UNIVERSITY OF ALBERTA

The Effects of Alcohol on Facial Emotion Recognition

by

Patricia Ting

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

Department of Psychiatry

Edmonton, Alberta

Spring 2006

Your file Votre référence
ISBN: 0-494-13897-1
Our file Notre référence
ISBN: 0-494-13897-1

ABSTRACT

Face perception is a complex perceptual skill that is important for social interactions. A distributed neural system of multiple brain regions mediates facial perception. The purpose of this thesis is to examine if the acute administration of alcohol affects the explicit recognition of emotions from facial expressions. While the neurochemical and physiological effects of alcohol have been studied in detail, there is no comprehensive explanation for alcohol's effect on social behavior. With this study, we aim to increase our understanding of how the brain recognizes social signals, how the effect of alcohol might contribute to problems with facial emotion recognition in substance abuse disorders and other mental disorders, and the implications of these potentially unwanted effects of alcohol on psychosocial functioning.

Previous studies have shown that pharmacological agents with partially selective effects on the GABAergic system impair anger recognition; alcohol is predicted to have similