses to repeated stimuli. This signal averaging method is based on the idea that the background EEG has no fixed temporal relationship with the point of time at which the stimulus was presented. Therefore, if a sufficient number of trials is collected and they are subject to signal averaging, the end result will reflect the brain activity at specific time points. ERP signals are characterised by measuring the position in time (latency) and the amplitude of the components induced by sensory stimulation. Figure 4 shows an example of an ERP after averaging 120 single responses to a randomly presented visual stimulus with three main components identified as the P100, Trough, and P200, respectively. The amplitude and position in time of the components corresponding to depolarization and re-polarisation activity characterises the cortical process evoked by the visual stimuli.

Figure 4. Example of an ERP averaged from 120 single responses of randomly presented visual stimuli. The position and amplitude in time of the components related to stimulus presentation (at t=0) allows parameterisation of the evoked response (averaged waveform)

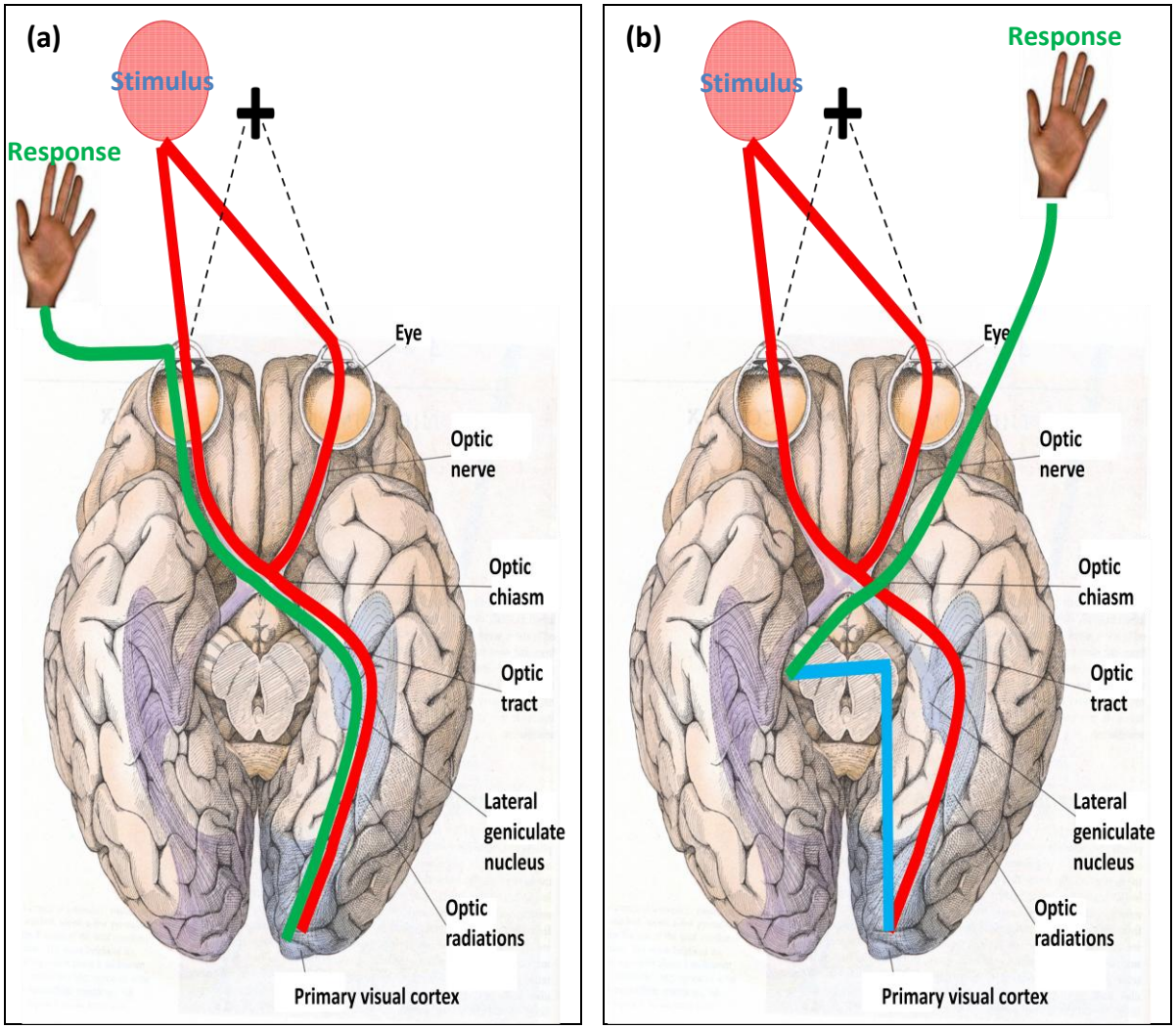


1.5.1. Interhemispheric transfer time

Cognitive neuroscience aims to identify the underlying neural mechanisms of cognition. It is difficult to correlate discrete cognitive tasks with specific brain regions as widespread regions are recruited for processing even simple cognitive tasks. In order to overcome this barrier, Poffenberger (1912) devised a task allowing "brain dynamics [to] be modeled and tested in anatomically localized subcircuits of the brain in something approximating real space and real time" (Braun 1992). The measure derived from the Poffenberger task uses the interhemispheric transfer time to index the latency of information transfer from one cerebral hemisphere to the other, primarily across the corpus callosum.

Poffenberger first investigated the interhemispheric transfer time by using a behavioural estimate in which participants responded to the detection of a brief visual stimulus presented to the left or right visual field (Poffenberger 1912). Behavioural reaction time was used to calculate interhemispheric transfer time by subtracting the reaction time of a response hand on the ipsilateral side to the visual field stimulation from the reaction time to contralateral stimulation. Hemispheric transfer is required when stimuli are presented ipsilaterally to the hemisphere controlling the responding hand (i.e. crossed route), but no transfer is required when stimuli are presented contralaterally to the hemisphere controlling the responding hand (i.e. uncrossed route). This time difference is also referred to as the crossed-uncrossed difference. Poffenberger suggested that the time difference between the crossed and uncrossed routes provided a reliable estimate of interhemispheric transfer time (see Figure 5).

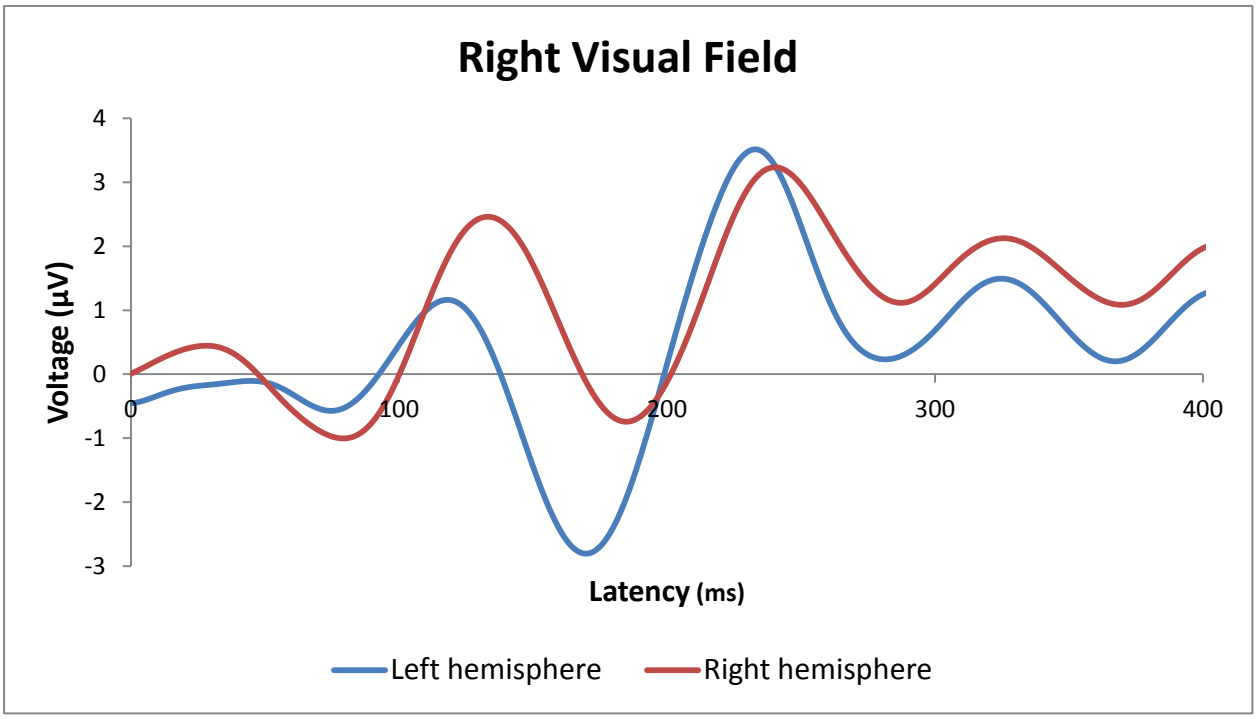
Figure 5. Diagram of the uncrossed (a) and crossed (b) condition of the Poffenberger task. Perceptive pathways are shown in red, motor pathways are shown in green. The additional callosal transfer of the crossed condition is shown in blue (pathways not shown anatomically correct)



However, there are some uncertainties about this method. It has been suggested that the behavioural method of using the reaction time to calculate interhemispheric transfer time may also involve some non-callosal pathways (Brown et al. 1998), therefore it might not be a true reflection of information transfer via the corpus callosum. It is also uncertain whether the behavioural reaction time provides information about the difference in interhemispheric transmission of sensory information or if it is confounded by motor information (Milner and Lines 1982). If the latter is the case, the integrity of information gathered using this method is subject to uncertainty.

In order to overcome some of the anatomical uncertainties related to using reaction time, recent studies have utilised ERPs to estimate interhemispheric transfer time (Nowicka et al. 1996; Rugg et al. 1984). During the collection of visual evoked potential ERPs, brain activity is simultaneously recorded from both cerebral hemispheres as the participant responds to visual stimuli presented to either one or the other visual field. Figure 6 shows a visual evoked potential to a stimulus in the right visual field; the visual stimulus is first registered in the left hemisphere (blue line; contralateral to visual stimuli) then in the right hemisphere (red line; ipsilateral to visual stimuli). This method uses the latency difference between visual evoked potential components registered in the ipsilateral hemisphere and the contralateral hemisphere of the stimulated visual field to calculate the interhemispheric transfer time.

Figure 6. Visual-evoked potential in the right visual field



1.5.1.1. Interhemispheric transfer time and the structural properties of the corpus callosum

The corpus callosum uses glutamate as its neurotransmitter (Kumar and Huguenard 2001). The main function of the corpus callosum is to facilitate interhemispheric communication by acting as a pathway transferring information between the two hemispheres (Lassonde 1986) and facilitating cortical connectivity in the brain (Innocenti 1980b). Cortical pyramidal cells produce synaptic activity caused by either EPSP or IPSP post-synaptic currents. The activation of a synapse causing an ionic current to flow in the cortical pyramidal cells will generate a post-synaptic potential change that is measured using EEG. Glutamate is the major excitatory neurotransmitter of the pyramidal neurons in the brain (Cotman and Monaghan 1987; McDonald 1996). Monoaminergic brainstem neurons are modulated by corticofugal glutamatergic neurons either directly or via GABAergic interneurons (Carlsson et al. 1999). The human corpus callosum consists of at least 200 million fibres of which most arise from excitatory and glutamatergic pyramidal neurons (Aboitiz 1992; Conti and Manzoni 1994; Peters et al. 1990; Tomasch 1954). The cells of neocortical callosal projections are almost exclusively pyramidal cells with excitatory asymmetric synapses on spines of pyramidal neurons in homo- and heterotopic regions of the contralateral cortex (Akers and Killackey 1978; Jacobson 1965; Jacobson and Trojanowski 1974; Wise and Jones 1976).

Furthermore, it is reported that only around 5% of callosal fibres are inhibitory and GABAergic (Hughes and Peters 1992; Voigt et al. 1988). However, the main effect of callosal activation appears to be inhibitory, rather than excitatory (Innocenti 1980b). This is because most callosal fibres terminate on pyramidal neurons which then activate GABAergic interneurons (Toyama and Matsunami 1976; Toyama et al. 1969). It is suggested that the corpus callosum does not simply produce any excitatory or inhibitory action on the contralateral hemisphere, but that it provokes brief EPSPs, followed by prolonged IPSPs. The EPSPs are known to be mediated by activation of glutamatergic non-NMDA receptors (Kawaguchi 1992; Schwartzkroin et al. 1975). It is hypothesised that the corpus callosum activates pyramidal neurons, which in turn activate these inhibitory GABAergic neurons (Innocenti 1980a). Both $GABA_A$ and $GABA_B$ receptor subtypes reportedly mediate

transcallosal responses in humans. It has been shown that $GABA_B$-agonist baclofen strengthened interhemispheric inhibition via postsynaptic $GABA_B$ receptors, whereas $GABA_A$ agonist midazolam caused attenuation of interhemispheric inhibition.

As previously mentioned, the corpus callosum is an essential structure and almost exclusively responsible for the transfer of information between the cerebral hemispheres (Cherbuin and Brinkman 2006a; Funnell et al. 2000; Gazzaniga 2000; Iacoboni and Zaidel 2004). Many have consistently demonstrated that split-brain or acallosal individuals are unable to perform tasks that involve simple visual stimuli affecting either left or right visual fields (Berlucchi et al. 1995; Eviatar and Zaidel 1994), and that acallosal individuals display a dramatically lengthened interhemispheric transfer time (e.g. 14 times longer) as measured by the Poffenberger task (Berlucchi et al. 1995). Traumatic brain injury resulting in lesions of the corpus callosum has also been linked to both temporary and permanent signs of interhemispheric disconnection (Peru et al. 2003). Any compromise in the integrity of information sharing between the two hemispheres has been linked to cognitive deficits. For example, faster interhemispheric transfer time has been reported in children with reading disability (Davidson and Saron 1992). On the other hand, delayed interhemispheric transfer may disrupt functions mediated predominantly by the left hemisphere (e.g. approach behaviour, language processing) and the right hemisphere (e.g. behavioural inhibition, emotion processing). In fact, delayed interhemispheric transfer, especially in the Right-to-Left direction, has been linked with affective and cognitive processing abnormalities (Barnett and Kirk 2005; Barnett et al. 2005).

Larger callosal size has been associated with improved accuracy of performance in a verbal task requiring callosal transfer (Hellige et al. 1998), greater interhemispheric connectivity (Brown et al. 1994) and reduced reaction time in a visual detection task (Madden et al. 2004). Of particular relevance, interhemispheric transfer time is asymmetric in healthy right-handed males; the speed of callosal transfer from Right-to-Left is faster than Left-to-Right (Brown et al. 1998), which is the result of "an asymmetry in callosal connections, with greater number of neurons projecting from the right hemisphere to the left, than vice versa" (Brown et al. 1998). Moreover, studies found that functional asymmetry of the corpus callosum may be associated with sex, as males showed more asymmetric transmission of verbal information with longer Left-to-Right transmission

(Nowicka and Fersten 2001; Nowicka et al. 1996). In contrast, left-handed individuals have been shown to differ from right-handed individuals in terms of brain morphology and anatomical and functional laterality, therefore they tend to have more symmetric interhemispheric transfer time compared to right-handed people (Cherbuin and Brinkman 2006b).

Since the corpus callosum is an essential structure for the communication between two hemispheres, the investigation of interhemispheric transfer time in the presence of psychoactive drugs could provide information about the integrity of interhemispheric processing. The following section will discuss the neuropharmacology and the interhemispheric transfer time.

1.5.1.2. Neuropharmacology and the interhemispheric transfer time

There is a small a number of studies reporting the effects of neuropharmacologically active compounds on interhemispheric transfer time. Acute ethanol intake in adults produced significantly delayed interhemispheric transfer (Khan and Timney 2007). The authors concluded that a reduction in processing efficiency was the underlying cause for alcohol-induced changes in temporal processing. In addition, consumption of piracetam has been reported to facilitate interhemispheric transfer (Buresova and Bures 1976).

There have been a few studies investigating transcallosal transfer using other approaches. Studies have suggested oestradiol affects functional cerebral asymmetries (Hollander et al. 2005), whereas high levels of progesterone are related to a reduction of lateralisation in humans (Hausmann et al. 2002; Hausmann and Gunturkun 2000). In normal cycling women, the effects of progesterone were evident for both left and right hemispheric tasks, word matching and figural comparison, face discrimination, respectively, therefore the authors concluded that progesterone modulates the interhemispheric inhibition via the corpus callosum (Hausmann et al. 2002; Hausmann and Gunturkun 2000), which is thought to be an essential mechanism in causing functional cerebral asymmetries (Chiarello and Maxfield 1996; Cook 1984). Findings from these behavioural studies were supported by a functional magnetic resonance imaging (fMRI) study that reported an increase of symmetric

activation in a semantic decision task which was positively related with progesterone levels (Fernandez et al. 2003). Furthermore, the neuromodulatory effects of oestradiol and progesterone are suggested to be mediated by transcallosal excitatory projections terminating on pyramidal neurons that activate inhibitory GABAergic interneurons (Kawaguchi 1992; Toyama and Matsunami 1976; Toyama et al. 1969).

It is suggested that glutamate and GABA play a major role in the functional regulation of the corpus callosum and the interhemispheric transfer of information (Bloom and Hynd 2005). Almost all neurons in the brain are under the control of a direct glutamatergic pathway and an indirect glutamatergic/GABAergic pathway (Carr and Sesack 1998) and both inhibitory and excitatory messages have been demonstrated to travel through the corpus callosum (Lassonde 1986).

Carlsson et al. (1999) proposed a hypothesis that the cortical regulation of the activity of the monoaminergic brainstem neurons is under the direct control of glutamatergic pathways (acting as an 'accelerator') and the indirect control of glutamatergic/GABAergic pathways (acting as a 'brake'; Figure 7).

Figure 7. Schematic diagram of the glutamatergic/GABAergic influences as 'accelerator/ brake' in subcortical systems. Reproduced from Carlsson et al. (1999) with permission from Elsevier (1999©)

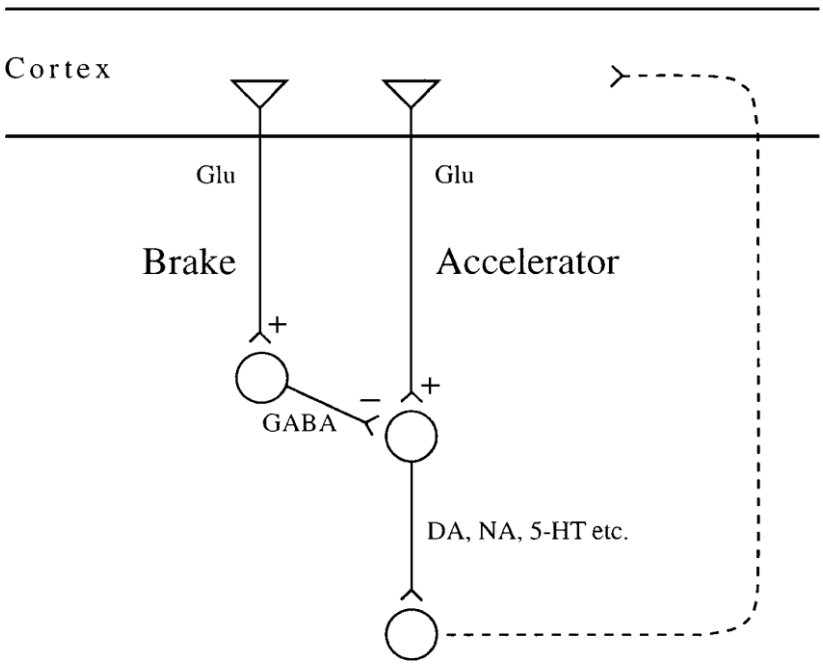


Figure 7 shows the cortical regulation of the activity of monoaminergic brainstem neurons by means of a direct glutamatergic pathway ('accelerator') and an indirect glutamatergic/GABAergic pathway ('brake'). DA, NA and 5-HT neurons seem to be controlled by corticofugal glutamatergic neurons. Under normal conditions, there seems to be a balance between the accelerator and the brake, but in the presence of a DA releaser (e.g. amphetamine) dopaminergic function is enhanced, which in turn activates a negative feedback regulation leading to a strong overweight of the brake.

It has been suggested that glutamatergic hypofunction may be responsible for disrupted interhemispheric communication in individuals with autism as indicated by neuropsychological tests (Carlsson 1998; Nyden et al. 2004). This theory was suggested after observing similarities between the symptoms produced by NMDA antagonist treatment and symptoms of autism (Carlsson 1998). Interestingly, the 5-HT_{2A} receptor agonist LSD emulated symptoms of autism in the aforementioned trial (Carlsson 1988). LSD is thought to exert psychotogenic effects by stimulating GABAergic interneurons in the limbic cortex, thus reducing corticostriatal glutamatergic tone (Gellman and Aghajanian 1991).

The findings from the studies suggest that the transmission may be under the influence of glutamatergic and GABAergic, as well as dopaminergic, noradrenergic and serotonergic systems. Therefore, the accelerator/brake theory could be helpful when explaining drug effects on interhemispheric transfer time.

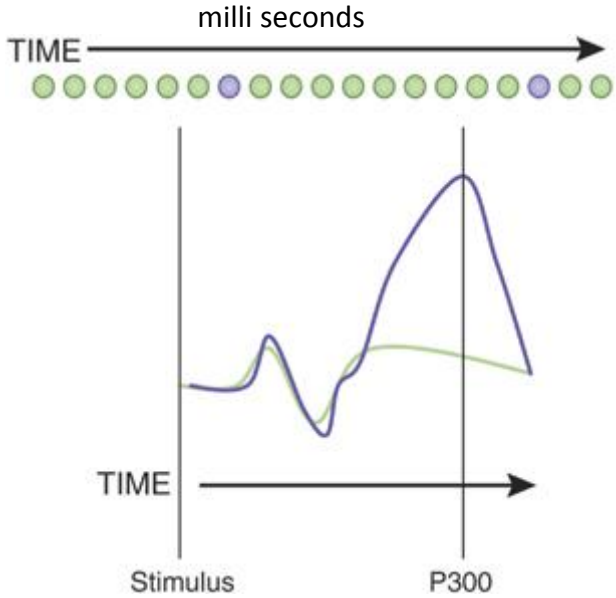
1.5.2. The P300

1.5.2.1. The oddball paradigm/components of the P300

First reported in 1965, the P300 ERP has been used extensively for investigating human cognition (Anderer et al. 1998a; Polich and Herbst 2000; Sutton et al. 1965). The P300 is considered be an index of cognitive processing as it represents cognitive neuroelectric phenomena such as attention allocation and activation of immediate memory

(Polich and Kok 1995). The P300 is evoked when a subject discriminates a novel stimulus from a non-novel one on some dimension such as visual or aural cue (Picton 1992). The novel stimuli are given during an 'oddball' paradigm, in which a random sequence of stimuli is presented (Donchin et al. 1978; Pritchard 1981). The stimuli can be classified into one of two categories, and the subject is instructed to respond to stimuli occurring infrequently (e.g. oddballs) by means of either counting or by pressing a button. The oddball stimuli elicit a P300. The P300 ERP occurs approximately 260-460 ms after the stimulus (Figure 8). The traditional two-stimulus oddball paradigm presents infrequent target stimuli in combination with frequent non-target stimuli.

Figure 8. A typical P300 set up and response. Successive green dots indicate frequent stimuli and infrequent purple dots represent 'oddballs' requiring a response (e.g. keyboard press). Reproduced from Kenemans and Kahkonen (2011) with permission from Nature Publishing Group (2011©)



P300 amplitude is reflective of the brain activity required to update working memory when changes occur in the stimulus environment (Kenemans and Kahkonen 2011; Polich and Herbst 2000). It is defined as the voltage difference between the pre-stimulus baseline and the largest positive peak of the P300 ERP. P300 amplitude is proportional to the amount of attentional resources available and memory performance, and it is regarded as a

measure of CNS efficiency to process and incorporate stimulus information (Polich and Herbst 2000). Superior memory performance has been associated with larger P300 amplitudes (Fabiani et al. 1990), therefore variation in P300 amplitude is thought to reflect the degree or quality of CNS activity when information is processed. For example, reduction in P300 amplitude has been reported in schizophrenia (Jeon and Polich 2003; McCarley et al. 1991; Muller et al. 2001; O'Donnell et al. 1999). In addition, reduced P300 amplitude was found to be a predictor of poor clinical outcome with antipsychotic treatment, incomplete remission and a higher risk for tardative dyskinesia (Ford et al. 1994; Hegerl et al. 1995; Strik et al. 1993).

P300 latency is related to the time required for stimulus evaluation, also reflecting the processes of attention allocation and immediate memory in both normal and clinical populations (Kutas et al. 1977; Polich and Herbst 2000). It is defined as the time difference between stimulus onset and the occurrence of the maximum positive peak. However, P300 latency is generally unrelated to response selection processes (McCarthy and Donchin 1981), and is therefore independent of behavioural reaction time (Duncan-Johnson 1981; Verleger 1997). P300 latency has been negatively correlated with mental capacity, with longer latencies associated with decreased cognitive performances (Goodin et al. 1978a; Goodin et al. 1978b). Prolongation of P300 latency has been found in patients with schizophrenia, dementia and idiopathic Parkinsonism (Blackwood et al. 1987; Ito et al. 1990; Pfefferbaum et al. 1990; Stanzione et al. 1991).

1.5.2.2. Biological determinants of the P300

There are also a number of external factors referred to as 'biological determinants' of the P300 that contribute to variance. By controlling or reducing extraneous sources of ERP variance, greater P300 sensitivity can be achieved (Polich and Kok 1995).

These natural factors i.e. biological determinants are able to influence the P300, regardless of experimenter-manipulated variables and refer to naturally varying phenomena that continuously and systematically influence CNS functions. For example, Geisler and Polich (1990) reported that although no statistically reliable association was found between time of day and P300 amplitude or latency, body temperature and heart rate significantly varied as a function of circadian rhythm. Both body temperature and heart rate increased gradually during the course of the day before declining during early evening. Changes in P300 latency correlated with these physiological measures, as a higher body temperature was associated with increasing P300 latency, whereas higher heart rate was associated with a shorter P300 latency. This suggests that time of day indirectly influences P300 latency.

In a study investigating the effect of food intake on the P300 throughout the day, P300 amplitude was decreased in individuals who had not recently eaten, and it increased just after eating while latency was unaffected (Geisler and Polich 1992). Furthermore, the study failed to identify a relationship between P300 and blood glucose levels. Consequently, it was hypothesised that recency of food ingestion affects the general level of arousal which in turn affects cognitive processing.

Limited research also suggests that the P300 is subject to modulation by ultradian rhythms, the menstrual cycle and seasonal variations. It was reported that ultradian fluctuations in arousal levels occur in 90-minute cycles and are reflected in the P300 ERP (Lloyd and Stupfel 1991).

Females display a larger variations in P300 amplitude in response to 'emotional' stimuli (e.g. nude males, babies etc) during ovulation compared to other times (Johnston and Wang 1991). In addition, females with late luteal phase dysphoric disorder also display a longer P300 latency compared to those without the disorder, suggesting that the P300 is also under the influence of hormonal changes (Ehlers et al. 1996). Females generally display

a larger P300 amplitude and shorter latency compared to males, although findings have been inconsistent between studies (Conroy and Polich 2007; Deldin et al. 1994; Hoffman and Polich 1999; Polich 1986). It has been suggested that these gender differences are a result of differences in gonadal hormones (Kimura and Hampson 1994), as well as a difference in brain structures between males and females (Highley et al. 1999; Potter and Graves 1988; Westerhausen et al. 2004).

Changes in the P300 ERP due to the variations with seasonal change have also been reported. Although the studies found no direct relationship between seasonal effects and P300 amplitude and latency, it was suggested that the changes could be related to arousal in response to varying amounts of daylight between different seasons (Deldin et al. 1994; Polich 1990). Therefore, caution should be taken when analysing P300 ERP data collected across seasons or geographical locations with differing amounts of daylight.

Numerous studies have reported that exercise can affect mental performance i.e. cognitive function (Bashore and Goddard 1993; Tomporowski and Ellis 1986). For example, individuals who exercise on a regular basis display a larger P300 amplitude and shorter latency compared to those who do not exercise (Bashore 1989).

Sleep deprivation is also known to negatively influence general cortical arousal and therefore the P300 ERP. When healthy volunteers were sleep-deprived, they displayed a smaller P300 amplitude and longer latency, as well as making more omission errors and taking longer to complete tasks. The P300 amplitude was decreased across all electrode sites in sleep deprived individuals, producing a global decrease in general arousal (Polich and Kok 1995).

Several studies have reported that the P300 amplitude is affected by handedness. In young adults, it was found that the P300 amplitude in the right hemisphere was greater than that in the left hemisphere, suggesting fundamental neurophysiological differences between hemispheres (Alexander and Polich 1997; Alexander et al. 1995; Hoffman and Polich 1999). Although the source of handedness effects on the P300 ERPs is unknown, factors such as differences in brain morphology, skull thickness or cranial differences between handedness groups have all been suggested to affect amplitude (Daniel et al. 1989). In addition, a strong correlation between handedness and callosal size has been

identified (Davatzikos and Resnick 1998; DeLacoste-Utamsing and Holloway 1982; Salat et al. 1997) and is likely to influence the P300 ERP.

1.5.2.3. Neuropharmacology and the P300

The neurotransmitters systems underlying P300 generation are as yet unclear, although a number of mechanisms have been suggested (Frodl-Bauch et al. 1999; Hansenne 2000b). The dopaminergic, noradrenergic, serotonergic and cholinergic systems have all been suggested to play an important role in the generation and the modulation of P300 (Duncan et al. 2009; Meador et al. 1987; Pineda et al. 1991).

Many studies provide strong support for dopaminergic involvement in the generation of the P300 waveform. First, support comes from a study where Parkinsonian patients with decreased levels of DA display a reduced P300 amplitude and increased latency (Hansch et al. 1982; Stanzione et al. 1991). Second, treatment with L-DOPA and benserazide in idiopathic Parkinsonian patients normalised previously lengthened P300 latency (Stanzione et al. 1991). Third, pharmacological studies using apomorphine found a correlation between DA mediation and P300 amplitude and latency in depressed patients (Hansenne et al. 1995). Although these studies were carried out in clinical population rather than healthy controls, these findings support the hypothesis that dopaminergic pathways contribute to P300 generation.

The locus coeruleus is a nucleus in the pontine region of the brain stem that consists of cells containing NA, which provide the primary source of noradrenergic innervations in the forebrain (Berridge and Waterhouse 2003). Because animals with lesions of the locus coeruleus display a significantly reduced P300 amplitude (Pineda et al. 1989), the locus coeruleus/noradrenergic system is also likely to be involved in its modulation. The administration of clonidine, an α_2-adrenergic agonist and microinjections of α_2 antagonists and agonists in the temporoparietal junctions in monkeys significantly reduced P300 amplitude (Pineda et al. 1991). Clonidine reduces the firing rate of the locus coeruleus, hence decreases P300 amplitude and lengthens P300 latency. However, clonidine also

produces anticholinergic effects that may contribute to P300 generation. In addition, studies using methylphenidate which inhibits NA and DA reuptake have not all provided consistent findings with regard to their ability to influence the P300 component (Halliday et al. 1983; Naylor et al. 1985). This is partly due to its lack of specificity for noradrenergic, dopaminergic, serotonergic and cholinergic pathways. In humans, the locus coeruleus/noradrenergic system has been implicated in the generation of P300 ERP in a simple target detection task, as well as in tasks requiring attention resources allocation (Kok 1997; Nieuwenhuis et al. 2005).

Pharmacological studies of the serotonergic modulation of the P300 amplitude and latency have reported inconsistent findings. For example, serotonergic antagonists such as fenfluramine and methysergide produced no significant effect on the P300 and Unrug et al. (1997) found the anxiolytic drug buspirone had no effect on P300 amplitude (Meador et al. 1989; Pritchard et al. 1987; Unrug et al. 1997). Flesinoxan, a 5-HT_{1A} agonist, decreased serotonergic function which was associated with a large P300 amplitude (Hansenne and Ansseau 1999). In contrast, Ito et al. (1990) found a positive relationship between the P300 amplitude and concentrations of 5-hydroxyindoleacetic acid, the major metabolite of 5-HT, in the cerebrospinal fluid. Moreover, a study demonstrated an interactive role between the serotonergic and cholinergic systems on P300 latency (Meador et al. 1995). These inconsistencies are likely due to methodological differences as they used a different paradigm and task performance in quite different subjects i.e. depression and dementia.

A number of studies have reported that acetylcholine is also an important neuromodulator of the P300, as increases in memory performance and P300 amplitude have been observed after administration of cholinergic drugs (Barbeau 1978; Dierks et al. 1994; Mohs and Davis 1985). For example, scopolamine, an anticholinergic drug, significantly reduced P300 amplitude and increased latency (Meador et al. 1987), whereas the muscarinic agonist RS 86 increased the P300 amplitude of patients with Alzheimer's disease (Hollander et al. 1987). In addition, animals with lesions in the septal nuclei produced attenuated P300 components (Buchwald 1990; Harrison et al. 1988). As the septal nuclei are the major source of cholinergic input to the hippocampus and the neocortex, it is likely that the cholinergic system indirectly modulates P300 generation.

Sedative GABAergic drugs such as midazolam, diazepam and clonazepam also decrease P300 amplitude and prolong latency (Domino et al. 1989; Ray et al. 1992; Reinsel et al. 1991; Rockstroh et al. 1991). It was suggested that these effects were produced by indirect inhibitory GABAergic influences on glutamatergic EPSPs, therefore GABAergic influences on P300 generation are most likely by indirect means (Frodl-Bauch et al. 1999).

In conclusion the evidence suggests that generation of the P300 seems to be under the complex influences of many neurotransmitters. Although further research is warranted to elucidate the precise involvement of each neurotransmitter in the generation of the P300, these findings provide justification of evaluating acute and chronic drug-induced changes on neurophysiological function.

1.5.2.4. P300 and neurological disorders

Many have suggested that the P300 ERP could be used in the diagnosis of various psychiatric disorders. For example, in a meta-analysis of patients with schizophrenia, a smaller P300 amplitude was reported in comparison to control subjects (Jeon and Polich 2001). It is believed that schizophrenia develops from abnormalities in the prefrontal and temporo-limbic networks, leading to disruptions in neural processing and symptoms of schizophrenia (Nuechterlein and Dawson 1984; Turetsky et al. 1995; Weinberger et al. 1992). As mentioned previously, the P300 is thought to be generated as a result of an interaction between frontal lobe and hippocampal/temporoparietal function (Demiralp et al. 2001a; Demiralp et al. 2002; Kirino et al. 2000; Knight 1996), therefore changes in the P300 measures could act as a valid biomarker of risk for the development of schizophrenia (Jeon and Polich 2001). Considering the *N*-methyl-*D*-aspartate (NMDA) and DA hypotheses of schizophrenia, alterations in glutamatergic and dopaminergic systems are likely to contribute to reduced P300 amplitude (Frodl-Bauch et al. 1999; Sohn et al. 1998).

In the early stages of Alzheimer's disease, patients displayed decreases in P300 amplitude and a longer peak latency. Systematic increases in P300 latency have been linked to increases in cognitive dysfunction, therefore the P300 ERP could also be used as a

diagnostic marker of dementia and used in the assessment of early Alzheimer's disease stage (Polich 1989; Polich et al. 1990).

Furthermore, it has been suggested that the P300 ERP could be a biomarker for attention deficit hyperactivity disorder (ADHD; Alexander et al. 2008), multiple sclerosis (Polich and Martin 1992), bipolar disorder (O'Donnell et al. 2004; Salisbury et al. 1999) and individuals at risk of alcoholism (Reese and Polich 2003). These findings suggest that the P300 may be a useful clinical tool for indexing cognitive functions in both normal and clinical populations. However, any brain disorder affecting the primary cognitive operations of attention allocation and immediate memory will inevitably influence P300 measures (Polich and Herbst 2000).

1.6. Rationale for the present study

Both preclinical and clinical studies of BZP, TFMPP and their combination report that these compounds possess stimulant-like properties resulting in their recreational use. Although research has reported the pharmacokinetic and mood effects of these drugs in humans, there have been no reports of their effects on human neural processing.

It is well established that transfer of information between the hemispheres is crucial in many cognitive tasks (Hoptman and Davidson 1994) and that the presence of the corpus callosum is critical to hemispheric interaction and interhemispheric communication (Cherbuin and Brinkman 2006a; Rugg et al. 1984; Tettamanti et al. 2002; Weber et al. 2005). There have been relatively few attempts, however, to identify the relationship between the interhemispheric transmission and neuropharmacologically active compounds (see section 1.5.1.2). Since the interhemispheric transfer time is modified under the influence of psychoactive drugs, it was hypothesised that BZP, TFMPP, BZP+TFMPP and dexamphetamine would speed the interhemispheric transfer time and absolute N160 latency on the Poffenberger task, as stimulants have been associated with superior neural processing. It was also hypothesised that these drugs however, would not influence the directional asymmetry of information transfer (e.g. faster Right-to-Left vs. Left-to-Right

transfer). We hypothesised this as the directional asymmetry of information transfer is more governed by factors that affect the anatomical structure of the corpus callosum (e.g. gender, handedness, presence of neurological disorder). Since all our participants were healthy, right-handed males, we did not anticipate the asymmetry of information transfer would be affected. In order to investigate the effects of BZP, TFMPP and their combination on the interhemispheric transfer of information, a modified Poffenberger task using visually evoked ERPs was carried out (Chapter Three). Compared to the original Poffenberger's behavioural measure of interhemispheric transfer time (refer to section 1.5.1), a more direct measure of interhemispheric transfer time can be derived from cortical evoked potentials by subtracting the latency of evoked potential components recorded in the hemisphere contralateral to stimulation (direct pathway) from that recorded from the hemisphere ipsilateral (callosal pathway) (Brown et al. 1994; Nowicka et al. 1996; Saron and Davidson 1989).

Since its discovery in 1965, the P300 ERP has been used extensively in scientific investigations of human cognition (Anderer et al. 1998b; Polich and Herbst 2000; Sutton et al. 1965). The P300 is thought to be an index of cognitive processes as it represents cognitive neuroelectric phenomena such as attention allocation and activation of immediate memory (Polich and Kok 1995). P300 amplitude is proportional to the amount of attentional resources available and memory performance, and it is regarded as a measure of CNS efficiency to process and incorporate stimulus information (Polich and Herbst 2000). P300 latency is related to the time required for stimulus evaluation, also reflecting the processes of attention allocation and immediate memory in both normal and clinical populations (Kutas et al. 1977; Polich and Herbst 2000).

As the P300 ERP provides an objective measure of brain activity, it has been used widely to study the pharmacology of drugs affecting the CNS. Chapter Four investigates the effects of BZP, TFMPP, BZP+TFMPP and dexamphetamine on P300 components using an auditory oddball task. The P300 ERP is very sensitive to neurochemical changes induced by pharmacological manipulations. Studies have reported that P300 is influenced by psychoactive drugs. Alcohol has been reported to reduce P300 amplitude while increasing latency (Jaaskelainen et al. 1996; Martin and Siddle 2003; Oscar-Berman 1987) and reaction time (Martin and Siddle 2003). It is suggested that alcohol produces a dose-related

reduction in P300 amplitude and increase in latency, reflecting a reduction in the amount of processing resources in the CNS (Polich and Kok 1995). Long-term MDMA users display reduced P300 amplitude, and both heavy and moderate MDMA users displayed smaller P300 amplitudes compared to controls suggesting that the use of MDMA affects cognitive function in humans (Casco et al. 2005). The authors suggested that MDMA induces alterations in cortical activity associated with attention and neural processing. Therefore we tested the hypothesis that P300 ERPs would be decreased in response to BZP, TFMPP and their combination, as these drugs have been shown to mimic neuropharmacological actions of MDMA (Baumann et al. 2005). In addition, we also tested the hypothesis that earlier components such as P100 and P200 would not be affected by these compounds.

Therefore, the aim of this thesis is to use a combination of behavioural (reaction time) and electrophysiological (EEG) measures to investigate interhemispheric transfer times and P300 in humans following the administration of BZP, TFMPP, their combination and dexamphetamine (a positive control) in humans.

CHAPTER TWO

PARTICIPANT RECRUITMENT, CHARACTERISTICS AND LIFESTYLE QUESTIONNAIRE

CHAPTER TWO: PARTICIPANT RECRUITMENT, CHARACTERISTICS AND LIFESTYLE QUESTIONNAIRE

2.1. Introduction

As described in Chapter One, human EEG is under the influence of many factors. Consequently, neuropharmacological EEG studies in humans are difficult to execute, as neurobiological variables (e.g. circadian rhythms, gender effects) can influence assessment outcomes (Polich and Criado 2006). Therefore, a careful plan was devised for this study. This section will describe the process of participant recruitment and provide an outline of inclusion and exclusion criteria. In addition, participant characteristics such as age, body weight and handedness are presented. The participants also completed a lifestyle questionnaire about their past/current use of recreational drugs, injury and current health, day-to-day well being, sleeping habits and recreational time. Results from the lifestyle questionnaire are also presented here.

2.2. Materials and methods

2.2.1. Participant recruitment

This study received ethical approval from the Northern X Regional Ethics Committee of New Zealand (NTX/06/04/032). Participants were recruited by word of mouth and by placing posters around the campuses of the University of Auckland and the Auckland University of Technology. An advertisement was also placed in the student newspaper, Craccum. Participants were asked to make initial contact by emailing the investigator. The investigator then sent out a study invitation outlining inclusion/exclusion criteria (Appendix I, page 131). The inclusion criteria were: physically healthy right-handed males, non-

smokers, no regular prescription drugs, no past self-reported history of alcohol or other drug addiction. Participants were excluded on the basis of a self-reported history of mental illness, cardiac disease, head trauma, epilepsy or endocrine disorder. Although additional criteria were employed to eliminate drug-dependent or substantial poly-drug users, we did not confirm this by carrying out urine screens for drugs of abuse. In light of the finding that approximately 10% of subjects denying any substance abuse may have positive urine screens for drugs of abuse, this added precaution should be implemented in future studies (Swerdlow et al. 1995).

Females were not recruited as human ERPs are affected by gender as previously detailed (Jeeves and Moes 1996; Nowicka and Fersten 2001). Once the participants understood what this research involved, they replied by email to set a study date. They were sent a letter inviting to participate in the study (Appendix II, page 132).

Twenty participants were excluded as they did not meet all the inclusion criteria; a total of 100 male participants were recruited for this research.

2.2.2. Study design and procedure

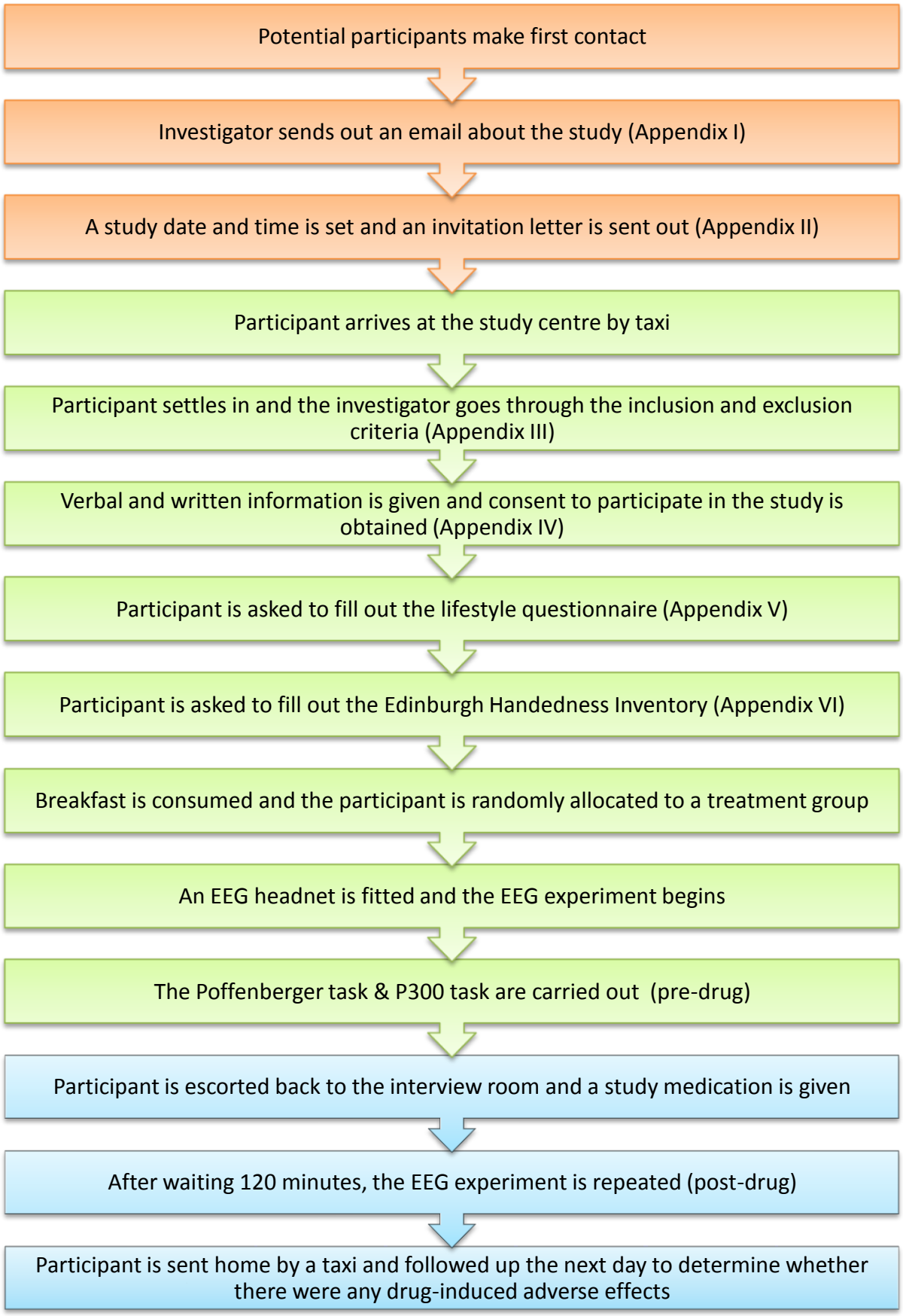
A typical experimental day followed the schedule as outlined in

Figure 9 (page 65). As EEG data are affected by circadian rhythm (Polich 1997), a maximum of two participants per day were allowed. Participants were asked to abstain from alcohol for 24 hours prior and caffeine for 12 hours prior to the study as consumption of alcohol and caffeine is known to affect ERPs (Lorist et al. 1994; Polich and Kok 1995).

On each study day, the first participant was scheduled to arrive at 8am, followed by a second participant at 9am. A taxi picked up each participant and brought them to the study centre at the Department of Psychology, the University of Auckland. Participants were explicitly advised not to drive to the study centre on the day as they were not able to drive home following drug administration. As requirement of the ethics committee, taxis were scheduled and paid for by the researchers.

Upon arriving, the participant was interviewed and the investigator checked through the exclusion criteria and lifestyle questionnaire (Appendix III, page 133). Once the investigator was satisfied that the participant met all criteria, the participant was enrolled. Participants were given verbal and written information (Appendix IV, page134) about the study, and we obtained written consent from all participants.

Figure 9. A typical EEG experimental day



The Edinburgh Handedness Inventory was administered to ensure participants were predominantly right-handed (Oldfield 1971); participants were considered right-handed if their laterality quotient was 50 or greater.

A standardised breakfast consisting of two pieces of toast with a choice of sugar free spread (e.g. peanut butter, marmite), a cup of decaffeinated coffee/tea (with or without milk) or water was provided. Consumption of sugar or caffeine is reported to affect the P300 ERP (Polich and Kok 1995), therefore it was important the participants did not consume these prior to the study. After the consent process and breakfast, participants were randomly assigned to a treatment group.

By 9am, the pre-drug session was underway. The first test was a Poffenberger task, followed by the auditory oddball task. A detailed method describing EEG data collection is provided in Chapter Three (page 80). The participant was then taken back to the interview room and given either BZP (200 mg, Sigma Aldrich), TFMPP (60 mg, Sigma Aldrich), BZP+TFMPP (100/30 mg, Sigma Aldrich), dexamphetamine (20 mg, Douglas Pharmaceuticals) or placebo (100 mg Methylcellulose, Sigma Aldrich) with 200 mL of water, and asked to wait for 120 minutes to allowing the drug to reach peak plasma concentration before conducting the post-drug session.

Upon completion of the study, the participant was then escorted to a taxi to return home. Participants were reimbursed with $40 of either movie or petrol vouchers. The participants were contacted the following day to enquire whether they were any drug-induced adverse effects.

2.3. Demographic data

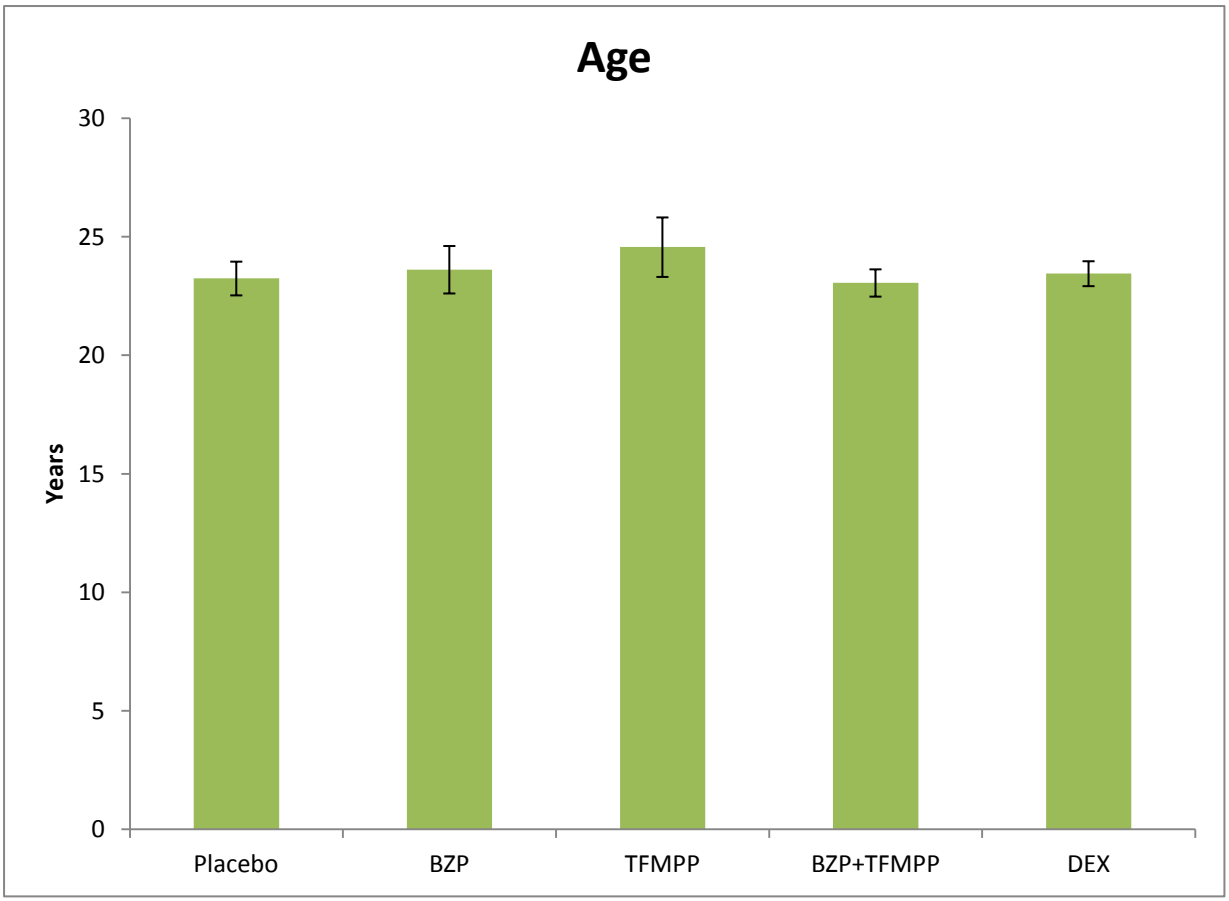
For each participant, data on age, body weight and handedness were collected as these factors are known to influence ERPs (Polich and Herbst 2000; Polich and Kok 1995); data were collected from all participants (n=100). To confirm that there were no sampling biases between participants in each drug group, data were subject to a one-way analysis of

variance (ANOVA) with α = 0.05 as criterion for significance. A summary of each measurement is presented below.

2.3.1. Age

There was no statistically significant difference in average age of participants in any treatment groups ($F_{(4,95)}$=0.442, p=0.778; Figure 10).

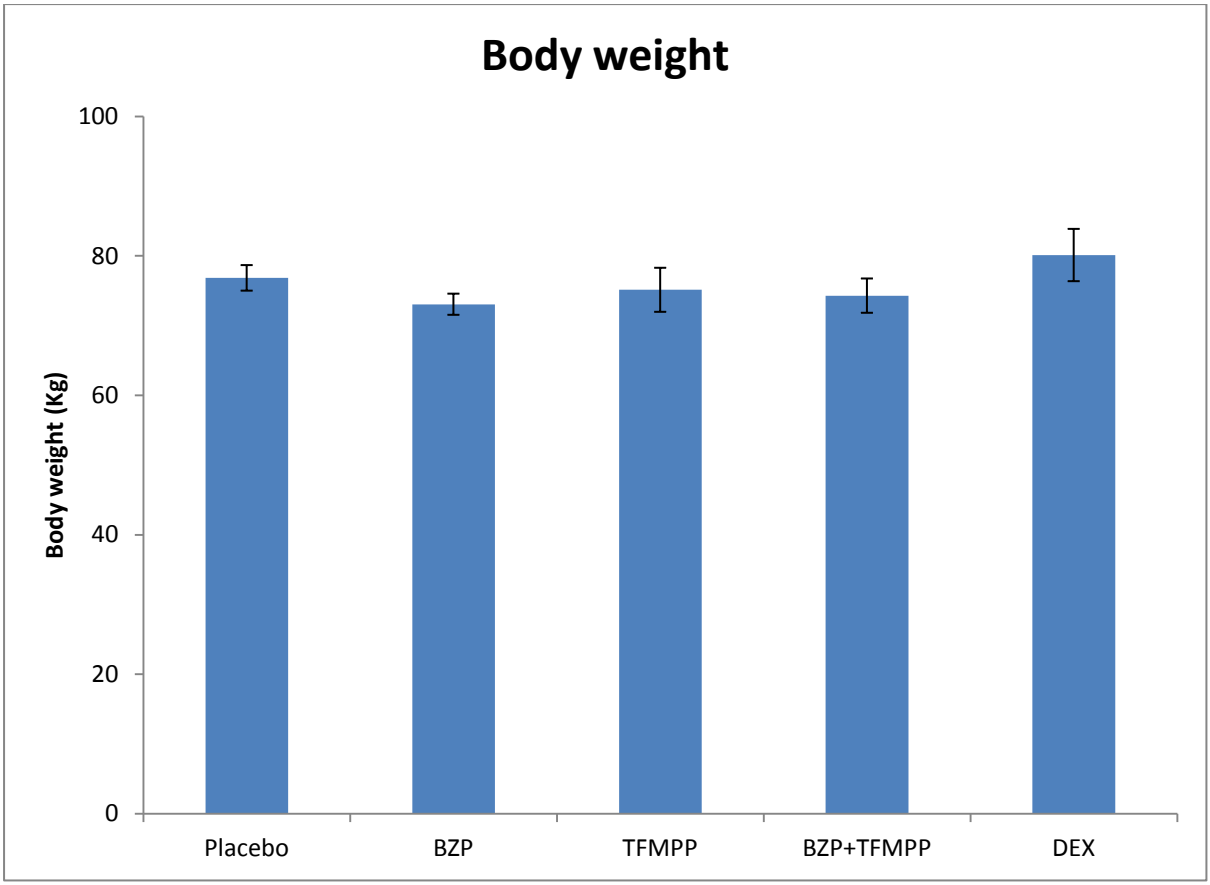
Figure 10. Average age of participants in each treatment group. Error bars represent standard errors of the mean.



2.3.2. Body weight

There was no statistically significant difference in average body weight of participants in any treatment groups ($F_{(4,95)}$=1.068, p=0.377; Figure 11).

Figure 11. Average body weight of participants in each treatment group. Error bars represent standard errors of the mean.

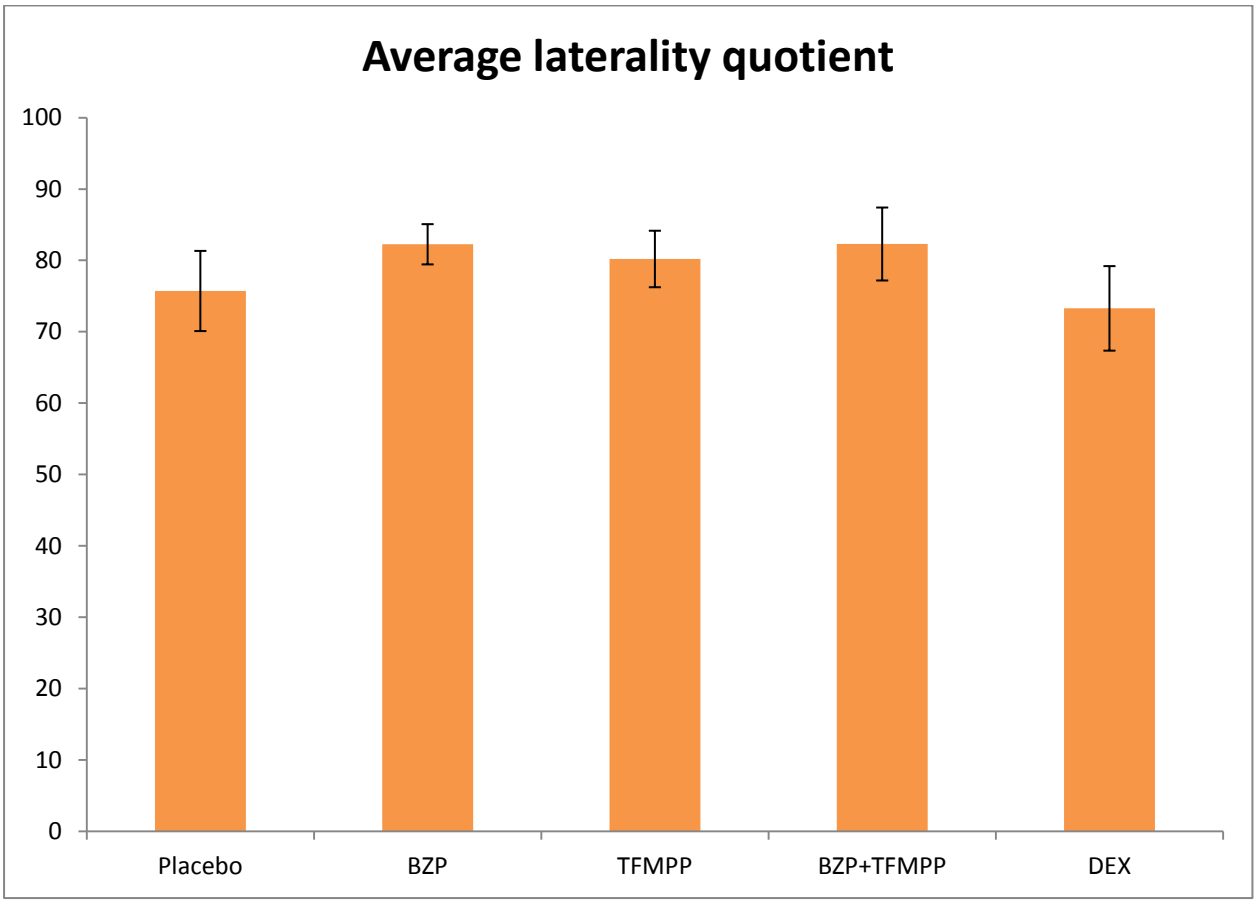


2.3.3. Handedness

Handedness was assessed by application of the Edinburgh Handedness Inventory (Oldfield 1971). All the participants were right-handed with an average laterality quotient of

78.96 ± 19.88. There was no statistically significant difference in the laterality quotient of participants in any treatment groups ($F_{(4,95)}$=1.068, p=0.377; Figure 12).

Figure 12. Average laterality quotient of participants in each treatment group. Error bars represent standard errors of the mean



2.4. Lifestyle questionnaire

Due to the nature of this study, it was important to check that the participants had past experience with recreational drugs such as caffeine, alcohol and nicotine as their consumptions influence the human ERPs (Polich and Herbst 2000; Polich and Kok 1995). In addition, it was preferred that they had tried Party Pills in the past. Data were collected about their history of drug use, pattern of consumption of caffeinated/alcoholic beverages

and smoking habits. Data about health status, well being, sleeping patterns, time spent on recreation were also collected. Human ERPs, especially P300 components, are influenced by these factors (Polich and Herbst 2000; Polich and Kok 1995; Polich and Lardon 1997). The results are presented below. To confirm that there were no sampling biases between participants in each drug group, we used a one-way ANOVA or χ^2 tests with $\alpha = 0.05$ as the criterion for significance. A summary of each measurement is presented below.

2.4.1. Have you ever taken part in recreational drug use?

When we tested whether participants in any particular drug group were more likely to have taken part in any recreational drug use, higher number of participants in BZP and BZP+TFMPP groups responded 'yes' (n_0=14; n_0=15, respectively) than was expected (n_e=12.5; n_e=14.6, respectively), whereas lower number of participants in TFMPP and dexamphetamine groups responded 'yes' (n_0=9; n_0=12, respectively) than was expected (n_e=10.4; n_e=12.5, respectively). According to χ^2 test of independence, this difference was not statistically significant, $\chi^2(4, N = 100) = 1.323$, $p = 0.857$, so we inferred that participants were not more likely to have taken part in any recreational drug use when placed in a particular treatment group.

2.4.2. Have you ever tried Party Pills?

When we tested whether participants in any particular drug group were more likely to have tried Party Pills, higher number of participants in placebo and TFMPP groups responded 'yes' (n_0=6; n_0=8, respectively) than was expected (n_e=5.8; n_e=6.7, respectively), whereas lower number of participants in BZP+TFMPP and dexamphetamine groups responded 'yes' (n_0=9; n_0=7, respectively) than was expected (n_e=9.4; n_e=8, respectively). According to χ^2 test of independence, this difference was not statistically significant, $\chi^2(4, N = 100) = 0.739$, $p = 0.946$, so we inferred that participants were not more likely to have taken Party Pills when placed in a particular treatment group.

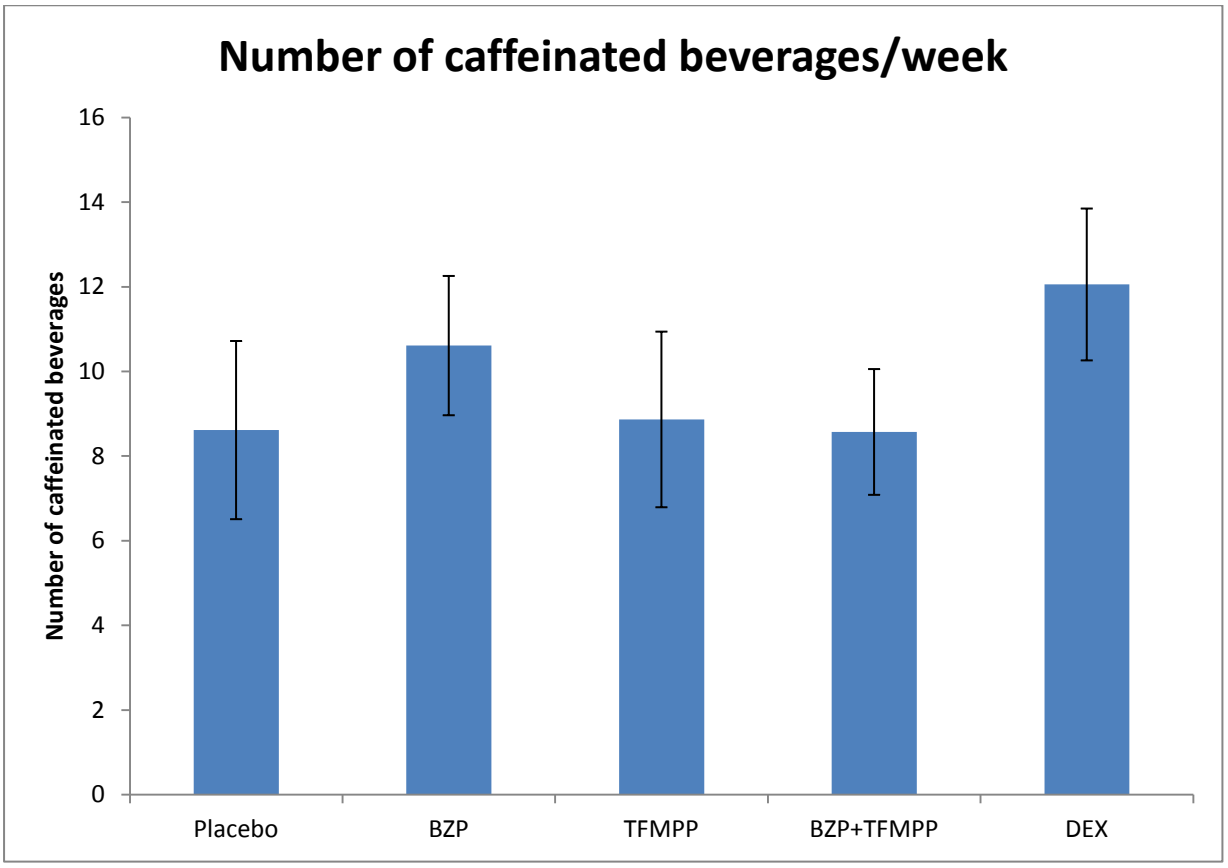
2.4.3. Would you say you are, or you have been, a regular user of Party Pills?

When we tested whether participants in any particular drug group were more likely to be or have been a regular user of Party Pills, higher number of participants in BZP and TFMPP groups responded 'yes' (n_0=1; n_0=2, respectively) than was expected (n_e=0.8; n_e=0.7, respectively), whereas lower number of participants in placebo, BZP+TFMPP and dexamphetamine groups responded 'yes' (n_0=0; n_0=1; n_0=0, respectively) than was expected (n_e=0.6; n_e=1.0; n_e=0.8, respectively). According to χ^2 test of independence, this difference was not statistically significant, $\chi^2(4, N = 100) = 4.050$, $p = 0.399$, so we inferred that participants were not more likely to be or have been a regular user of Party Pills when placed in a particular treatment group.

2.4.4. How many caffeinated beverages (e.g. coffee, tea, Coke®, energy drinks) in an average week?

There was no statistically significant difference in the number of caffeinated beverages consumed by participants in any drug groups ($F_{(4,95)}$=0.768, p=0.549; Figure 13).

Figure 13. An average number of caffeinated beverages consumed per week in each treatment group. Error bars represent standard errors of the mean



2.4.5. Do you take part in "binge drinking" (i.e. consume double the recommended drinking per day of 8 units of alcohol)?

When we tested whether participants in any particular drug group were more likely to take part in binge drinking, higher number of participants in placebo, BZP, TFMPP and BZP+TFMPP groups responded 'yes' (n_0=6; n_0=10; n_0=9; n_0=7, respectively) than was expected (n_e=5.8; n_e=8.0; n_e=6.7; n_e=9.4, respectively), whereas lower number of participants in dexamphetamine group responded 'yes' (n_0=6) than was expected (n_e=8.0). According to χ^2 test of independence, this difference was not statistically significant, $\chi^2(4, N = 100) = 4.328$, $p = 0.363$, so we inferred that participants were not more likely to take part in binge drinking when placed in a particular treatment group.

2.4.6. Have you ever smoked?

When we tested whether participants in any particular drug group were more likely to have smoked, higher number of participants in placebo and dexamphetamine groups responded 'yes' (n_0=9; n_0=14, respectively) than was expected (n_e=8.7; n_e=12.1, respectively), whereas lower number of participants in BZP, TFMPP and BZP+TFMPP groups responded 'yes' (n_0=10; n_0=10; n_0=14, respectively) than was expected (n_e=12.1; n_e=10.1; n_e=14.1, respectively). According to χ^2 test of independence, this difference was not statistically significant, $\chi^2(4, N = 100) = 2.045$, p= 0.728, so we inferred that participants were not more likely to have smoked when placed in a particular treatment group.

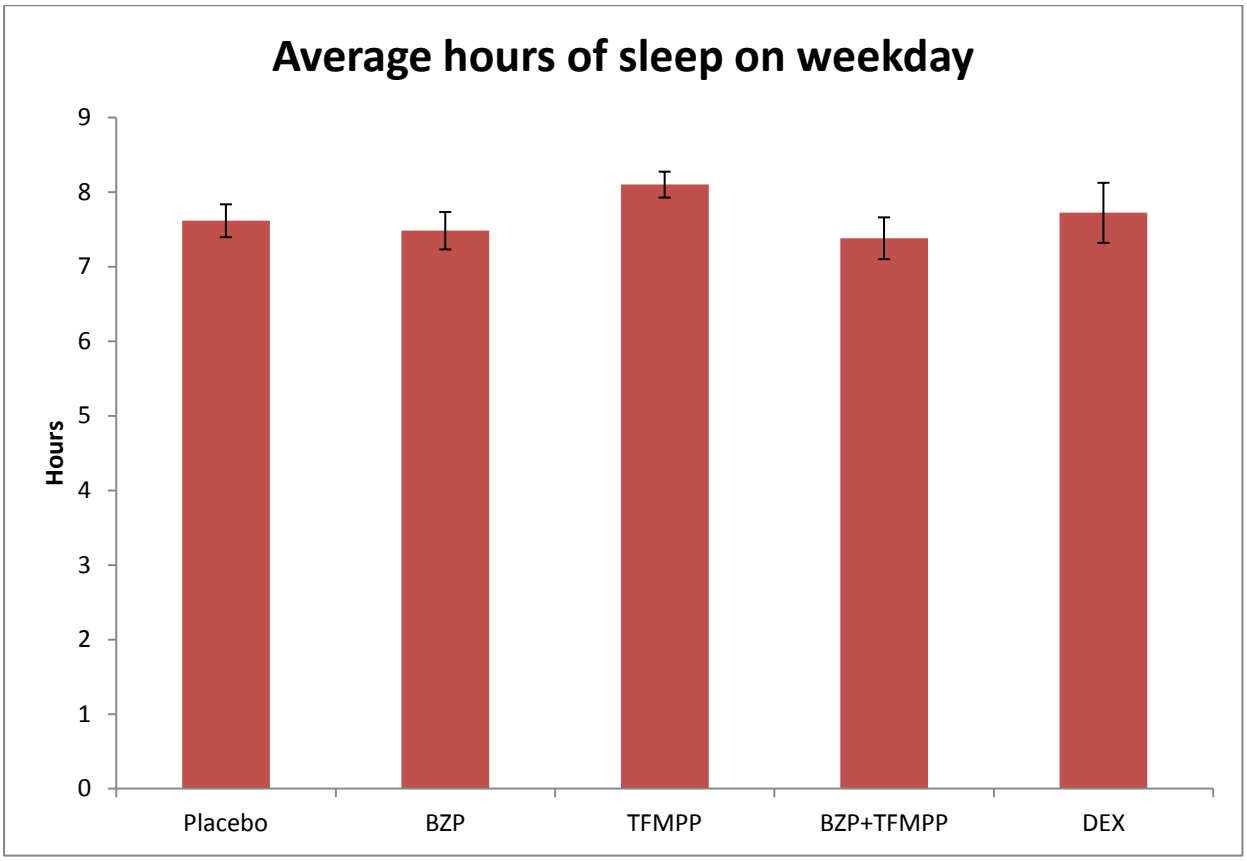
2.4.7. Have you had/experienced any head trauma?

When we tested whether participants in any particular drug group were more likely to have experienced any head trauma, higher number of participants in BZP and TFMPP groups responded 'yes' (n_0=5; n_0=2, respectively) than was expected (n_e=2.1; n_e=1.8, respectively), whereas lower number of participants in placebo, BZP+TFMPP and dexamphetamine groups responded 'yes' (n_0=1; n_0=0; n_0=2, respectively) than was expected (n_e=1.5; n_e=2.5; n_e=2.1, respectively). According to χ^2 test of independence, this difference was not statistically significant, $\chi^2(4, N = 100) = 7.497$, p= 0.112, so we inferred that participants were not more likely to have experienced any head trauma when placed in a particular drug treatment group.

2.4.8. How many hours of sleep do you get on an average weeknight?

There was no statistically significant difference in the hours of sleep on an average weeknights among participants in any treatment groups ($F_{(4,95)}$=0.896, p=0.470; Figure 14).

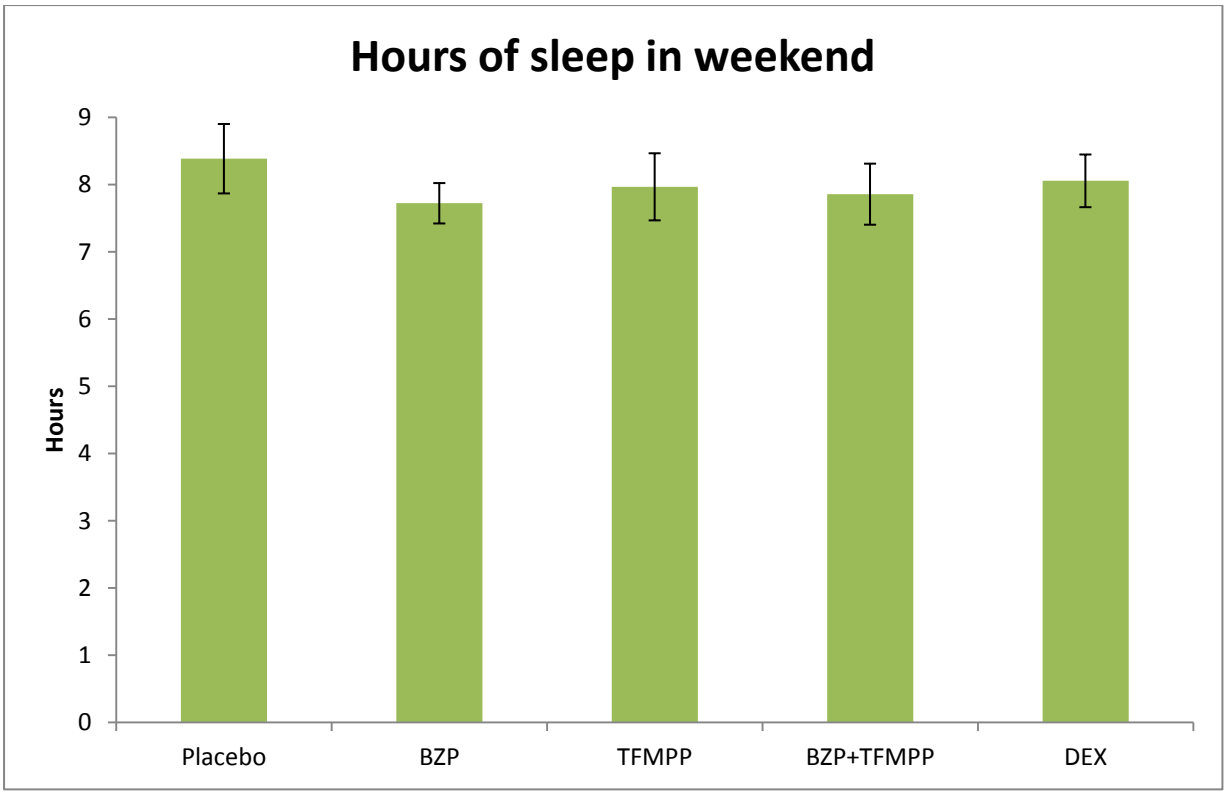
Figure 14. The number of hours of sleep on an average weekday in each treatment group. Error bars represent standard errors of the mean



2.4.9. How many hours of sleep do you get on an average night on the weekend?

There was no statistically significant difference in the hours of sleep on an average night on the weekend among participants in any treatment groups ($F_{(4,95)}$=0.293, p=0.881; Figure 15).

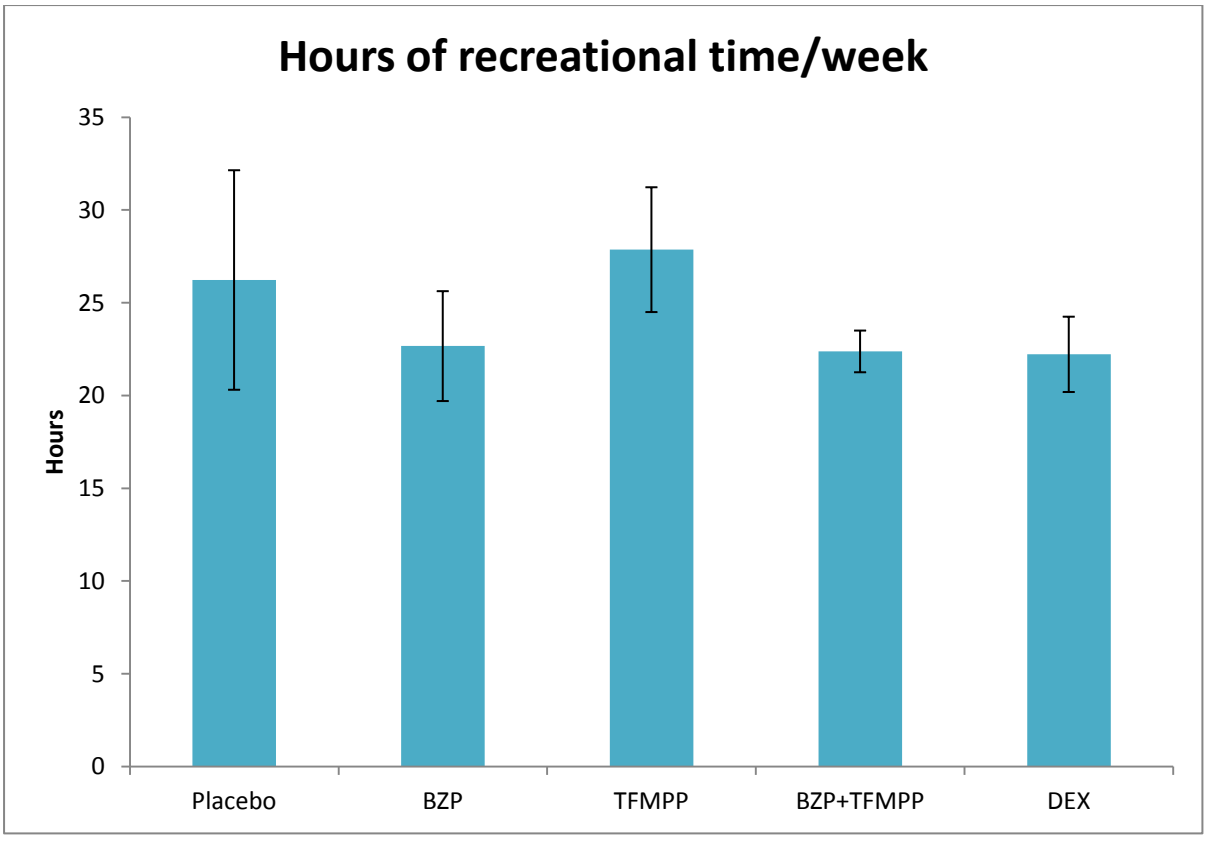
Figure 15. The number of hours of sleep on an average night on the weekend in each treatment group. Error bars represent standard errors of the mean



2.4.10. How many hours of recreational/leisure time do you get in an average week?

There was no statistically significant difference in the hours of recreational time in an average week among participants in any treatment groups ($F_{(4,95)}$=0.703, p=0.592; Figure 16).

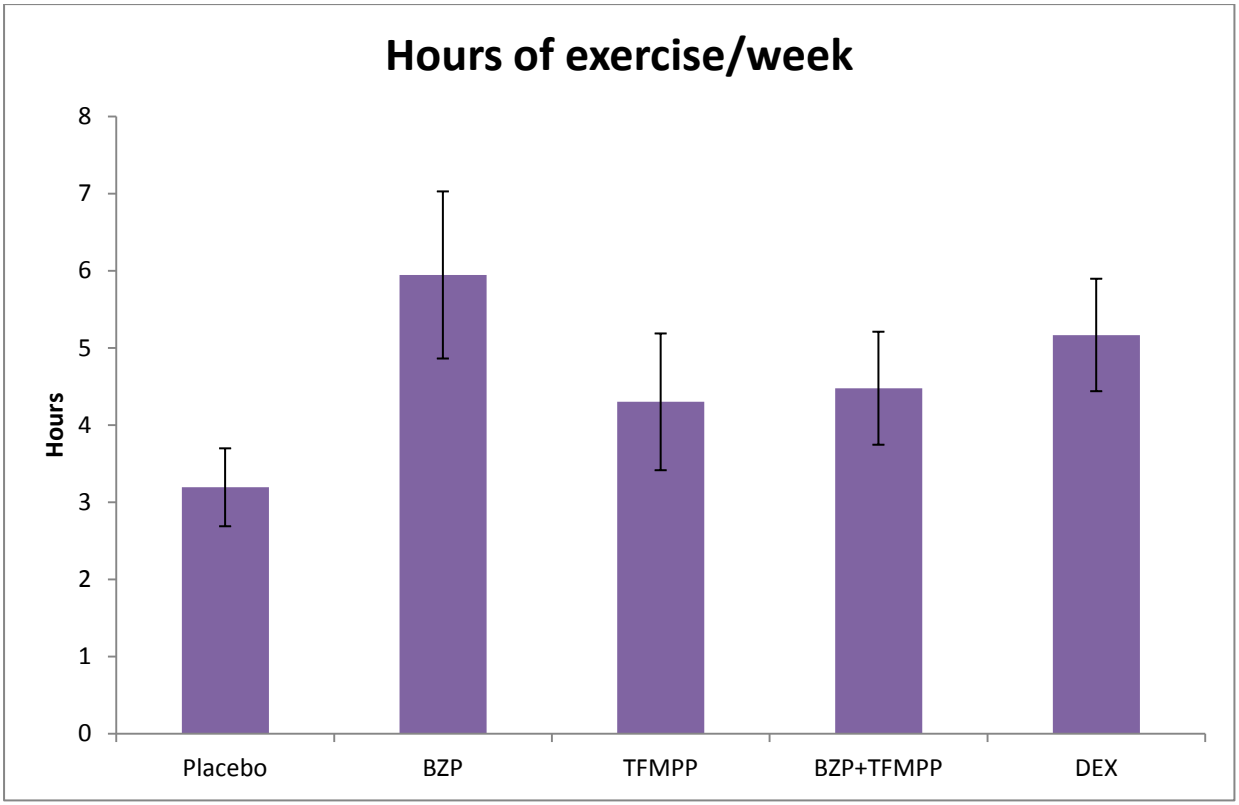
Figure 16. The number of hours spent on recreational time in an average week in each treatment group. Error bars represent standard errors of the mean



2.4.11. How many hours of exercise do you do in an average week?

There was no statistically significant difference in the hours of exercise in an average week among participants in any treatment groups ($F_{(4,95)}$=1.362, p=0.254; Figure 17).

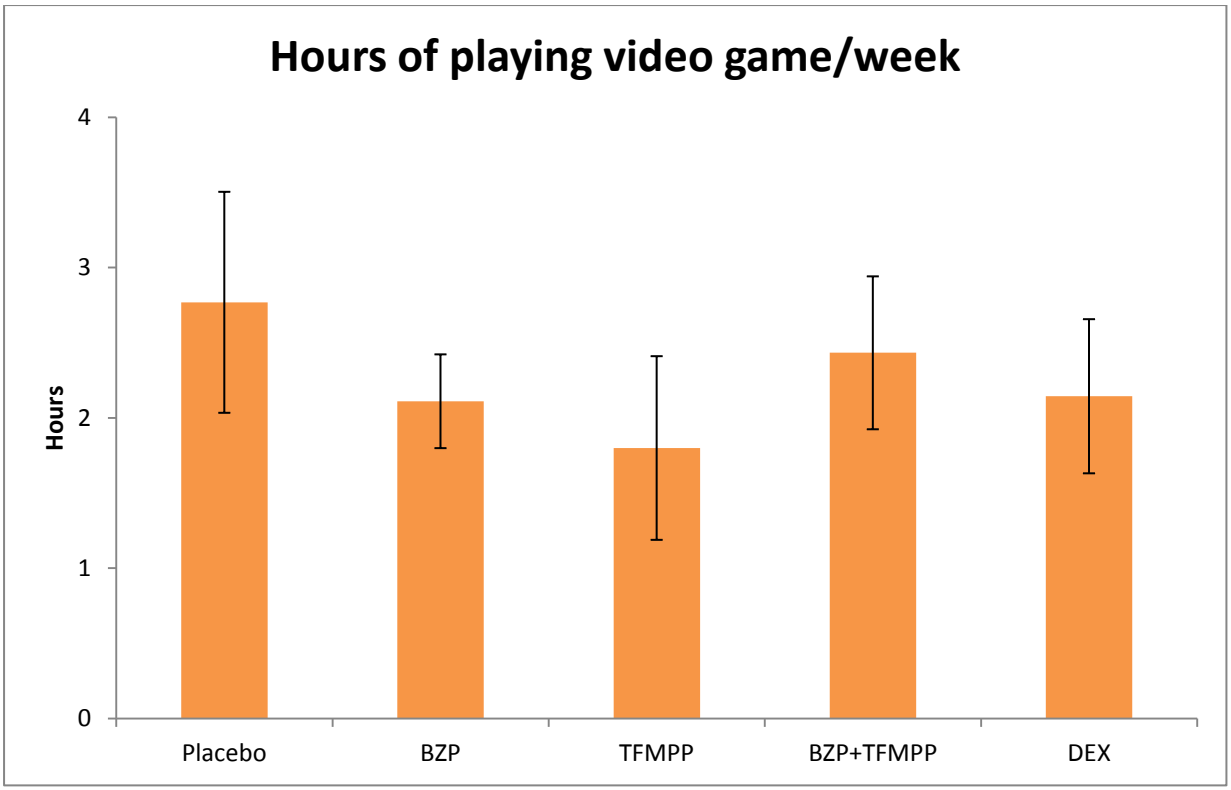
Figure 17. The number of hours of exercise in an average week in each treatment group. Error bars represent standard errors of the mean



2.4.12. How many hours do you play video games or arcade games in an average week?

There was no statistically significant difference in the hours playing video/arcade games in an average week among participants in any treatment groups ($F_{(4,95)}$=1.362, p=0.254; Figure 18).

Figure 18. The number of hours playing video/arcade games in an average week in each treatment group. Error bars represent standard errors of the mean



2.5. Summary

As human ERPs are subject to many influencing factors, it was important to collect comprehensive demographic data (e.g. age, body weight and handedness) and lifestyle factors such as their past history of drug use, stimulant intake and patterns of daily life.

The demographic data revealed that participants' ages ranged from 18 to 39 years, with an average of 22.74 ± 4.22 years. Their body weight ranged from 59.5 to 120 kg, with an average of 77.04 ± 12.25 kg, and all the participants were right-handed with an average laterality quotient of 78.96 ± 19.88. One-way ANOVA analyses revealed that there were no statistically significant differences between each treatment group.

The lifestyle questionnaires revealed that participants had some experience with taking recreational drugs and Party Pills, which was desirable as they were familiar with the effects of Party Pills. In addition, the participants had relatively balanced lifestyles as they allocated similar amounts of time for recreational activities such as playing video games, but also for exercising. One-way ANOVA analyses and χ^2 tests revealed that there were no statistically significant lifestyle differences between each treatment group.

CHAPTER THREE

EFFECTS OF BZP, TFMPP, BZP+TFMPP AND DEXAMPHETAMINE ON INTERHEMISPHERIC TRANSFER TIME

CHAPTER THREE: EFFECTS OF BZP, TFMPP, BZP+TFMPP AND DEXAMPHETAMINE ON INTERHEMISPHERIC TRANSFER TIME

3.1. Introduction

The purpose of study was to evaluate the effects of acute administration of BZP, TFMPP, the combination of BZP+TFMPP and dexamphetamine on central neural processing in humans. To the best of our knowledge, this study is the first of its kind to investigate the effects of the recreational drugs BZP, TFMPP and BZP+TFMPP on interhemispheric transfer time. Psychoactive drugs such as alcohol, nicotine and marijuana are thought to influence neural processing in the CNS by interfering with neurotransmitter release and reuptake of DA and 5-HT (Koelega 1993; Polich and Criado 2006). Therefore, it was hypothesised that BZP, TFMPP, BZP+TFMPP and dexamphetamine would decrease the time taken for interhemispheric transfer of information during the Poffenberger task. It was also hypothesised that these drugs however, would not influence the directional asymmetry of information transfer (e.g. faster Right-to-Left vs. Left-to-Right transfer). It should be noted that some parts of this section (TFMPP data) have been published (Lee et al. 2011).

3.2. EEG acquisition

Depending on the head circumference of the participant, a small/medium/large size net (Electrical Geodesics Inc., Eugene, Oregon, USA) was fitted over the head. The EEG net was soaked in a solution made from one teaspoon of potassium chloride (Sigma Aldrich) and

one teaspoon of baby shampoo (Johnson's Baby Shampoo) mixed with 1L of warm water to increase the conductance. The middle of the head (position where the reference electrode was positioned) was found by measuring the mid-point of narium to inium and from one ear to the other ear. See Appendix V (page 137) for the positions of the electrodes on the head.

EEG experiments were carried out in an electrically shielded Faraday chamber that was dimly illuminated while the participants were monitored by two internally mounted cameras. EEG was continuously recorded (1000 Hz sampling rate, analogue band-pass 0.1-400 Hz) using an Electro Geodesics Inc. 128-channel Ag/AgCl electrode net. The impedance of the electrodes ranged between 35 and 40 kΩ. Visual stimuli were presented on a SVGA monitor (640x480 pixel resolution) at a distance of 57 cm from the participant's eyes, which presented the stimuli at a visual angle of 4° to the left or right of the fixation cross. The stimuli were black-and-white chequered circles, which flashed in either the left visual field or the right visual field. The stimuli were presented for a duration of 92 ms, which was below the 150 ms threshold that would result in an eye saccade (Kalesynkas and Hallett 2002). Participants were instructed to focus on the fixation cross in the centre of the screen and respond as quickly as possible to the onset of the stimulus in any position by pressing the space bar on the keyboard. Four blocks of trials using the right hand (RH) and the left hand (LH) were presented in the following sequence in order to counterbalance: RH-LH-LH-RH or LH-RH-RH-LH. The experiment was randomised with 120 trials presented to the left visual field and 120 to the right visual field. In each trial, EEG recording started 100 ms before the presentation of stimulus and lasted 600 ms.

3.3. Data analysis

EEG segments contaminated by eye blinks (rejection criterion of 70 µV in eye channels) were rejected and automatic eye-movement correction was conducted (Jervis et al. 1985). The data were separated by the two visual fields: left visual field or right visual field. Recordings of each participant were segmented into epochs with a pre-stimulus baseline of 100 ms and a post-stimulus period of 500 ms, which were then averaged for two

visual fields. EEG recordings were band-pass filtered using a bidirectional three-pole Butterworth filter between 0.1 and 40 Hz (Alarcon et al. 2000).

The N160 components were determined as the greatest negative peak between 140 and 250 ms after stimulus onset and were acquired separately for each participant. This study focussed on the N160 component as N160 latencies have been argued to be a more reliable measure of interhemispheric transmission (Brown and Jeeves 1993). Initial analysis of 30 electrodes (15 each on either side of the head) produced noisy data, making it difficult to clearly identify N160 peaks. Close inspection of waves obtained from individual electrodes led to the final selection of 10 electrodes for the analysis of the interhemispheric transfer time (5 on either side of the head; Figure 19). This is in line with other studies that found only electrodes over the parietal sites of two hemispheres yielded statistically significant changes in N160 latency (Iwabuchi and Kirk 2009; Nowicka and Fersten 2001). In addition, maximal N160 activities of electrodes over the parietal sites were topographically determined (Figure 20).

Figure 19. Position of five electrodes used for final N160 analysis

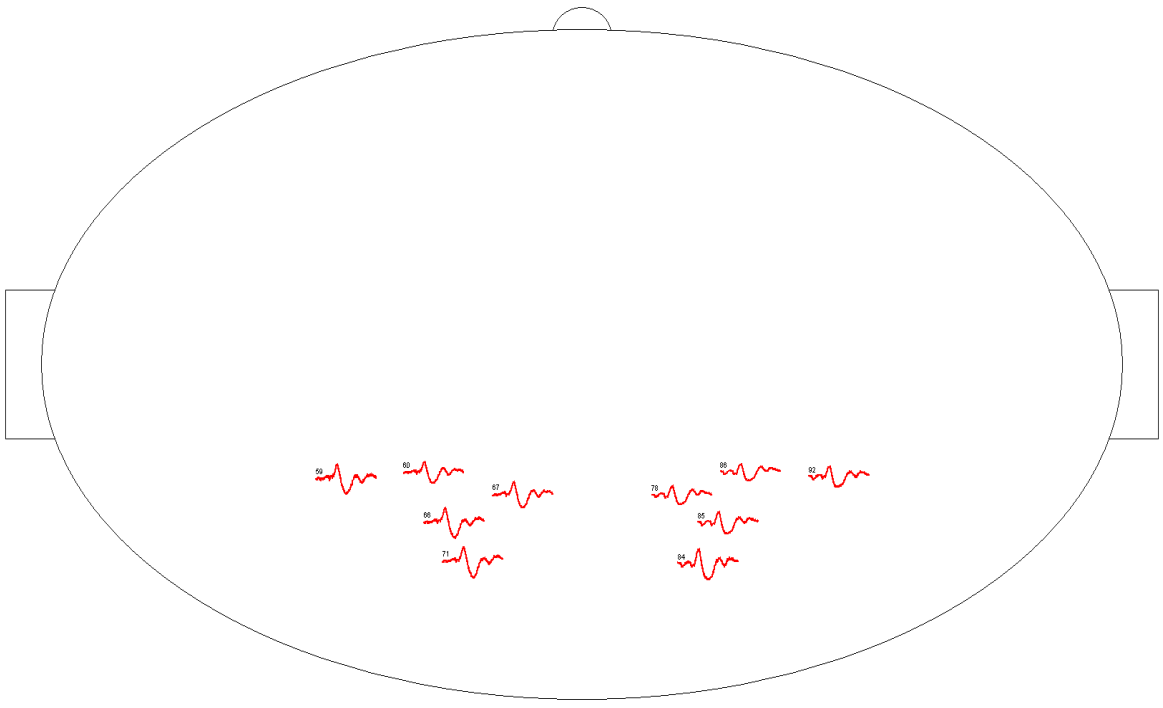
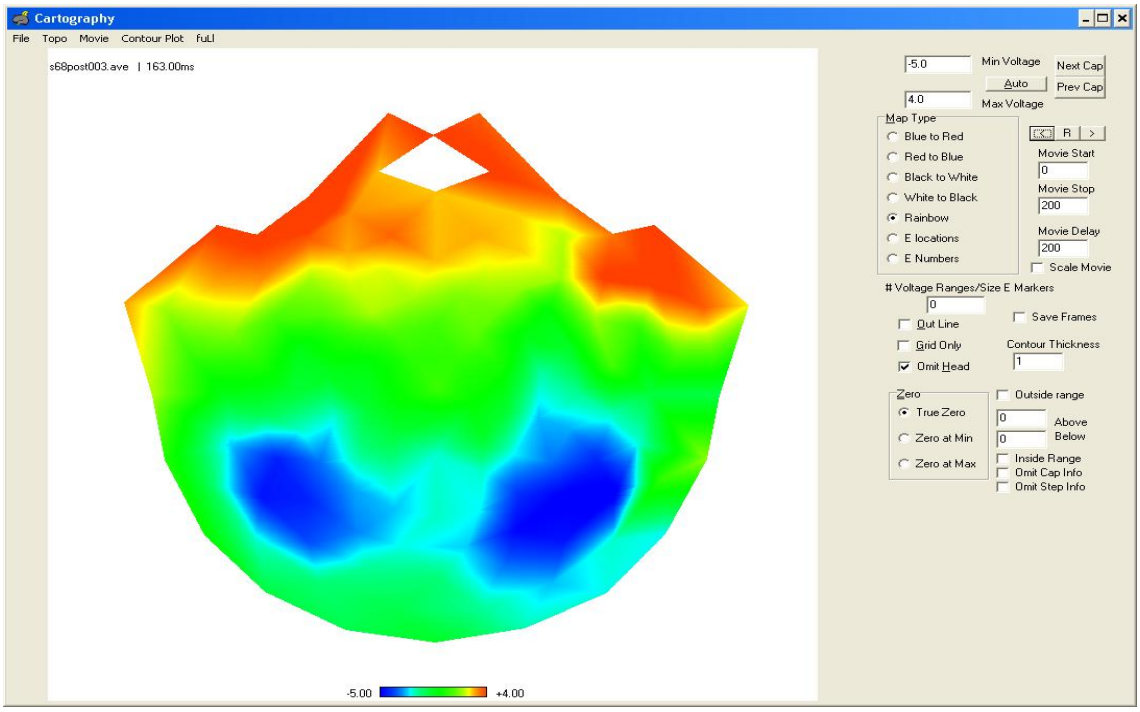


Figure 20. Topography of electrodes over the parietal sites with maxima N160 latency (maximum activity indicated in blue)

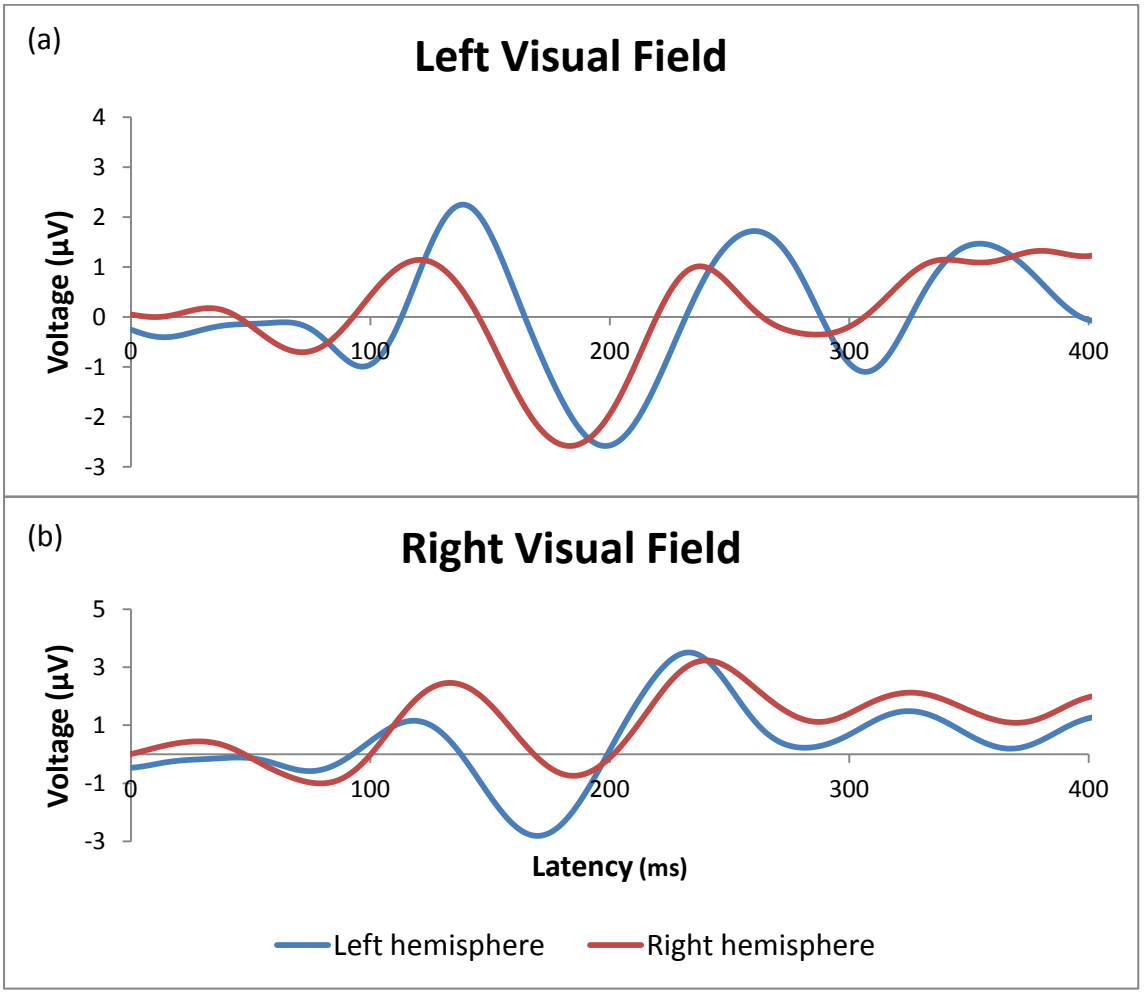


The interhemispheric transfer time was calculated by subtracting the peak N160 latency obtained in the ipsilateral hemisphere from the peak N160 latency obtained in the hemisphere contralateral to a visual stimulus. In the past, our lab has used independent component analysis (Barr et al. 2005; Teyler et al. 2005) to analyse visually evoked N160; however, the peak of N160 was used in current study as it is considered to be more accurate measure of visual-evoked potentials (Barnett and Kirk 2005; Iwabuchi and Kirk 2009; Patston et al. 2007; Saron and Davidson 1989). In addition, this is in line with other studies that define N160 as the only component that provides a valid estimate of interhemispheric transfer time (Brown et al. 1994; Saron and Davidson 1989).

The absolute value of the latency difference was used to represent interhemispheric transfer time. Figure 21 represents a visual evoked potential of a right-handed participant for the (a) left visual field and the (b) right visual field stimulations. When the visual stimulus is presented to the left visual field, it is registered first in the contralateral visual field (in the right hemisphere; red line), followed by in the ipsilateral visual field (in the left

hemisphere; blue line). Similarly, when the visual stimulus is presented to the right visual field, it is registered first in the contralateral visual field (in the left hemisphere; blue line), followed by in the ipsilateral visual field (in the right hemisphere; red line).

Figure 21. Visual-evoked potential of a right-handed participant for the (a) left visual field stimulation and (b) right visual field stimulation conditions



Mean reaction time for all participants was obtained and analysed using E-Prime (Psychology Software Tools). The absolute N160 latency, interhemispheric transfer time and reaction time data were analysed using the Statistical Package for the Social Sciences Version 15.0 (SPSS Inc., Chicago, Illinois, USA). To determine group differences for the N160 latency, a mixed factorial ANOVA was performed, with hemisphere (left, right), time (pre, post), and visual field (left, right) as within-participants factors and drug (BZP, TFMPP, BZP+TFMPP, dexamphetamine, placebo) as the between-participants factor. The

interhemispheric transfer time was subject to the same statistical analysis, with hemispheric transfer direction (Left-to-Right, Right-to-Left), and time (pre, post) as within-participants factors and drug (BZP, TFMPP, BZP+TFMPP, dexamphetamine, placebo) as the between-participants factor. To determine group differences in mean reaction time, a 2×2 ANOVA was performed, with time (pre, post) as the within-participants factor and drug (BZP, TFMPP, BZP+TFMPP, dexamphetamine, placebo) as the between-participants factor. Data were deemed to be statistically significant with $p<0.05$.

3.4. Results

3.4.1. N160 latency

Of a total of 100 participants, data from 82 participants displayed identifiable peaks and were subject to statistical analysis (Table 7). This resulted in unequal sample sizes for each drug group. To check that the assumption of equality of variance was not violated due to unequal sample size, each analysis was subject to homogeneity test in SPSS. We examined Box's test of equality of covariance matrices, and the results were nonsignificant for N160 latency ($p>0.05$), interhemispheric transfer time ($p>0.05$) and reaction time ($p>0.05$).

Table 7. The number of participants in each treatment group

Treatment Group	Total Collected (n)	Total Used (n)
BZP	18	13
TFMPP	16	15
BZP+TFMPP	20	15
Dexamphetamine	18	16
Placebo	28	23
Total	100	82

Table 8 displays a number of significant interactions as revealed by the statistical analysis.

Table 8. Main effects and interactions for the absolute latency of the N160 visual evoked potential (denotes p<0.05)*

Effect	df	F	p	sig
Hemisphere	1,77	2.290	0.134	-
Time	1,77	6.856	0.011	*
VF	1,77	20.484	0.000	*
Hemisphere×Time	1,77	6.580	0.012	*
Hemisphere×VF	1,77	657.978	0.001	*
Hemisphere×Drug	4,77	0.519	0.722	-
Time×VF	1,77	0.688	0.410	-
Time×Drug	4,77	5.007	0.001	*
VF×Drug	4,77	2.902	0.027	*
Hemisphere×Time×VF	1,77	7.599	0.007	*
Hemisphere×Time×Drug	4,77	0.543	0.704	-
Hemisphere×VF×Drug	4,77	1.149	0.340	-
Time×VF×Drug	4,77	0.183	0.947	-
Hemisphere×Time×VF×Drug	4,77	1.066	0.379	-

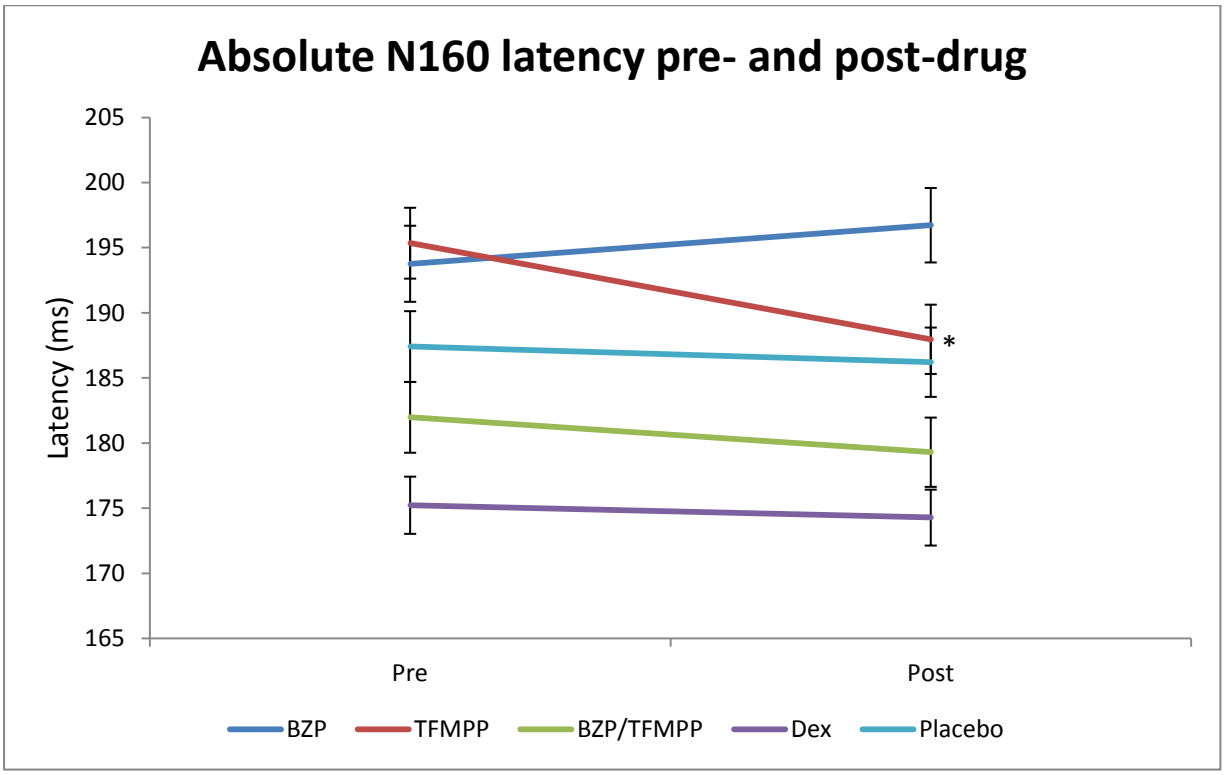
There was a significant Hemisphere×VF effect, ($F_{(1,77)}$=657.98, p≤0.001), indicating the occurrence of interhemispheric transfer of information through transcallosal commissures (Endrass et al. 2002; Nowicka and Fersten 2001). The Time×Drug interaction ($F_{(4,77)}$=5.007, p≤0.001; Table 9) was also significant indicating that N160 latency changed pre- vs. post-drug treatment. Contrast analysis revealed that TFMPP ($F_{(1,77)}$=17.30, p≤0.001) significantly reduced the absolute N160 latency post-drug.

Table 9. Time×Drug interaction of the mean absolute N160 latency pre- and post-drug (±SE) (denotes p<0.05)*

Drug	Pre-drug	Post-drug
BZP	193.77 (2.92)	196.73 (2.86)
TFMPP	195.35 (2.72)	187.97 (2.66)*
BZP+TFMPP	181.98 (2.72)	179.30 (2.66)
Dexamphetamine	175.23 (2.63)	174.28 (2.57)
Placebo	187.41 (2.20)	186.21 (2.15)

Since the visual stimuli were presented to either the left or right visual field, the significant VF×Drug interaction ($F_{(4,77)}$=2.902, p≤0.05) is also important, as it indicates that the N160 latency registered in both the left and right visual field was influenced by drugs. Contrast analysis revealed both TFMPP ($F_{(1,77)}$=17.30, p≤0.001) and placebo ($F_{(1,77)}$=15.08, p≤0.001) groups were different from other groups. In sum, the analysis of absolute N160 latency reveals that only TFMPP significantly reduced the absolute N160 latency. The directional asymmetry of information transfer (i.e. faster Right-to-Left) was maintained with both TFMPP and placebo administration, but it was abolished with BZP, BZP+TFMPP and dexamphetamine administration. See Figure 22 for a graphical representation of absolute N160 latency pre- and post-drug.

Figure 22. Absolute N160 latency pre- and post-drug. Error bars represent standard errors of the mean (denotes p<0.05)*



3.4.2. Interhemispheric transfer time

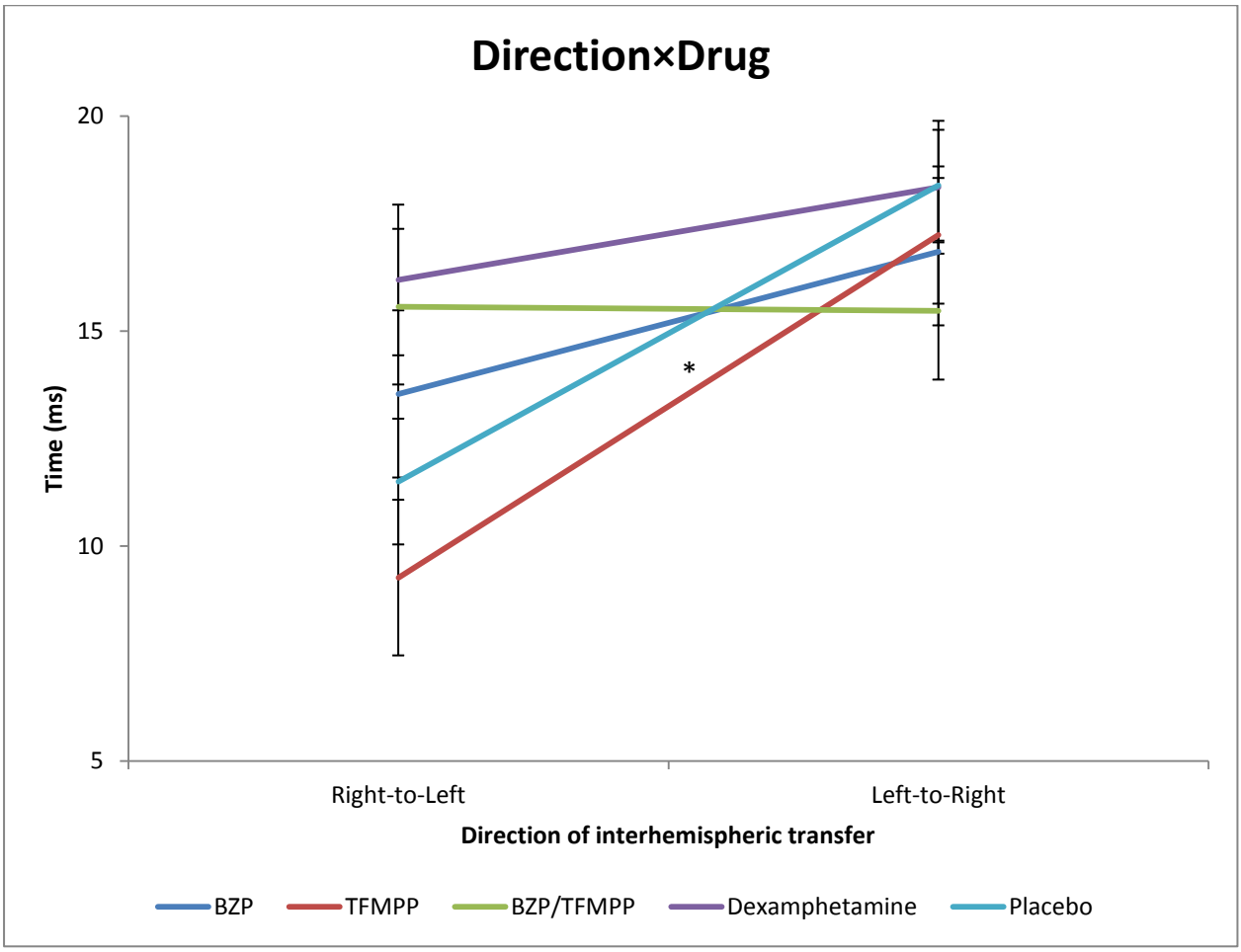
Information transfer between hemispheres was assessed by determining the interhemispheric transfer time, the N160 latency difference between ipsilateral and contralateral hemispheres. The initial mixed group effect MANOVA revealed a number of significant effects and they are summarised in Table 10 below for the following variables: time (pre- or post-drug), direction of information transfer (i.e. from Left-to-Right, Right-to-Left) as within-participants factors and drug (BZP, TFMPP, BZP+TFMPP, dexamphetamine or placebo) as the between participant factor.

Table 10. Main effects and interactions of the interhemispheric transfer time (denotes p<0.05)*

Effect	Df	F	p	significance
Direction	1,77	20.484	0.001	*
Time	1,77	7.599	0.007	*
Direction×Drug	4,77	2.902	0.027	*
Time×Drug	4,77	1.066	0.379	-
Direction×Time	1,77	0.688	0.410	-
Direction×Time×Drug	4,77	0.183	0.947	-

There was a significant effect of Direction ($F_{(1,77)}$=20.484, p≤0.001), suggesting the speed of interhemispheric transfer time was faster when going from Right-to-Left compared to Left-to-Right. This is in agreement with previous research carried out in right-handed males (Barnett and Kirk 2005; Iwabuchi and Kirk 2009). Figure 23 (page91) shows interhemispheric transfer time in each direction for drug groups pre- vs. post-drug. There was a significant Direction×Drug interaction ($F_{(4,77)}$=2.902, p≤0.027), indicating that drug treatment affected interhemispheric transfer time in each direction. Two separate contrast analyses were carried out: the first analysis tested which drug groups preserved the asymmetry of directional transfer and the second analysis tested which drug significantly affected the interhemispheric transfer time. Both TFMPP ($F_{(1,77)}$=15.08, p≤0.001) and placebo ($F_{(1,77)}$=17.30, p≤0.02) maintained the asymmetry of information transfer (i.e. faster Right-to-Left vs. Left-to-Right). In addition, only the TFMPP group ($F_{(1,77)}$=5.266, p≤0.02) reduced the interhemispheric transfer time in both directions (i.e. Right-to-Left and Left-to-Right). These findings from the interhemispheric transfer time study confirm the previous N160 latency data, where only TFMPP reduced the N160 latency in both directions while maintaining asymmetry. There was no significant difference between Left-to-Right and Right-to-Left transfer speed for those given BZP, BZP+TFMPP and dexamphetamine.

Figure 23. Interhemispheric transfer time in each direction for treatment group. Error bars represent standard errors of the mean (denotes p<0.05)*



3.4.3. Reaction time

The pre-drug mean reaction times for all five treatment groups decreased post-drug but this difference was not significant (Figure 24). There was a significant main effect of Time ($F_{(1,77)}$=39.350, p≤0.001), however no significant interaction between Time×Drug ($F_{(4,77)}$=0.373, p>0.05) implies that behavioural reaction times did not differ significantly between groups pre- and post-drug (Table 11).

Figure 24. Mean reaction time pre- and post-drug. Error bars represent standard errors of the mean

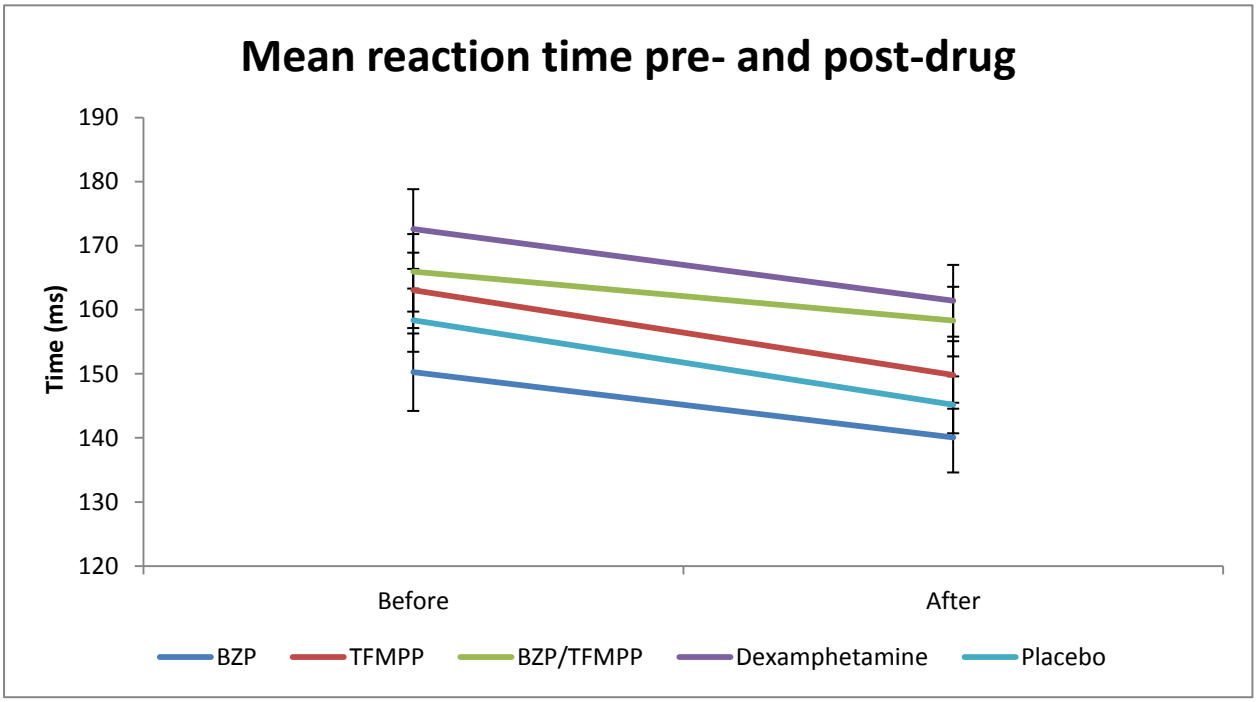


Table 11. Main effects and interactions of the reaction time (denotes p<0.05)*

Effect	df	F	p	sig
Time	1,77	39.350	0.001	*
Time×Drug	4,77	0.373	0.827	-

3.5. Summary

We investigated the effects of BZP, TFMPP, BZP+TFMPP and dexamphetamine on absolute N160 latency, interhemispheric transfer time and the mean reaction time pre- and post-drug in healthy males. Based on findings from previous literature, it was hypothesised that reduction in interhemispheric transfer time would be observed following drug administration in comparison to placebo. However, our results show that only TFMPP significantly reduced the interhemispheric transfer time while BZP, BZP+TFMPP and dexamphetamine had no effect. Moreover, we hypothesised these drugs would not influence the directional asymmetry of information transfer. Surprisingly, the asymmetry was preserved with TFMPP (i.e. faster Right-to-Left transfer) and placebo administration but this asymmetry was not present (i.e. similar transfer times in each direction) after BZP, BZP+TFMPP and dexamphetamine. Although both dexamphetamine and BZP groups displayed positive slopes in Figure 23, they were not statistically significant.

An important point to note is that the reaction time data failed to reveal any differences. The current study finds a discrepancy between behavioural (i.e. no group differences) and electrophysiological (i.e. interhemispheric transfer time and asymmetry) differences. Our results show that five treatment groups may perform similarly on a simple task at the behavioural level, yet EEG analysis may reveal differences that could serve as an electrophysiological marker. A summary of results is shown below in Table 12 and the implications will be discussed in Chapter Five (page 112).

Table 12. Summary of the Poffenberger task (denotes p< 0.05)*

Poffenberger task	BZP	TFMPP	BZP+TFMPP	Dexamphetamine	Placebo
N160 Latency	-	↓*	-	-	-
Interhemispheric transfer time	-	↓*	-	-	-
Asymmetry	↓	-*	↓	↓	-*
Reaction time	-	-	-	-	-

CHAPTER FOUR

EFFECTS OF BZP, TFMPP, BZP+TFMPP AND DEXAMPHETAMINE ON P300COMPONENTS

CHAPTER FOUR: EFFECTS OF BZP, TFMPP, BZP+TFMPP AND DEXAMPHETAMINE ON COMPONENTS OF P300

4.1. Introduction

This study is an investigation of the effects of BZP, TFMPP, the combination of BZP+TFMPP in comparison to and dexamphetamine and placebo, on human neural processing by employing EEG to determine the P300 and mean reaction time. It has been reported that components of the P300 vary under the influence of psychoactive drugs (Frodl-Bauch et al. 1999; Polich and Criado 2006). Therefore, we hypothesised that BZP, TFMPP, BZP+TFMPP would reduce the P300 amplitude. Since the combination of BZP+TFMPP has shown drug-drug synergism in rodents, we hypothesised BZP+TFMPP would produce the largest reduction in the P300 amplitude. To best of our knowledge, this is the first study to investigate the effects of BZP and TFMPP on the P300 ERP.

4.2. EEG acquisition

Data acquisition was carried out immediately after the experiment described in Chapter Three (page 80). A two-tone auditory oddball discrimination task was used in this study to elicit the P300 ERP (Donchin and Coles 1988). Participants were presented with a frequent non-oddball auditory tone (1000 Hz, probability (p)=0.8) or an infrequent oddball auditory tone (2000 Hz, p=0.2). They were instructed to respond to the oddball tone only by pressing the space bar on the keyboard as quickly as possible and to ignore the frequent non-oddball tone. The duration of each tone was 50 ms with a one second interstimulus interval. A total of 250 tones, consisting of 200 non-oddball and 50 oddball tones were

presented in four separate trial blocks per trial. Participants were instructed to keep their eyes on a fixation cross on the computer screen during the trial in order to minimise unnecessary eye movements. Task performance was assessed by the number of correct and incorrect responses, as well as the mean reaction time to hits. Reaction time was measured as the latency of the response from the onset of the target.

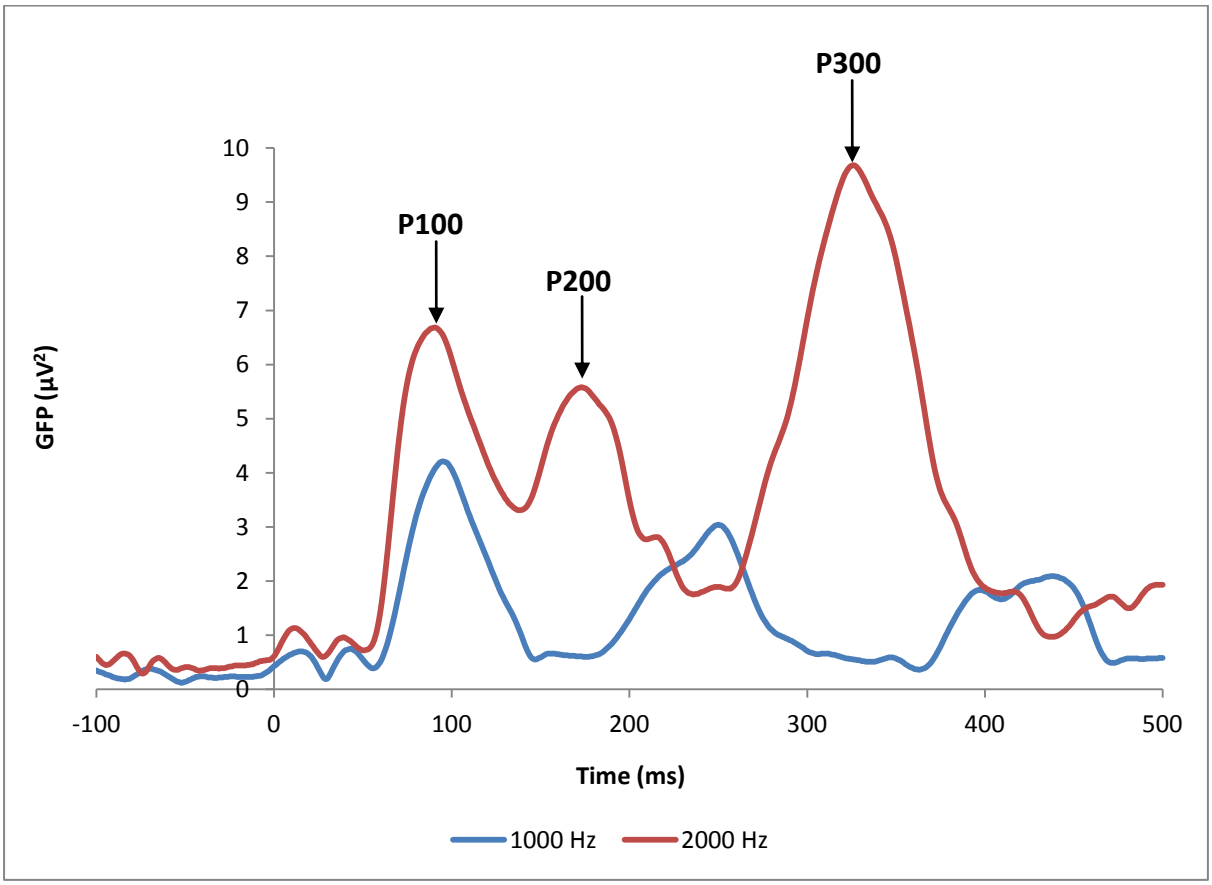
4.3. Data analysis

For each participant, eye-movement-corrected epochs from each participant were averaged to produce a total of four ERPs (two time conditions and two tone conditions). Grand-average of ERPs was calculated for each condition by averaging individual participants' ERPs (200 trials were averaged for oddball task and 50 trials were averaged for non-oddball task). The data was then filtered off-line using a digital three-pole Butterworth filter (Alarcon et al. 2000) bandpassed at 0.1 Hz and 40 Hz. The Global Field Power (GFP) was calculated to determine the latency and amplitude of the P300 component. This procedure reduces the data from multiple electrodes into a single time series and is a reference-free power measurement of field, using the root of the mean of the squared potential differences between all possible electrode pairs within the field (Lehmann and Skrandies 1980).

The P300 waveform was identified as the largest positive peak occurring between 260-460 ms after stimulus presentation. In addition, earlier components such as P100 and P200 were analysed. These two components were analysed to determine whether the drugs also affected basic neural processing. The P100 was identified as the largest negative peak between 80 and 150 ms post-stimulus and P200 was identified as the largest negative peak between 180 and 250 ms post-stimulus. Figure 25 (page97) shows P100 and P200 peaks. In addition, target auditory tones (oddball) elicited P300 waveforms, whereas non-oddball tones did not elicit P300 waveform (data from one participant). Segmented data were corrected for eye movements (Jervis et al. 1985). Segments with incorrect responses (i.e. pressed the space bar when a non-oddball tone was presented or did not press the space bar when an oddball tone was presented) were excluded from data analysis. Mean

reaction time for all participants was obtained by custom written software using Turbo Pascal (Borland Software Corporation).

Figure 25. Waveforms of responses to non-oddball (low; 1000 Hz; p=0.8) and oddball (high; 2000 Hz; p=0.2) tones from one participant. Oddball tones elicited the P300 waveform in all participants. P100 and P200 peaks are also indicated



In line with many other studies previously carried out, we used the Global Field Power that enabled easy identification of the peaks for P100, P200 and P300 (Polich 2007; Polich et al. 1997; Polich and Criado 2006; Polich and Herbst 2000; Polich et al. 1994; Pritchard et al. 2004). Amplitude was calculated as the voltage difference between the respective peak and a pre-stimulus baseline. The time taken for the peak was regarded as the latency.

Group P100, P200 and P300 amplitudes and latencies were examined separately using the Statistical Package for the Social Sciences Version 19.0 (SPSS Inc., Chicago, Illinois,

USA). Mixed Factorial Repeated Measures ANOVA with time (pre, post) as the within-participants factor and treatment (placebo, BZP, TFMPP, BZP+TFMPP, dexamphetamine) as the between-participants factor was carried out. When there was a significant Time×Drug interaction, additional interaction contrasts were run to test differences between pre- and post-dosing data, as well as differences between the five group both pre- and post-drug dosing. Statistical significance was determined by $p<0.05$.

4.4. Results

On average, 49.5 epochs (out of 50 epochs) were used for data analysis for the oddball (2000 Hz) tone for both pre-and post-drug conditions. This indicated that participants made few mistakes during the P300 oddball trial.

If a clear peak for P100, P200 or P300 could not be identified, it was excluded from analysis. From a total of 100 participants, data from 87 participants displayed clearly identifiable peaks (Table 13).

Table 13. The number of participants in each treatment group

Treatment Group	Total Collected (n)	Total Used (n)
BZP	18	13
TFMPP	16	13
BZP+TFMPP	20	18
Dexamphetamine	18	16
Placebo	28	27
Total	**100**	**87**

4.4.1. P100

4.4.1.1. P100 Amplitude

Statistical analysis of P100 amplitude is summarised in Table 14 below. Neither the main effect of Time ($F_{(1,82)}$=0.388, p>0.05) nor the Time×Drug interaction ($F_{(4,82)}$=0.680, p>0.05) was significant. Table 15 shows the means of the Time×Drug interaction for the P100 amplitude.

Table 14. Main effects and interactions of P100 amplitude

Effect	Df	F	P	sig
Time	1,82	0.388	0.535	-
Time×Drug	4,82	0.680	0.608	-

Table 15. Time×Drug interaction of P100 amplitude pre- and post-drug (±SE)

Drug	Pre-drug (μV^2)	Post-drug (μV^2)
BZP	2.275 (0.230)	2.093 (0.212)
TFMPP	2.443 (0.220)	2.234 (0.203)
BZP+TFMPP	1.871 (0.180)	1.863 (0.166)
Dexamphetamine	1.872 (0.204)	2.012 (0.188)
Placebo	2.296 (0.147)	2.321 (0.135)

4.4.1.2. P100 Latency

Statistical analysis of P100 latency is summarised in Table 16 below. Neither the main effect of Time ($F_{(1,82)}$=0.370, p>0.05) nor the Time×Drug interaction ($F_{(4,82)}$=0.919, p>0.05) was significant.

Table 16. Main effects and interactions of P100 latency

Effect	Df	F	P	sig
Time	1,82	0.370	0.545	-
Time×Drug	4,82	0.919	0.458	-

Error! Not a valid bookmark self-reference. shows the means for the Time×Drug interaction of P100 latency.

Table 17. Time×Drug interaction of P100 latency pre- and post-drug (±SE)

Drug	Pre-drug (ms)	Post-drug (ms)
BZP	93 (7.561)	102.818 (6.917)
TFMPP	107.909 (7.561)	112.045 (6.917)
BZP+TFMPP	120.111 (5.910)	113.500 (5.407)
Dexamphetamine	114.643 (6.702)	113.071 (6.131)
Placebo	104.426 (4.826)	107.407 (4.415)

4.4.2. P200

4.4.2.1. P200 Amplitude

Statistical analysis of P200 amplitude is summarised in Table 18 below. The main effect of Time ($F_{(1,82)}$=0.048, p>0.05) and the Time×Drug interaction ($F_{(4,82)}$=1.430, p>0.05) were both not significant. Table 19 shows the means for the Time×Drug interaction of P200 amplitude.

Table 18. Main effects and interactions of P200 amplitude

Effect	Df	F	P	sig
Time	1,82	0.048	0.828	-
Time×Drug	4,82	1.430	0.234	-

Table 19. Time×Drug interaction of P200 amplitude pre- and post-drug (±SE)

Drug	Pre-drug (μV^2)	Post-drug (μV^2)
BZP	1.514 (0.205)	1.571 (0.232)
TFMPP	2.782 (0.224)	2.353 (0.255)
BZP+TFMPP	2.009 (0.172)	2.031 (0.195)
Dexamphetamine	1.895 (0.214)	2.185 (0.243)
Placebo	2.249 (0.155)	2.410 (0.176)

4.4.2.2. P200 Latency

Statistical analysis of P200 latency is summarised in Table 20 below. Neither the main effect of Time ($F_{(1,82)}$=0.308, p>0.05) nor the Time×Drug interaction ($F_{(4,82)}$=0.460, p>0.05) was significant. Table 21 shows the means for the Time×Drug interaction of P200 latency.

Table 20. Main effects and interactions of the mean reaction time

Effect	Df	F	P	sig
Time	1,82	0.308	0.581	-
Time×Drug	4,82	0.460	0.765	-

Table 21. Time×Drug interaction of P200 latency pre- and post-drug (±SE)

Drug	Pre-drug (ms)	Post-drug (ms)
BZP	189.833 (6.783)	192.917 (6.569)
TFMPP	204.200 (7.430)	201.850 (7.196)
BZP+TFMPP	198.765 (5.699)	195.647 (5.519)
Dexamphetamine	206.273 (7.084)	203.364 (6.861)
Placebo	197.476 (5.127)	197.881 (4.966)

4.4.3. P300

4.4.3.1. P300 Amplitude

Statistical analysis of the P300 amplitude revealed a number of significant main effects and interactions summarised in Table 22 below.

Table 22. Main effects and interactions of the P300 amplitude. (denotes p<0.05)*

Effect	Df	F	P	sig
Time	1,82	16.764	0.001	*
Time×Drug	4,82	2.379	0.05	*

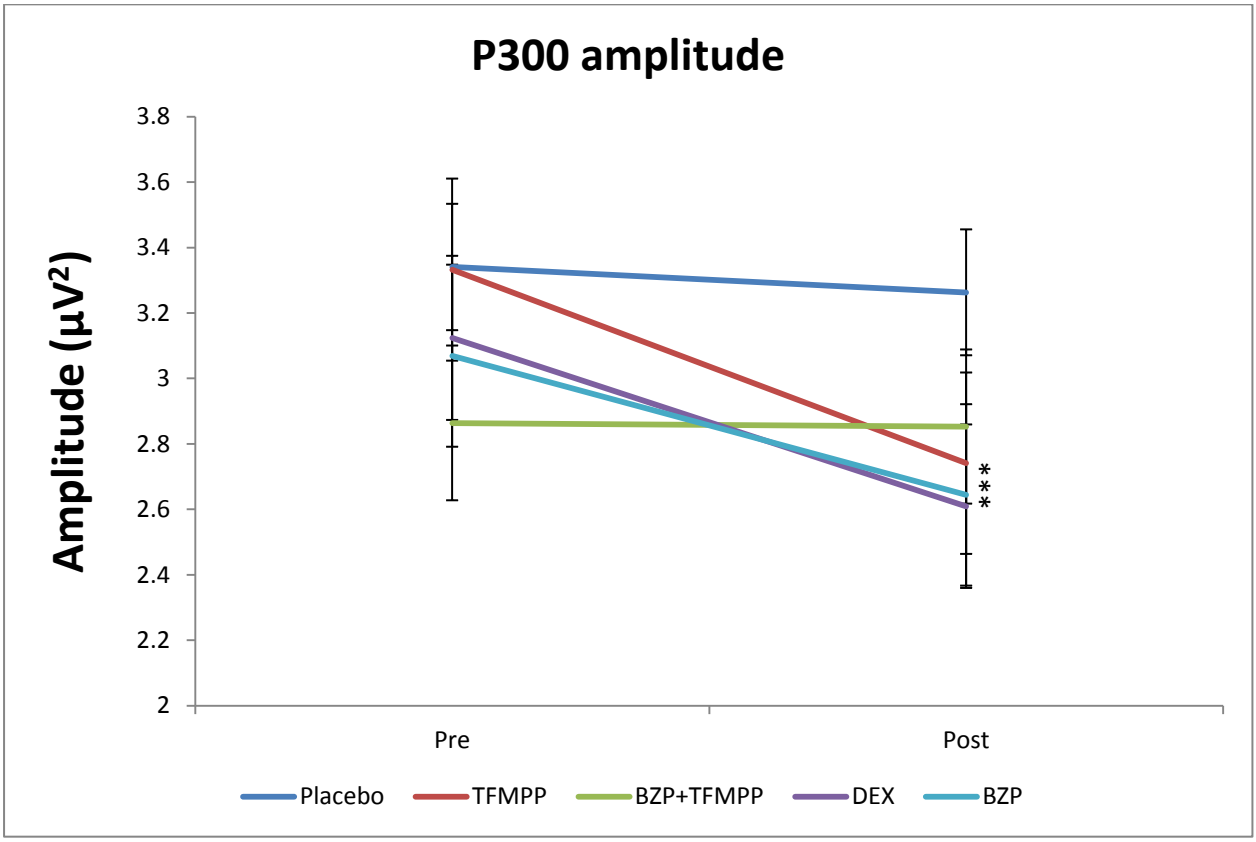
There was a main effect of Time ($F_{(1,82)}$=16.764, p≤0.001) and a Time×Drug interaction ($F_{(4,82)}$=2.379, p≤0.05; Table 23). Contrast analysis revealed both placebo and the combination of BZP+TFMPP were statistically different from the other drug groups ($F_{(1,82)}$=9.09, p≤0.004), suggesting the P300 amplitude was not significantly reduced after giving BZP+TFMPP or placebo.

Table 23. Time×Drug interaction of P300 amplitude pre- and post-drug (±SE) (denotes p<0.05)*

Drug	Pre-drug (μV^2)	Post-drug (μV^2)
BZP	3.069 (0.278)	2.644 (0.277)*
TFMPP	3.332 (0.278)	2.741 (0.277)*
BZP+TFMPP	2.864 (0.236)	2.853 (0.236)
Dexamphetamine	3.124 (0.251)	2.609 (0.250)*
Placebo	3.340 (0.193)	3.263 (0.192)

Figure 26 shows mean amplitude of the P300 ERP pre- and post-drug for five drug groups.

Figure 26. Mean amplitude of P300 ERP pre- and post-drug for five treatment groups. Error bars represent standard errors of the mean (denotes p<0.05)*



Figures 27 and 28 show plotted grand averages of the P300 amplitude for BZP and TFMPP groups. The P300 amplitude significantly reduced following BZP and TFMPP administration.

Figure 27. Grand average P300 of the BZP group. The P300 amplitude was significantly reduced following BZP administration (denotes p<0.05)*

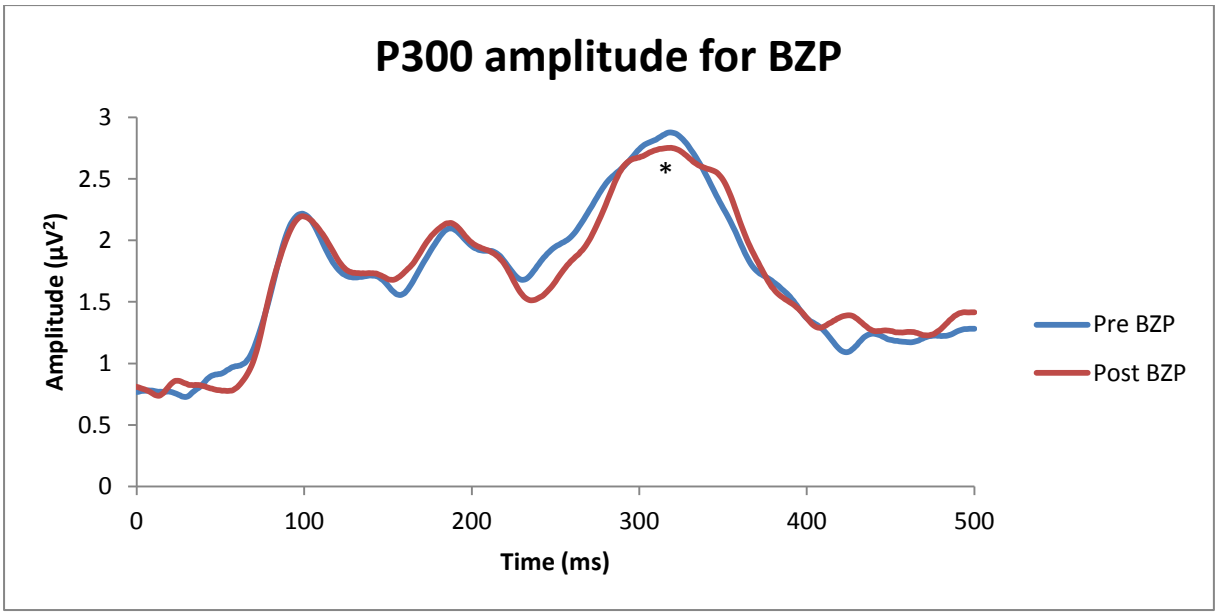
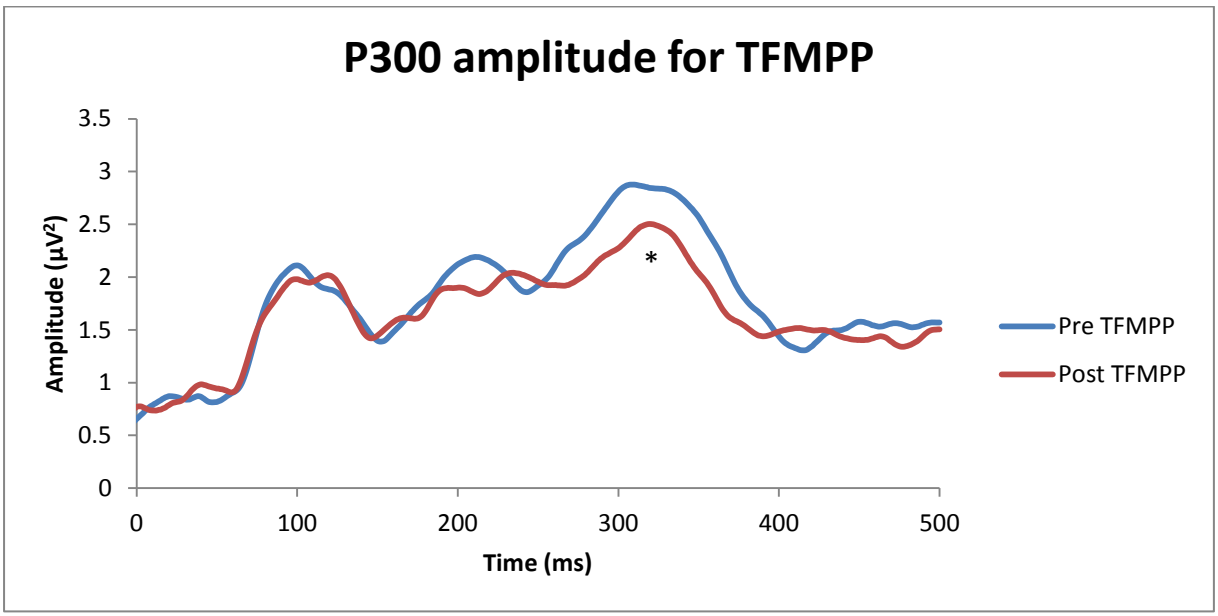


Figure 28. Grand average P300 of the TFMPP group. The P300 amplitude was significantly reduced following TFMPP administration (* denotes p<0.05)



Figures 29 and 30 show plotted grand averages of the P300 amplitude for BZP+TFMPP and dexamphetamine groups. The P300 amplitude was not significantly reduced after the administration of BZP+TFMPP, but it was significantly reduced after dexamphetamine.

Figure 29. Grand average P300 of the BZP+TFMPP group. The P300 amplitude did not change following BZP+TFMPP administration

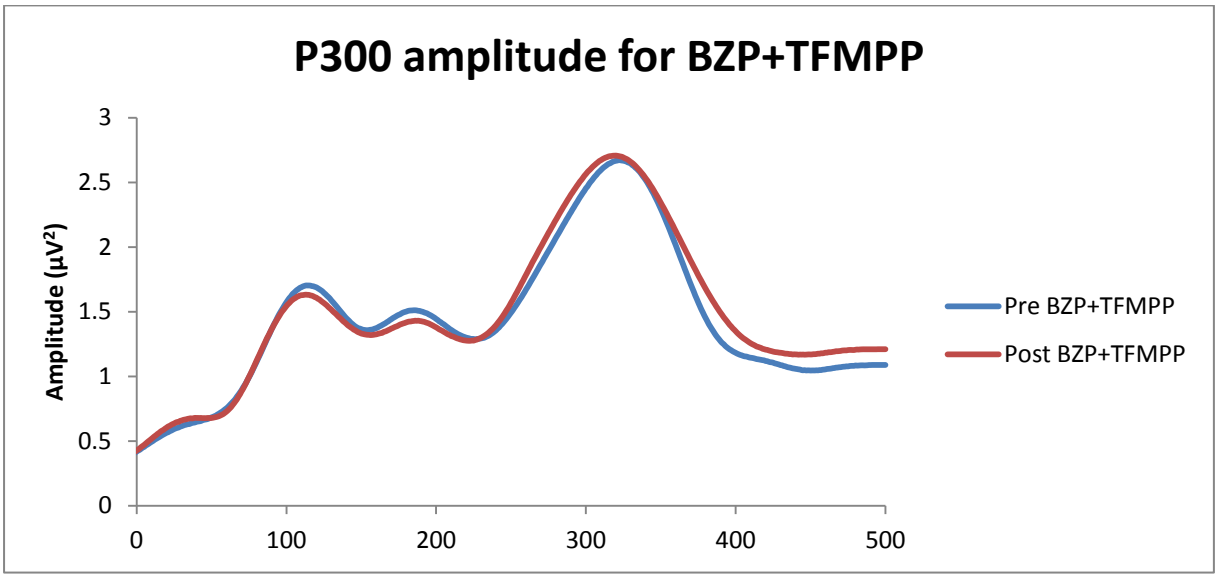


Figure 30. Grand average P300 of the dexamphetamine group. The P300 amplitude was significantly reduced following dexamphetamine administration (denotes p<0.05)*

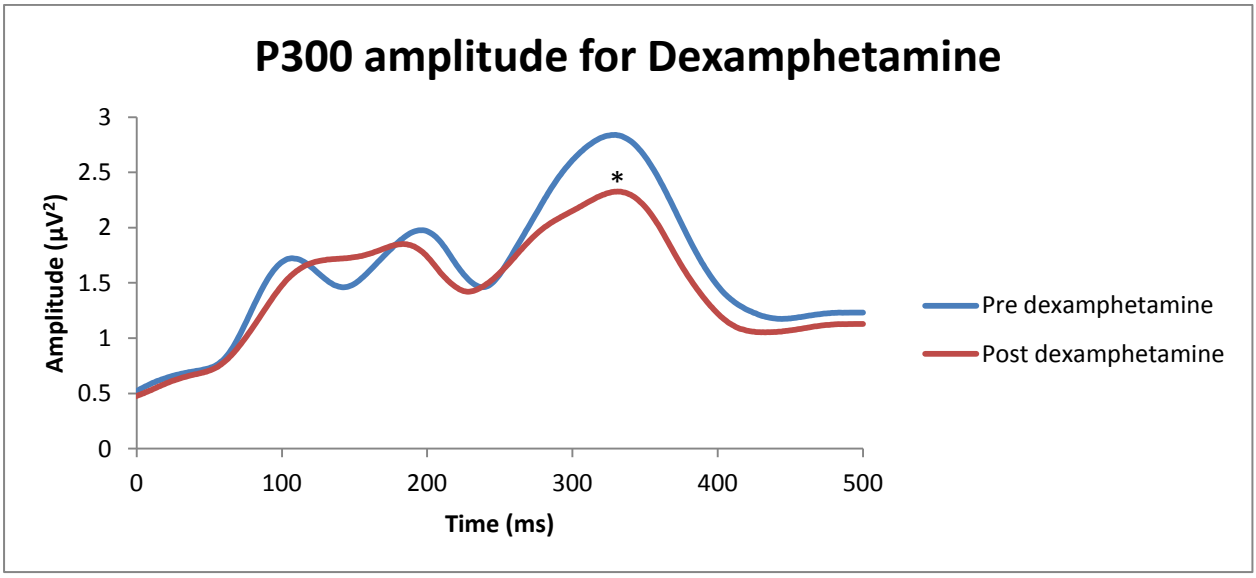
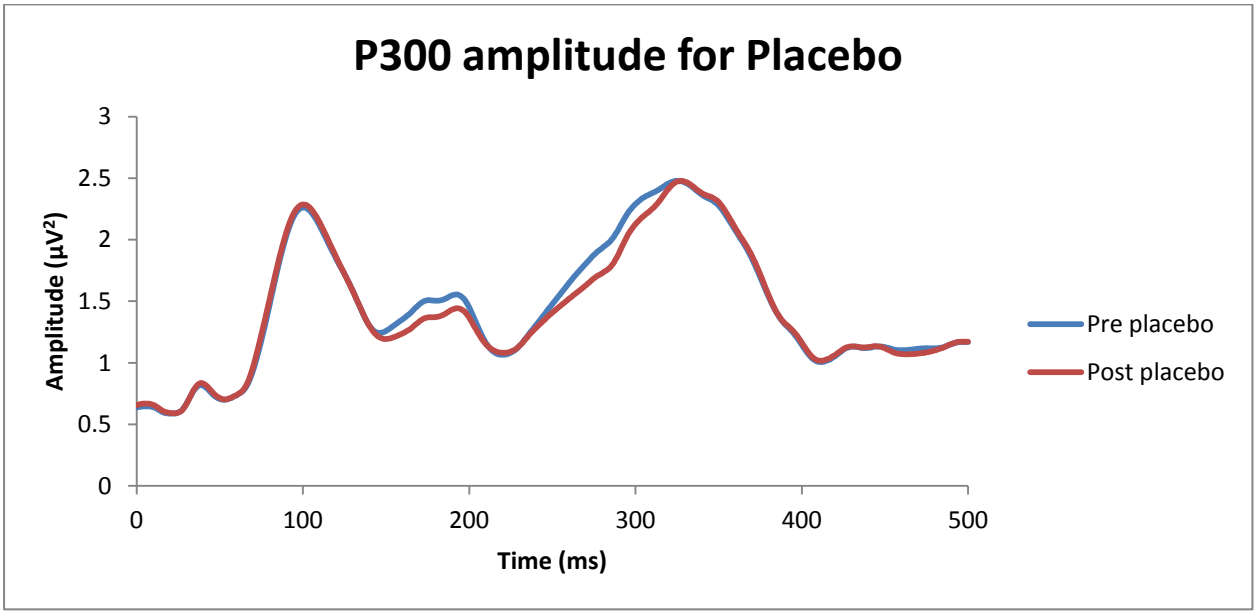


Figure 31 shows a plotted grand average of the P300 amplitude for placebo group. The P300 amplitude did not change after placebo administration.

Figure 31. Grand average P300 of the placebo group



4.4.3.2. P300 latency

Statistical analysis of the P300 latency is summarised in Table 24 below. Neither the main effect of Time ($F_{(1,82)}$=1.844, p>0.05) nor the Time×Drug interaction ($F_{(4,82)}$=0.339, p>0.05) was significant.

Table 24. Main effects and interactions of the P300 latency

Effect	Df	F	P	sig
Time	1,82	1.844	0.178	-
Time×Drug	4,82	0.339	0.851	-

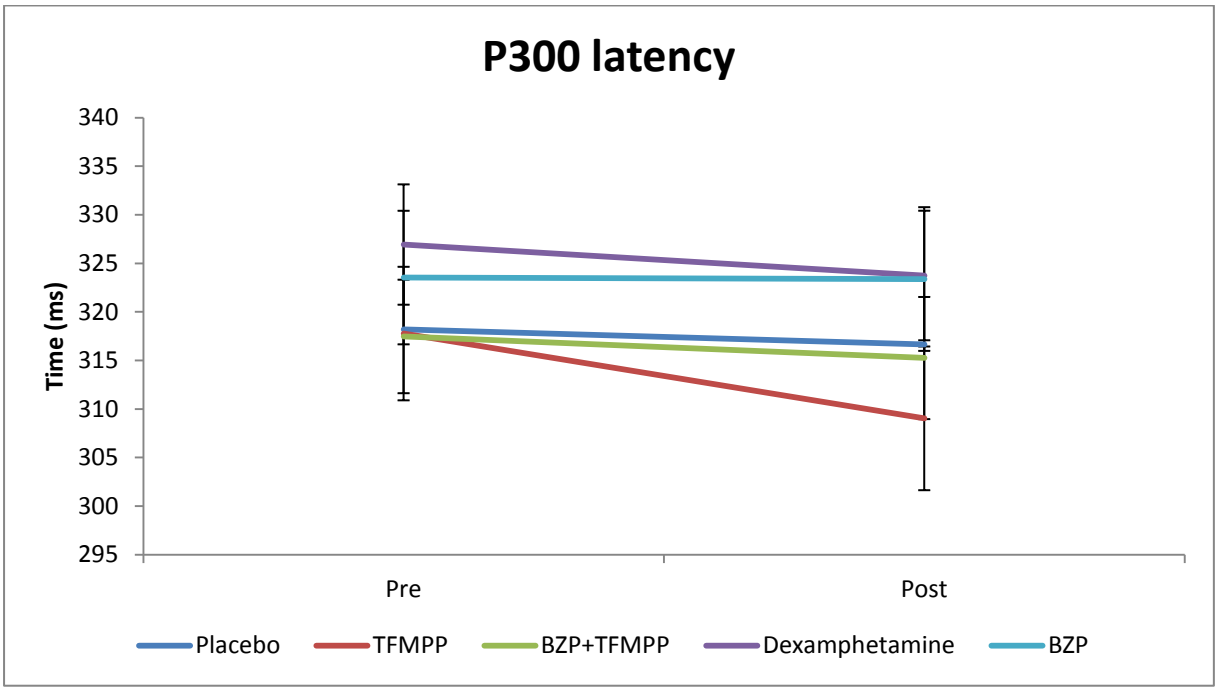
Table 25 shows means of the Time×Drug interaction of the P300 latency.

Table 25 Time×Drug interaction of P300 latency pre- and post-drug (±SE)

Drug	Pre-drug (ms)	Post-drug (ms)
BZP	323.538 (6.876)	323.385 (7.401)
TFMPP	317.769 (6.876)	309.038 (7.401)
BZP+TFMPP	317.472 (5.844)	315.250 (6.289)
Dexamphetamine	326.938 (6.198)	323.750 (6.671)
Placebo	318.204 (4.771)	316.648 (5.135)

Figure 32 shows the mean latency of the P300 ERP pre- and post-drug for the five treatment groups.

Figure 32. Mean latency of the P300 ERP pre- and post-drug for five treatment groups. Error bars represent standard errors of the mean



4.4.3. Reaction time

Statistical analysis of mean reaction time is summarised in Table 26 below. Neither the main effect of Time ($F_{(1,82)}$=3.252, p>0.05) nor the Time×Drug interaction ($F_{(4,82)}$=1.274, p>0.05) was significant. Figure 33 shows the mean reaction time of the five treatment groups. There was no significant effect of any drug on reaction time.

Table 26. Main effects and interactions of the mean reaction time

Effect	Df	F	P	sig
Time	1,82	3.252	0.075	-
Time×Drug	4,82	1.274	0.287	-

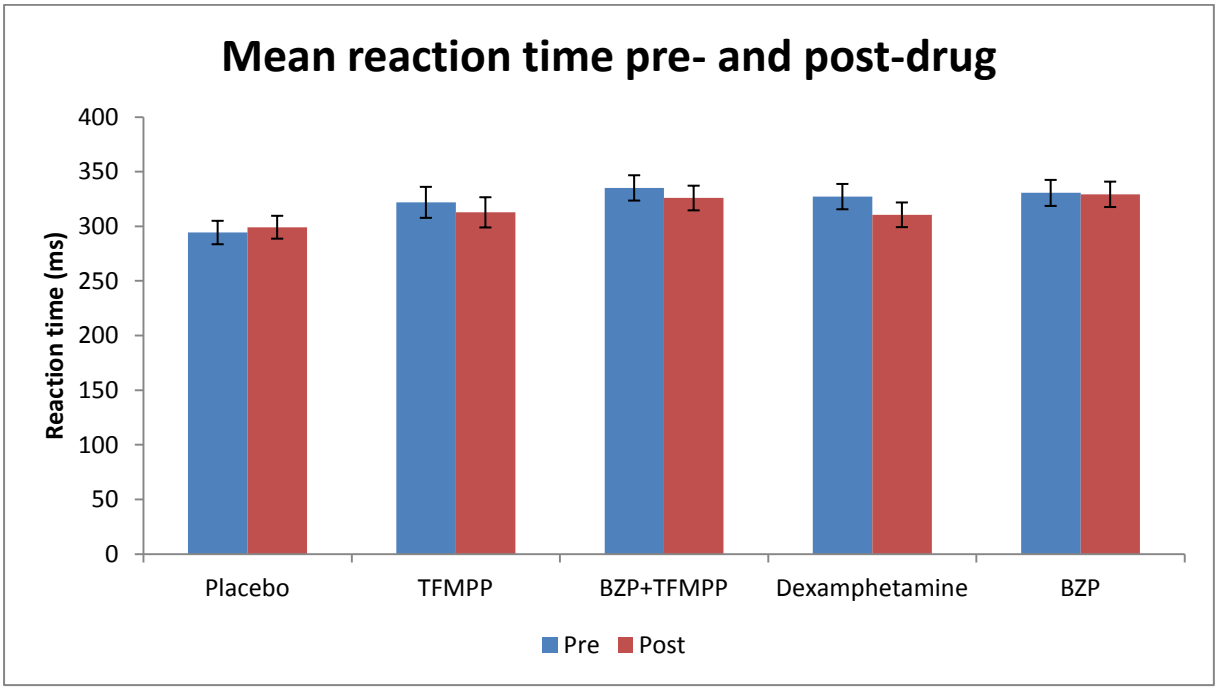
Table 27 shows means of the Time×Drug interaction of reaction time.

Table 27. Time×Drug interaction of P300 latency pre- and post-drug (±SE)

Drug	Pre-drug (ms)	Post-drug (ms)
BZP	330.592 (11.918)	329.308 (11.623)
TFMPP	321.948 (14.186)	312.810 (13.834)
BZP+TFMPP	335.176 (11.582)	325.927 (11.296)
Dexamphetamine	327.216 (11.582)	310.546 (11.296)
Placebo	294.320 (10.723)	299.117 (10.458)

Figure 33 shows mean reaction time pre- and post-drug.

Figure 33. Mean reaction time pre- and post-drug. Error bars represent standard errors of the mean.



4.5. Summary

This chapter reported the effects of BZP, TFMPP, BZP+TFMPP and dexamphetamine in comparison to placebo, on the P300 ERP as well as P100 and P200 using an auditory oddball task. The amplitude, latency and mean reaction time were collected and compared pre- and post-drug. Since dopaminergic, serotornergic and noradrenergic pathways are involved in the modulation of the P300 component, we hypothesised we would observe changes following the administration of BZP, TFMPP, BZP+TFMPP and dexamphetamine. Analysis of the P300 amplitude revealed that combination of BZP+TFMPP did not cause any significant changes in comparison to BZP, TFMPP and dexamphetamine. This was most surprising as drug-drug synergism has been reported in animals when BZP and TFMPP were administered together (Baumann et al. 2004). The P300 latency and the mean reaction times were not affected by any of the drug treatments. Considered together, the administration of BZP, TFMPP and dexamphetamine affected the performance of neural processing (i.e. P300 amplitude) but not processing speed (i.e. P300 latency) or motor response (i.e. reaction time). The P300 results are summarised in Table 28 below and the findings will be discussed in Chapter Five (page 112). In addition, analysis of earlier components such as P100 and P200 revealed no significant changes following the administration of drugs, demonstrating that these drugs are specifically affecting the P300.

Table 28. Summary of auditory oddball task (denotes p< 0.05)*

Auditory Oddball	BZP	TFMPP	BZP+TFMPP	Dexamphetamine	Placebo
P100 amplitude	-	-	-	-	-
P100 latency	-	-	-	-	-
P200 amplitude	-	-	-	-	-
P200 latency	-	-	-	-	-
P300 amplitude	↓*	↓*	-	↓*	-
P300 latency	-	-	-	-	-
Reaction time	-	-	-	-	-

CHAPTER FIVE

GENERAL DISCUSSION

CHAPTER FIVE: GENERAL DISCUSSION

5.1. General discussion

Party Pills containing BZP and TFMPP have gained huge popularity in recent years, especially in New Zealand (Wilkins et al. 2006). Their ability to mimic the effects of MDMA and amphetamines resulted in growing popularity amongst young people around the world (Drug Enforcement Administration 2010; EMCDDA 2007; Europol 2007). Animal studies of BZP and TFMPP reported that they mirror MDMA *in vivo* by increasing the concentrations of monoamines such as 5-HT and DA (Baumann et al. 2004; 2005). It has been shown that BZP possesses higher selectivity for increasing DA, whereas TFMPP shows higher selectivity for increasing 5-HT *in vivo*. The combination of BZP+TFMPP at high doses displays drug-drug synergism and causes dose-dependent seizures in rats (Baumann et al. 2004; 2005). In humans, BZP caused increases in heart rate and blood pressure, as well as inducing MDMA- and amphetamine-like effects such as increased vigour and euphoria (Lin et al. 2009). On the other hand, TFMPP produces fenfluramine- and LSD-like effects such as increases in tension and confusion (Jan et al. 2010). The combination of BZP+TFMPP produces a mixture of amphetamine- and LSD-like effects in humans (Lin et al. 2011). Until now, there have been no studies describing the central effects of these compounds in humans. This thesis reports on the first studies examining the effects of these agents on neural processing in humans using EEG.

The second chapter of this thesis described participant recruitment and their characteristics such as their body weight, age and handedness. In addition, a history of past drug use (i.e. recreational drugs, Party Pills), caffeine/alcohol/nicotine intake, state of current health, day-to-day wellbeing, sleeping patterns and recreational time was collected via the lifestyle questionnaire. It was important that we collected this information as human ERPs are influenced by these factors and so they could potentially confound our results. Strict inclusion/exclusion criteria ensured we recruited healthy, right-handed males

with no history of mental illness, head trauma or drug addiction (see Appendix III for the full list of exclusion criteria). Briefly, participants were required to be non-smokers with no regular prescription drugs, no past self-reported history of alcohol or other drug addiction. In addition, participants were excluded on the bases of a history of head trauma, epilepsy or endocrine disorder, as these factors were likely to affect the human ERP recordings (Polich and Kok 1995). Furthermore, females were not recruited as gender affects the human ERPs (Jeeves and Moes 1996; Nowicka and Fersten 2001). A total of 100 participants were recruited for the current trial and with a mean age of 22.74 ± 4.22 years and body weight of 77.04 ± 12.25 kg. In addition, the handedness of each participant was determined using the Edinburgh Handedness Inventory so all the participants were right handed with a mean laterality quotient of 78.96 ± 19.88. The lifestyle questionnaire revealed that three in five participants had tried recreational drugs in the past and two in five participants had tried Party Pills before participating in this research. However, none of the participants reported consuming any recreational or constituents of Party Pills at least two weeks prior to taking a part in this research. The participants also regularly consumed both caffeinated and alcoholic beverages each week. On the whole, the participants were generally healthy and not stressed. One-way ANOVA and χ^2 analyses revealed no differences between the five treatment groups (e.g. BZP, TFMPP, BZP+TFMPP, dexamphetamine and placebo) on demographic measures.

The third chapter of this thesis described the investigation of the effects of BZP, TFMPP, BZP+TFMPP and dexamphetamine on neural processing using a modified Poffenberger task. As noted in Chapter One, underlying changes to neurotransmitter systems arising from the acute administration of psychoactive drugs or disease states are measurable using interhemispheric transfer time. Therefore, we hypothesised that these drugs would increase the speed of interhemispheric transfer of information, reflecting the neuromodulatory effects of these drugs in humans. We reported surprising findings from the interhemispheric transfer study as only TFMPP significantly reduced the interhemispheric transfer time while preserving the asymmetry of directional transfer (e.g. faster Right-to-Left vs. slower Left-to-Right). BZP, BZP+TFMPP and dexamphetamine all failed to produce significant reduction in interhemispheric transfer time. Furthermore, contrast analysis revealed that the asymmetry of directional transfer was preserved with

TFMPP ($F_{(1,77)}$=15.08, p≤0.001) and placebo ($F_{(1,77)}$=17.30, p≤0.02) groups, but this asymmetry was not present in BZP, BZP+TFMPP and dexamphetamine groups (Figure 23). In contrast, reaction time was not affected by any drug treatment suggesting a discrepancy between electrophysiological and behavioural measures. The possible reason for this discrepancy is discussed in section 5.5, below.

The fourth chapter of this thesis described the investigation of the central effects of BZP, TFMPP, BZP+TFMPP and dexamphetamine in comparison to placebo using an auditory oddball task to elicit the P300 ERP. The P300 ERP is thought to reflect working memory capacity and speed of neural processing. In addition, the P300 ERP is reportedly affected by many psychoactive drugs and the presence of neurological disorders (see Chapter One). P300 amplitude was significantly reduced after the administration of BZP, TFMPP and dexamphetamine but remained unchanged after the combination of BZP+TFMPP and placebo. P300 latency and mean behavioural reaction time were not changed after receiving any of the drugs at these doses. Furthermore, analyses of P100 and P200 components revealed no group differences pre- and post-drug, suggesting that, in contrast to the processes measured by the P300, initial sensory processing was not influenced by any of the drug treatments.

In summary, this study presents the findings that the Party Pill constituent TFMPP significantly affected interhemispheric transfer time during the Poffenberger task, whereas BZP and TMFPP significantly modified P300 neural processing during the oddball task in humans. However, a half-dose combination of BZP and TMFPP did not have any effect; showing a lack of additive or synergistic effects of these drugs.

5.2. Interhemispheric transfer time

There are three important findings from the present experiments carried out using the Poffenberger task. Firstly, the N160 latency and interhemispheric transfer time were significantly reduced following TFMPP administration, but not the other drugs. Secondly, the asymmetry of information transfer (i.e. faster Right-to-Left vs. Left-to-Right transfer)

was preserved with TFMPP and placebo groups, but this asymmetry was not present in the BZP, BZP+TFMPP and dexamphetamine groups. These findings suggest that BZP, TFMPP, BZP+TFMPP and dexamphetamine influence the speed and integrity of information transfer between the hemispheres in humans. The third important finding was that the reaction time data failed to reveal any differences. The findings suggest differences between behavioural (e.g. reaction time) and electrophysiological (e.g. EEG findings) experiments (see section 5.4 for discussion).

The interhemispheric transfer time in both directions reported in this study ranged between 9.27 and 18.39 ms, in line with previous literature reporting visually-evoked interhemispheric transfer time ranges from 5 to 20 ms (Brown et al. 1998). In addition, our findings that interhemispheric transfer from Right-to-left was faster than Left-to-Right in the pre-drug condition only is in line with other studies reporting asymmetry of interhemispheric transfer in healthy right-handed males using visual-evoked potentials (Brown et al. 1998; Brown and Jeeves 1993; Iwabuchi and Kirk 2009; Marzi 1999).

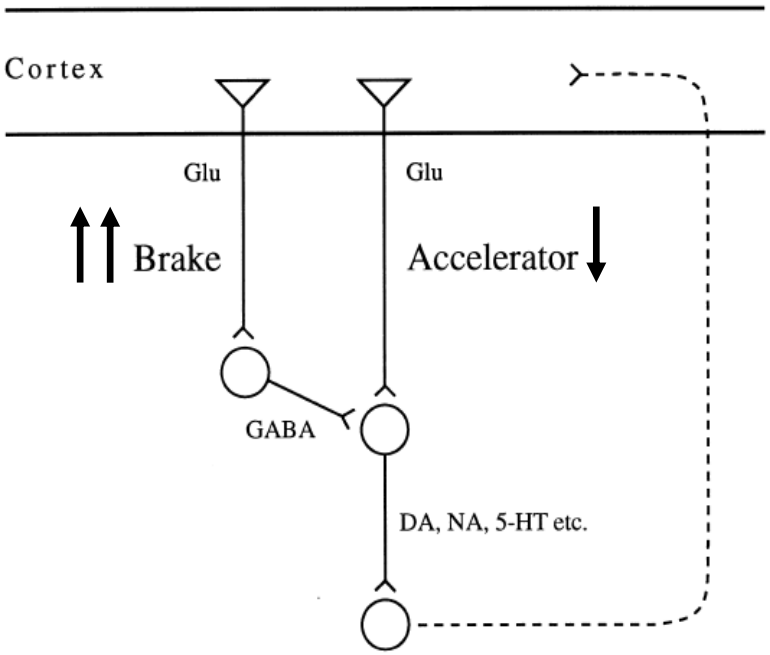
As previously mentioned in Chapter One, the speed and the integrity of interhemispheric transfer time is largely dependent on the structural properties of the corpus callosum (Cherbuin and Brinkman 2006a; Funnell et al. 2000; Gazzaniga 2000; Iacoboni and Zaidel 2004). Factors such as the gender, age and handedness are reported to influence the structural properties of the corpus callosum. In the present study, we report that acute pharmacological intervention also affected the speed and the asymmetry of interhemispheric transfer time. The following section offers possible explanations for the observed changes.

As previously mentioned in section 1.5.1.2, it is suggested that glutamate and GABA play a major role in the functional regulation of the corpus callosum and the interhemispheric transfer of information (Bloom and Hynd 2005). The accelerator/brake theory proposed by Carlsson (1999) proposes that the cortical regulation of the activity of monoaminergic brainstem neurons is governed by a direct glutamatergic pathway (acting as an accelerator) and an indirect glutamatergic/GABAergic pathway (acting as a brake).

We propose three possible mechanisms of TFMPP-mediated cortical regulation of the neurotransmitter pathways (Figure 34). Firstly, TFMPP has been shown to directly cause

hypoglutamatergia by decreasing the extracellular glutamate levels (Golembiowska and Zylewska 1999; Srkalovic et al. 1994) and this would lead to less weight on the 'accelerator' Furthermore, TFMPP has been shown to indirectly reduce extracellular glutamate levels via 5-HT_{1B} receptors (Srkalovic et al. 1994), and this also would lead to hypoglutamatergia. Secondly, TFMPP causes an increase of 5-HT release (Baumann et al. 2004). This surge of 5-HT would then trigger the 'brake' via the negative feedback loop. Lastly, TFMPP may also activate $GABA_B$ receptors via 5-HT_{2A} receptors adding more weight on the 'brake' (Alhaider et al. 1993; Titeler et al. 1987).

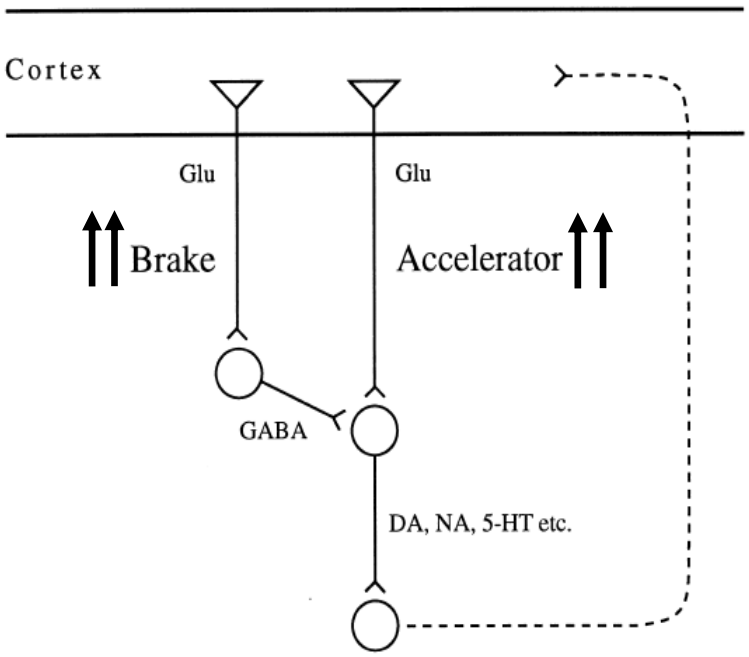
Figure 34. The hypothesis of TFMPP-mediated cortical regulation of neurotransmitter pathways. Arrows represent TFMPP effect. Reproduced and modified from Carlsson et al. (1999) with permission from Elsevier (1999©)



Similarly, Figure 35 is a representation of BZP, BZP+TFMPP and dexamphetamine-mediated cortical regulation of the neurotransmitter pathways. Our results demonstrate a reduction in lateralisation after the administration of BZP, BZP+TFMPP and dexamphetamine. Compared to TFMPP alone, BZP and the combination of BZP+TFMPP selectively elevated dialysate DA levels *in vivo* (Baumann et al. 2004). In addition,

dexamphetamine has been shown to increase dialysate DA concentrations up to 15 times above baseline *in vivo* (Miele et al. 2000). Amphetamine has also been shown to dramatically increase extracellular concentrations of glutamate and DA (Del Arco et al. 1999). Therefore, we propose that enhanced DA release induced by BZP, BZP+TFMPP and dexamphetamine, coupled with hyperglutamatergia leads to more weight on the 'accelerator'. Although the brake may be activated via negative feedback in the cortex, it may not be sufficient to counteract the surge of DA, which leads to increased activation of the excitatory pathway in the corpus callosum.

Figure 35. The hypothesis of BZP, BZP+TFMPP, or dexamphetamine-mediated cortical regulation of neurotransmitter pathways. Arrows represent the effect of one of the drugs or their combination. Reproduced and modified from Carlsson et al. (1999) with permission from Elsevier (1999©)



The function of the corpus callosum is predominantly that of interhemispheric communication by transferring information between the two hemispheres (see section 1.5.1). Alterations to the integrity of interhemispheric transfer under the influence of

psychoactive compounds may provide an insight to the involvement of different neurotransmitters (see section 1.5.1.2). Our findings also highlight how the administration of BZP, TFMPP and BZP+TFMPP leads to changes in the pattern of information transfer. Interhemispheric transfer time reflects the efficiency with which simple information is processed and transferred from one hemisphere to the other.

The findings from this study suggest that BZP, TFMPP and BZP+TFMPP may influence callosal transfer leading to disrupted interhemispheric transfer of information in humans. TFMPP facilitated the speed of interhemispheric transfer, whereas BZP, BZP+TFMPP and dexamphetamine disrupted the asymmetry of directional information transfer. It is suggested that in this study, disturbances of interhemispheric processing maybe related to functional neuromodulatory properties of the constituents of Party Pills on GABAergic, glutamatergic and monoaminergic neurons within the corpus callosum. Moreover, the Poffenberger task proved to be sufficiently sensitive to detect neuromodulatory effects of BZP, TFMPP, their combination and dexamphetamine on interhemispheric transfer of information in humans. Beyond these findings of changes of interhemispheric transfer via the corpus callosum, the results of the present study suggest that the interhemispheric transfer time relationships may prove to be important for the study of functional asymmetries of the human brain, and of the effect of psychoactive drugs.

5.3. The P300 ERP

There are three important findings from the present experiments carried out using the auditory oddball task. Firstly, the P300 amplitude was significantly reduced following BZP, TFMPP or dexamphetamine, but not after BZP+TFMPP compared to placebo. However, the P300 latency was not changed following any of the treatments (e.g. BZP, TFMPP, BZP+TFMPP, dexamphetamine, placebo). Secondly, the treatment groups did not differ in the amplitude or latency of the P100 and P200 components that reflect early processing. Thirdly, the behavioural reaction time data did not show any differences (see section 5.4 for discussion). To our knowledge these results provide some of the very first EEG evidence of

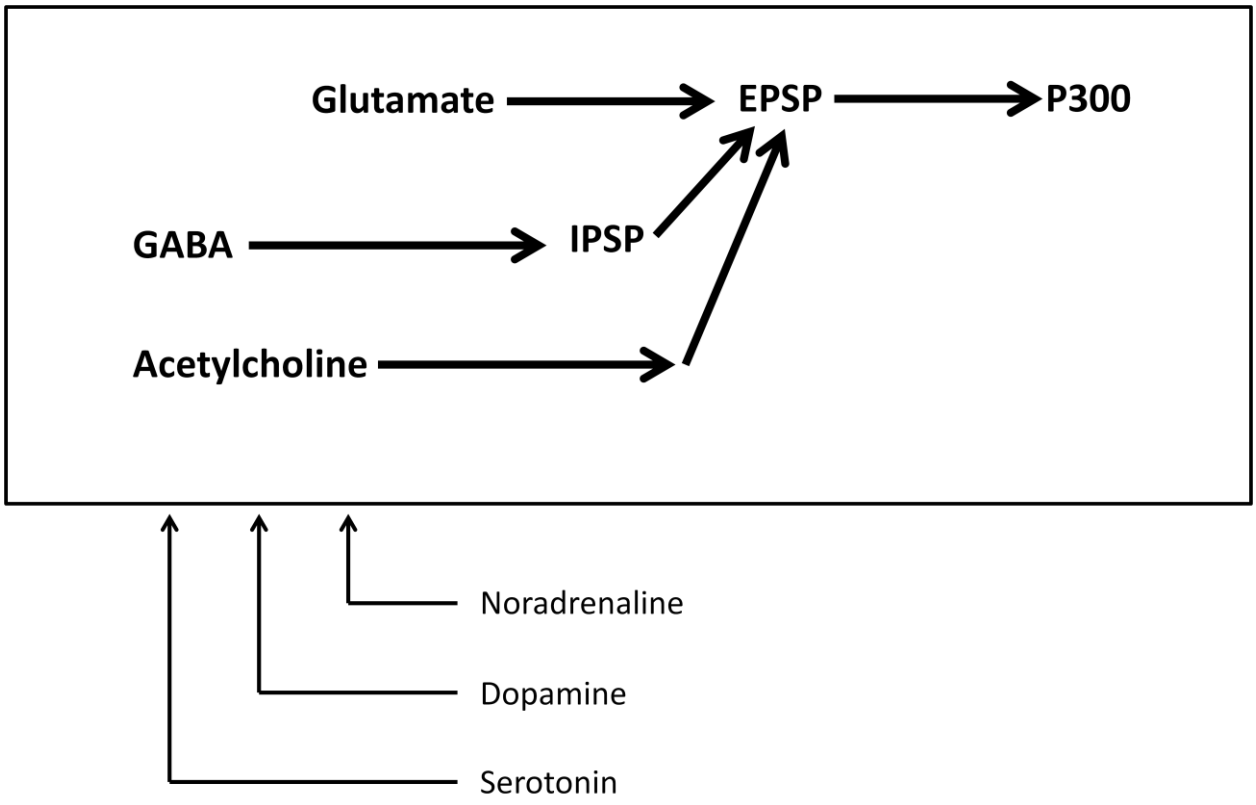
an acute effect of BZP and TFMPP administration on P300 ERPs elicited by the auditory oddball task.

As previously discussed in Chapter One, a large number of studies have provided evidence for the influence of various neurotransmitter systems on the regulation of P300 ERPs (for reviews see Frodl-Bauch et al. 1999, Hansenne 2000b and Nieuwenhuis et al. 2005). In the present study, we report that administration of BZP, TFMPP and dexamphetamine significantly reduced the P300 amplitude, but not the latency. The following section offers possible explanations of how these pharmacological agents may have influenced different neurotransmitter systems to induce changes in the P300 amplitude.

A large number of studies of the anatomical structures and cellular processes underlying ERPs have contributed to understanding of ERPs and their basic neurophysiology. It is now widely accepted that ERPs arise from intracortical currents generated by EPSPs and IPSPs which are produced by the release of neurotransmitters. ERPs reflect postsynaptic effects of neurotransmitters such as glutamate and GABA and indirect modulating effects from neuromodulators like ACh, NA, DA or 5-HT. Although the neurotransmitter systems underlying P300 generation are as yet clearly identified, the information may be important for a clearer understanding of current findings.

Findings about neurochemical substrates of the P300 are suggested in Figure 36 representing a hypothetical model of P300 generation. Glutamatergic neurotransmission directly triggers EPSPs, which elicit the P300. These EPSPs and P300 are under both indirect modulation of Ach, enhancing P300 amplitude and decreasing P300 latency, and GABA, reducing P300 amplitude and prolonging P300 latency. The noradrenergic, dopaminergic and serotonergic systems also seem to have indirect neuromodulatory influences on the indirect effects of the acetylcholinergic and GABAergic systems, and thus have produced inconsistent results concerning P300 in humans.

Figure 36. Hypothetical model of P300 generation. Reproduced and modified from Frodl-Bausch et al. (1999) with permission from Elsevier (1999©)



In this thesis, we report BZP, TFMPP and dexamphetamine reduced the P300 amplitude, which is regarded an index of allocation of attentional resources (Donchin 1984; Kok 2001; Polich et al. 1994). Decreased P300 amplitude suggests that the ability of participants to allocate neural resources to the oddball task was altered. Although there was a trend towards decreased P300 latency, none of the drug treatments caused significant changes. Since only the P300 amplitude was affected by BZP, TFMPP and dexamphetamine, it appears that these three drugs selectively modulate the stimulus evaluation process. It should be noted that none of the drugs affected the mean behavioural reaction time, despite reports that psychostimulants decrease reaction time (Frowein and Sanders 1978; Halliday et al. 1994). In summary, the P300 latency was not affected by BZP, TFMPP or dexamphetamine, but the P300 amplitude was altered.

As suggested previously in section 5.2, TFMPP seems to behave in the same manner on the P300 amplitude, as on the interhemispheric transfer time (Figure 34). Firstly, as

mentioned previously, TFMPP directly decreases the extracellular glutamate levels leading to hypoglutamatergia (Golembiowska and Zylewska 1999; Srkalovic et al. 1994) and this would lead to inhibitory influences on glutamatergic EPSPs, and as a consequence reduce the P300 amplitude. Furthermore, TFMPP has been shown to indirectly reduce extracellular glutamate level via 5-HT_{1B} receptors (Srkalovic et al. 1994), and this also would cause hypoglutamatergia leading to indirect inhibitory influences on glutamatergic EPSPs. Secondly, TFMPP, via 5-HT_{2A} receptors, activates $GABA_B$ receptors and this would lead to indirect inhibitory influences on GABAergic IPSPs. The GABAergic influences decrease EPSPs and therefore reduce P300 amplitude (Alhaider et al. 1993; Titeler et al. 1987). This observation is in line with other studies where GABAergic agents reduced the P300 amplitudes (Reinsel et al. 1991; Rockstroh et al. 1991).

Figure 37. Hypothetical model of TFMPP-mediated P300 amplitude modulation. Reproduced and modified from Frodl-Bausch et al. (1999) with permission from Elsevier (1999©)

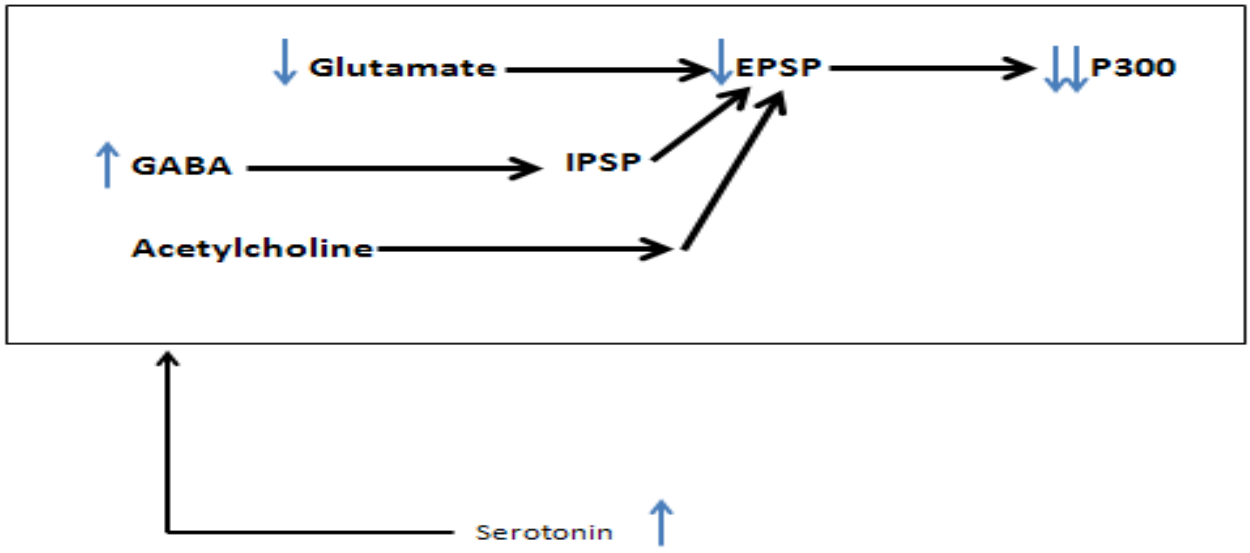
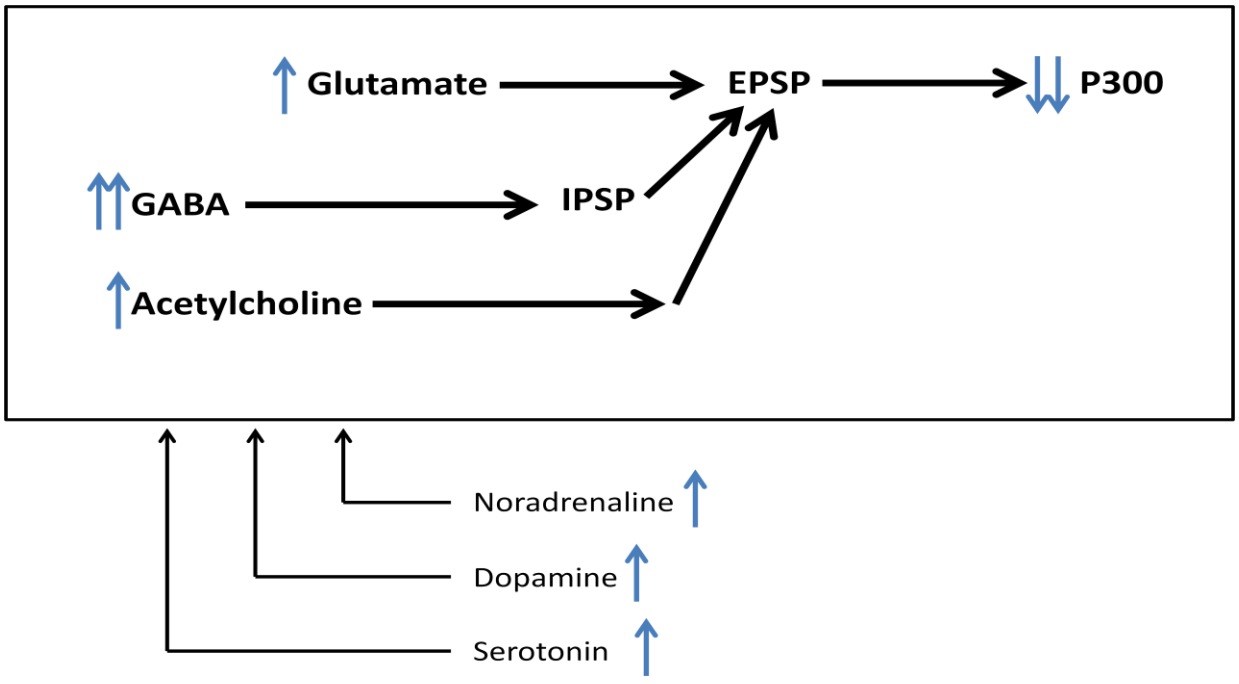


Figure 38. Hypothetical model of BZP/dexamphetamine-mediated P300 amplitude modulation. Reproduced and modified from Frodl-Bausch et al. (1999) with permission from Elsevier (1999©)



Similarly, Figure 38 is a representation of BZP and dexamphetamine-mediated P300 amplitude modulation. BZP selectively elevates dialysate DA levels as well as modulating serotonergic and noradrenergic systems *in vivo* (Baumann et al. 2004; Magyar et al. 1986; Meririnne et al. 2006; Szucks et al. 1987; Tekes et al. 1987). Hence, increased dopaminergic neurotransmission following BZP administration could lead to modulation of other neurochemical systems as shown in Figure 38. Similarly, dexamphetamine has been shown to increase dialysate DA concentrations up to 15 times above baseline *in vivo* (Miele et al. 2000). Furthermore, amphetamine has been shown to increase the extracellular concentration of glutamate, and also of 5-HT, DA, GABA and ACh, leading to the imbalance of neurotransmitter activity (Del Arco et al. 1999; Hernandez et al. 1987; Mandel et al. 1994; Mora and Porras 1993; Parker and Cubeddu 1986; Porras and Mora 1993). Therefore, increased neurotransmission following dexamphetamine administration could lead to reduction in P300 amplitude. The overall reduction of the P300 amplitude following BZP and dexamphetamine administration resembles that seen in schizophrenia where the imbalance of cortical regulation of the activity of glutamate, DA and GABA has been a suggested basis for schizophrenia (Carlsson et al. 1999; Carlsson et al. 2001; Carlsson et al. 2000; Carlsson and Carlsson 1990).

In our study, dexamphetamine reduced auditory P300 amplitudes in healthy volunteers. A recent study using dexamphetamine (0.45 mg/kg) in healthy volunteers also found a significant reduction in P300 amplitude (Albrecht et al. 2010). In contrast, several others report that dexamphetamine has no effect on P300 amplitude in healthy humans (Halliday et al. 1994; Nishimura et al. 1995; Oranje et al. 2006). These discrepancies have been reported elsewhere as dopaminergic agonists have demonstrated a biphasic effect (i.e. increase/ decrease) on P300 amplitude (Hansenne 2000a). In our study, we administered higher dose of dexamphetamine (an average dose of 0.28 mg/kg for a 70 kg person), and consequently observed a significant reduction in P300 amplitude.

Due to the reported drug-drug synergism produced by combining BZP with TFMPP in rats (Baumann et al. 2004), it was expected that significant changes in ERPs would also be observed. As expected, the combination of BZP+TFMPP disrupted the laterality of asymmetry of information transfer using Poffenberger task; however, the combination did not produce any significant change in the P300 amplitude, latency or reaction time. Our

participants only received half of the amount of BZP (100 mg) and TFMPP (30 mg) in combination, compared to receiving 200 mg of BZP or 60 mg of TFMPP when taken separately. This conservative approach was used because BZP and TFMPP inhibit each other's metabolism when given in combination, leading to higher concentration of drugs in the body (Antia et al. 2009a). The apparent lack of change observed following the BZP+TFMPP combination in the oddball task may also be attributed to an interaction between the DA and 5-HT. The combination of BZP+TFMPP have been found to produce less reinforcing effects than BZP alone in rhesus monkeys and this was attributed to TFMPP's ability to inhibit the motor-stimulant properties of BZP (Fantegrossi et al. 2005). 5-HT_{1B} receptors have also been attributed to the inhibition of $GABA_B$-receptor-mediated activation of dopaminergic neurons *in vitro* (Johnson et al. 1992). As reported previously, TFMPP has mixed affinity for 5-HT receptor subtypes such as 5-$HT_{1B/2C}$ (McKenney and Glennon 1986). Therefore, it is possible that TFMPP-induced activation of 5-$HT_{1B/2C}$ receptors attenuates the activity of the dopaminergic system.

The precise relationship between attentional demands set by a very simple auditory oddball task and the strong P300 amplitude effect following BZP, TFMPP or dexamphetamine administration is not yet evident. Some researchers suggest that a substantial portion of P300 variation is linked to fluctuation in the arousal state of the subject. Indeed P300 components are thought to be induced by the activation state rather than by the task (Kok 1990; Kulikowski et al. 1984). Since we used a very easy task for all drug groups, the effect of BZP, TFMPP or dexamphetamine administration on P300 amplitude could possibly be interpreted as a result of a non-specific reduction of the whole organism's activity level (Lindsley 1961). However, we found an amplitude effect on a specific stimulus-dependent component (i.e. P300) but not on other components (i.e. P100 or P200). Therefore, these findings do not indicate that BZP, TFMPP or dexamphetamine affect overall cortical activity in human brain. Moreover, if these compounds produced a general arousing effect, it is expected that they would facilitate the alerting effect of sensory processes that would be reflected in both early (i.e. P100 and P200) and late (i.e. P300) components (Kulikowski et al. 1984).

To conclude, these results suggest that cortical activity associated with low levels of neural processing is altered following administration of BZP, TFMPP or dexamphetamine,

but not following BZP+TFMPP. At the behavioural level, a decrease of P300 amplitude is usually interpreted as a disturbance of the mechanisms involved in stimulus evaluation (Callaway 1984). We observed no changes in P100 or P200 ERPs and these findings suggest that the drug treatments did not affect the processes concerning stimulus classification or orientation time and therefore specifically influence only the higher order responses around 300 ms (Renault 1983; Sutton et al. 1967).

5.3.1. The relationship between P300 and event-related theta EEG activity

The EEG consists of the activity of many neural generators producing rhythmic activity (i.e. oscillations) in several natural frequency ranges, namely: delta (1.0 – 3.0 Hz), theta (3.5 – 7.5 Hz), alpha (8.0 – 11.5 Hz), beta (12.0 – 28.0 Hz), and gamma (28.5 – 50.0 Hz). These oscillations are seemingly random at resting state, however, with the application of sensory stimulation, they become coupled and act together coherently (Porjesz et al. 2004). Evidence suggests that event-related oscillations undergo "phase resetting" in response to sensory or cognitive stimulation (Basar 1980). Furthermore, it is suggested that ERPs are the result of oscillatory changes due to sensory or cognitive processes which influence the dynamics of ongoing EEG rhythms of different frequency bands (Basar-Eroglu and Basar 1991; Demiralp et al. 2001b; Schurmann et al. 2001; Yordanova and Kolev 1996). Brain oscillations represent important correlates of human information processing and theta rhythms have been reported to be associated with cognitive processes such as conscious awareness, recognition memory, and episodic retrieval (Basar-Eroglu et al. 2001; Doppelmayr et al. 1998; Klimesch et al. 2001a; Klimesch et al. 2001b; Klimesch et al. 1994).

Many studies have provided evidence that the P300 component of the ERP is primarily the outcome of theta during stimulus and cognitive processing (Basar-Eroglu and Basar 1991; Basar-Eroglu et al. 1992; Yordanova and Kolev 1996). High correlations between the P300 amplitude and theta response magnitude were reported suggesting that theta power may contribute to oddball P300 waveform (Yordanova and Kolev 1998). The P300 component consists of theta at frontal sites, increasing 50% during the performance of

an oddball task to the target stimulus. In addition, it is reported that reciprocal synchronisation occurs in the theta range between hippocampus and frontal and parietal regions of the brain (Karakas et al. 2000). Furthermore, a strong relationship between P300 amplitude and pre-stimulus theta amplitude further suggested that P300 is strongly related with processing in the theta frequency channel of the EEG as reflected by the spontaneous, pre-stimulus, and early phase-locked ERP theta activity (Basar-Eroglu et al. 1992; Basar 1992; Intriligator and Polich 1994). In summary, the compelling body of evidence indicate that event-related theta activity may not only contribute directly to P300 waveform expression, but may also modify P300 via other processes in the theta frequency channel of the EEG. Therefore, future human pharmaco-EEG studies of P300 ERPs should consider the functional implications for theta activity.

With regards to the P300 ERPs reported in this thesis (see Figures 27-31), it is fair to say that they were produced by evoked-potentials rather than phase reset. In addition, neither P100 nor P200 were affected by the drugs and therefore they were not part of a P300 phase reset complex.

5.4. Reliability of reaction time and visually-evoked potentials

The current study finds a discrepancy between behavioural (i.e. no treatment group differences) and electrophysiological (i.e. interhemispheric transfer time and P300 ERPs) differences. Using a high density EEG we found that, while interhemispheric transfer time was reduced following TFMPP administration, this effect was not evident in the reaction time data. Similarly, while the P300 amplitude was significantly reduced following a single administration of BZP, TFMPP or dexamphetamine, the reaction time data failed to reveal any differences between the active treatment groups and the placebo. Our results show that participants in different treatment groups may perform similarly on a simple task at the behavioural level, yet EEG analysis may reveal differences that could serve as an electrophysiological marker.

Reaction times have been demonstrated to be valuable tools to characterise the function of the transcallosal pathway. For example, early attempts to study callosal function during interhemispheric transfer focused on simple manual reaction time paradigm (Poffenberger 1912). However, the reaction time method is a less reliable measure of interhemispheric transfer time as it may also involve some non-callosal pathways as well as motor response time (Brown et al. 1998; Milner and Lines 1982). Saron and Davidson (1989) demonstrated the superiority of using evoked potentials compared to behavioural reaction time and found that these measures were poorly correlated to each other. The authors reported that while 94% of the visually-evoked potential estimates were in the anatomically predicted direction, only 70% of the reaction time estimates were. Therefore, they concluded that the evoked potential waveforms were less variable than motor reaction time responses. Similarly, the lack of relationship between P300 amplitude, latency and behavioural reaction time might suggest that while behavioural measures may not pick up differences, these may be detected using a more direct measure such as EEG.

5.5. Limitations of this research and future direction

Although the corpus callosum is the primary axonal pathway connecting the two cerebral hemispheres, subcortical commissures such as the anterior commissure and hippocampal commissure are also involved in interhemispheric communication (Milner and Jeeves 1979). The existence of these additional commissures is an important confound for the Poffenberger task. Therefore it is important that future research investigates and validates the possible roles of these additional commissures (Hellige 1993).

The work described in this thesis was conducted in healthy right-handed males. Since gender and handedness differences in functional neuroanatomy are well established, future pharmaco-EEG studies should further explore whether gender and handedness differences influence the effects of these drugs. In addition, gender differences in drug addiction and treatment are thought to result from differences in dopaminergic function in the striatum (Becker 1999; Nelson-Zlupko et al. 1995). Preliminary findings from our own

laboratory revealed that females showed no difference in interhemispheric transfer time or the P300 ERP pre- vs. post-BZP compared to males (Bangs et al. 2007).

The present study provides clear and important evidence of speeded information transfer by TFMPP. Disruptions in central neural processing lead to cognitive processing abnormalities and behaviour as demonstrated in this thesis. A future study should employ imaging technology such as positron-emission tomography (PET) or single photon emission computed tomography (SPECT) may offer more direct pharmacologic evidence of DA involvement (Hietala et al. 1994; Laruelle et al. 1996). Studying the function of several other neurotransmitters (e.g. NA, 5-HT, ACh, glutamate and GABA) in relation to BZP and TFMPP in living intact brain is more difficult (Carlsson et al. 1999). However, researchers have used radiolabelled precursor (5-hydroxytryptophan) to measure the turnover of serotonin in patients using PET (Agren et al. 1991). Although human EEG offers excellent temporal resolution, it does not have good spatial resolution, as the brain coverings such as the meninges and scalp tend to smear the electrical signal. Therefore it is difficult to differentiate neural generators that may give rise to EEG and hence, EEG is not a useful measure of structural neuroanatomical differences (Burgess and Gruzelier 1997). This can be overcome by using diffusion tensor imaging technique as allows investigation of the white matter connectivity of the brain. For example, the function of callosal fibre pathways could be examined using diffusion tensor imaging to shed light on the relationship between structural and functional properties of corpus callosum. Moreover, fMRI studies would enable the identification of brain structures affected by the administration of BZP, TFMPP or dexamphetamine. In fact, a number of experiments carried out recently in our lab have identified a significant difference in activation in frontal regions of the brain following BZP, TFMPP, BZP+TFMPP and dexamphetamine in humans (Curley et al. 2011).

Since the present study investigated the acute effects of a single oral dose of BZP, TFMPP or BZP+TFMPP, this limits the applicability of these results to discovering their effects following chronic use. In New Zealand prior to 2008, individuals reported taking more than 50+ Party Pills in 12 months with 19% of the respondents having binged (e.g. taking 10+ Party Pills on one occasion; Wilkins et al. 2006). Chronic abuse of MDMA and methamphetamine have been linked to structural changes in the brain as these compounds are neurotoxic (Berman et al. 2008; Daumann et al. 2005; Moeller et al. 2004). On the basis

of these findings, it is possible that chronic consumption of BZP, TFMPP may also result in structural and functional abnormalities accompanied by behavioural changes. Therefore a future study investigating the effect of these drugs on the brain after chronic use is warranted.

Appendix I: Participant invitation

Dear Participant,

Thanks for your email regarding our Party Pill study. As I'm sure you are aware were looking for healthy right handed males with no history of heart disease, diabetes, significant head trauma, epilepsy or mental illness such as depression etc. We need people who would be willing to participate in the morning for approximately 4-5 hours. The idea is to fit what looks like a hair net over your head with a lot of tiny and very sensitive sensors capable of measuring the electrical activity of your brain.

Following this we'll get you to work through some simple computer-based, this is no reflection of IQ etc. Then we will give you some capsules that contain either placebo or BZP and TFMPP (the active ingredients of party pills) then wait for just over an hour and ask you to repeat the tests. For doing this we insist on supplying breakfast before you start and then provide a taxi ride home at the end of testing with either 4 movie vouchers or the equivalent in petrol vouchers as recompense for your time.

We are currently looking for people to take part on either Wednesdays or Saturdays so let me know what you think. Thank you for your interest and I hope to hear from you again.

Yours sincerely,

HeeSeung Lee

Appendix II: Invitation letter to the study

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES
SCHOOL OF PHARMACY

To: The Participant.

First of all I would like to thank you for volunteering to take part in the study designed to "Determine the effects that BZP and TFMPP have on the brain of healthy people between 18-40 years of age by using EEG recording". If you have any questions please feel free to contact me either by phone or email to discuss them. On the day of your participation and immediately before the study begins either one of my co-investigators or I will work through the Participant Information Sheet and the Consent form with you, during which time you will have the opportunity to discuss the study and raise any issues or concerns that you might have. I would like to remind you that you may withdraw from the study without consequence. In addition, after you have taken the tablets a taxi will be provided to return to your usual residence.

You are invited to participate in this study at **9 am on the morning of 2nd July 2008**. The study will take place at the Department of Psychology in the Human Sciences Building, 10 Symonds Street, Level 3, and Room 312.As discussed please don't eat any breakfast before you attend, we will provide you with breakfast on arrival. Most importantly do not consume any caffeine containing beverages such as tea, coffee, coca cola, pepsi, Red Bull, V, chocolate or those high in sugar such as fruit juice. Also as discussed please refrain from alcohol or other drug consumption (with the exceptions of paracetamol, aspirin or ibuprofen) in the preceding 24 hours. In addition could you please wash your hair on the morning of the study day and not wear hair products such as gel etc. I forgot to ask whether you wear contact lenses, sorry, but if you do, could you please wear glasses instead, the room ventilation is rather dry and lenses tend to dry out.

Yours faithfully

HeeSeung Lee

Appendix III: Exclusion factors

Illegal drugs/ recreational drugs/ high use of party pills

None in the past 5 days

- Less than 20 in a month
- Not a past heavy user (due to the long term side effects)

Stimulants including

- High amounts/ recent caffeine or caffeine containing products
- Cigarettes (heavy smoker)
- Alcohol consumption exceeding the safe drinking criteria (21 units for a male, 14 units for a female with a maximum of 4 units per night)

Head trauma, History of seizures including epilepsy

Those who are currently unwell

Those who are undergoing any kind of radiotherapy or treatment for chronic or acute illnesses

Stressed individuals

- High workplace stress
- Financial stress
- Physical stress – over exertion
- Personal life

Diabetics, Epileptics, Parkinson's disease or any other neurological diseases

Metabolic disorders, anyone with cardiovascular problems

Uncontrolled asthma

Prescription medicines

- Anti-depressants
- Muscle relaxants
- Antipsychotics
- Anxiolytics
- Sedatives/ hypnotics
- Other CNS agents including methylphenidate and dexamphetamine
- Chemotherapeutic agents
- Immunosuppressants

Shift work, Recent travel across time zones (past 5 days)

Undisturbed sleeping habits/ insufficient sleep

High use of video game machines

Must have a moderately healthy diet e.g. no on-going crash diet

Appendix IV: Participant information

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES
SCHOOL OF PHARMACY

PARTICIPANT INFORMATION SHEET

Electroencephalograph Study

Title of Project: Determination of the effects of Benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) on neurophysiological function and regional brain activation in humans using electroencephalogram (EEG) recording.

Sub-study - Determining the effects that BZP and TFMPP have on the brain of healthy people between 18-40 years of age and comparing them dexamphetamine by using EEG recording.

Researchers: Contact Details

Dr Bruce Russell, b.russell@auckland.ac.nz, School of Pharmacy Ph 09 3737599 Ext 86429

Associate Professor Ian Kirk, i.kirk@auckland.ac.nz, Dept. of Psychology, 09 373 7599 Ext 88524

Professor Robert Kydd, r.kydd@auckland.ac.nz, Dept. of Psychological Medicine 09 373 7599 Ext 83774 at the University of Auckland

You are invited to participate in this research. This will involve having a net of recording electrodes placed on the surface of your head and then carrying out a simple test of your memory followed by taking an oral dose of either placebo, BZP and/or TFMPP or dexamphetamine and then repeating the same task 2 hours later.

During the experiment you will be seated in a quiet room, and the experimenter will continuously view you via a closed circuit video monitor. No deception is involved in the

testing. It takes about ¼ hour to place the net of electrodes on the scalp; with the total time involved per testing session is approximately 4 hours.

This experiment is testing for changes in brain function that are thought to take place after a single dose of BZP and/or TFMPP, the active constituents of the so called "Party Pills" or "Legal Herbal Highs" and comparing them with dexamphetamine. BZP/TFMPP are illegally used for recreational purposes. The experiment uses a method of measuring human brain function called electroencephalography. This involves placing sponge-covered sensors, which have been soaked in a conductive solution of water, salt and shampoo, on the surface of the scalp. These sensors are able to detect the very weak electrical signals generated by human brains. We hope to measure these signals, while carrying out a test of memory both before and several hours after taking a single dose of either BZP and/or TFMPP or dexamphetamine.

Professor Rob Kydd will prescribe up to 25 mg of dexamphetamine for participants when required. Dexamphetamine has some well known side effects which you might experience e.g. sleeplessness, restlessness, decreased appetite, euphoria, dizziness, headache, dry mouth, sweating, palpitations and very rarely convulsions. If any of these side effects occur after testing you are expected to report these to Dr Russell who will endeavor to contact you by either phone or email within 24 hours of completing the trial.

You must only participate in this study if you are willing to return home in a taxi provided by the researchers following completion of the study and then remain in the company of another responsible adult for the remainder of the day/evening.

If you have had any history of epilepsy or seizures (fits), mental illness or significant head trauma you must not participate in this study.

There is a remote possibility that the BZP and/or TFMPP will result in a seizure if you have undiagnosed epilepsy.

In the unlikely event that a potential abnormality is detected in your EEG, you will be advised of this and referred to an appropriate medical specialist.

We realize that pregnancy will not occur for all women for a variety of reasons however, because of safety issues, one of the requirements for taking part in the study is that you are not pregnant. Therefore we are offering you a pregnancy test which is not compulsory but you can only take part in the study if you are certain you are not pregnant or the test returns a negative result.

Your participation is entirely voluntary (your choice). You do not have to take part in this study. If you do agree to take part, you are free to withdraw at any stage of the testing (between now and the end of the study (22/06/09). You do not have to give any reason for your decision and there will be no penalty of any sort for withdrawing. There are no repercussions (academic or otherwise) to students who do withdraw or do not wish to participate.

Any participants in this research may have access to the information collected about them including the results of the testing and the final published report of the study.

Before participation you will be asked to estimate your prior use of drugs (legal and illegal). All personal information is strictly confidential and no material that could personally identify you will be used in any reports on this study. Your name will only appear on the Participation Consent Form. These forms will be coded with a unique number that will be used to identify individual subjects' performances in all other data records. The Participation Consent Forms will only be seen by you and the investigator and will be kept in a secure filing cabinet. After completion of the study all data will be kept for the required period of ten years and will then be destroyed.

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

The experiment will be carried out in Room 312, Human Sciences Building, University of Auckland, Symonds Street.

Please feel free to contact the researchers if you have any questions about this study. Further information can be obtained from Associate Professor Ian Kirk at the Dept. of Psychology, (Ph 373-7599 ext 88524) or Dr Bruce Russell, School of Pharmacy, or Professor Rob Kydd (Ph 373-7599 ext 83774) Department of Psychological Medicine, University of Auckland.

The Head of Department is Prof. Diane McCarthy x88516/88555

If you have any queries or concerns regarding your rights as a participant in this study you may wish to contact an independent Health and Disability Advocate,

Telephone: 0800 555 050

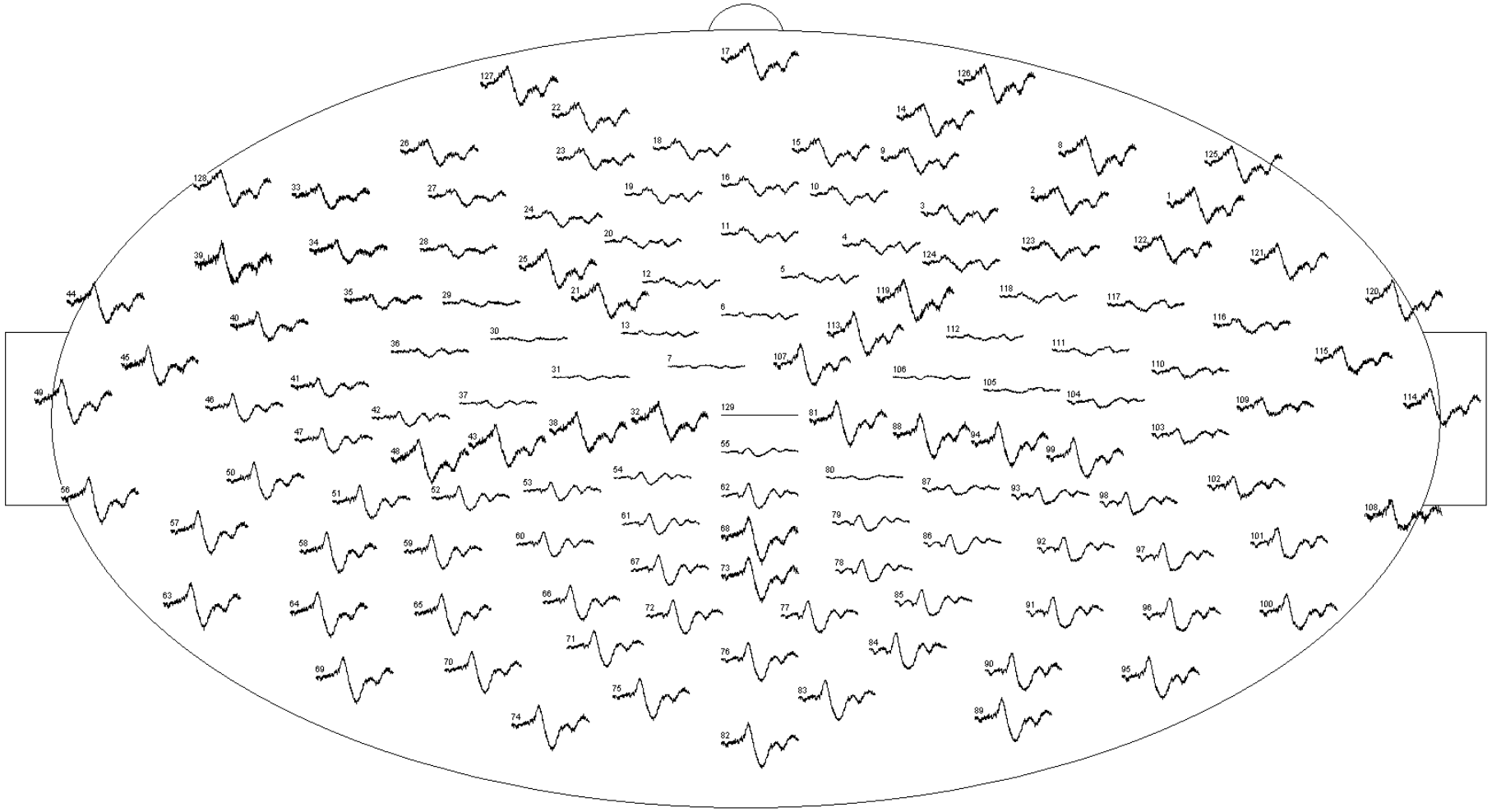
Free Fax: 800 2787 7678 (0800 2 SUPPORT)

Email: advocacy@hdc.org.nz

Approved by The Northern X Regional Ethics Committee on 22/06/2006

For a period of 3 years, from 22/06/2006 Reference NTX/06/04/032

Appendix V. Position of electrodes on the head



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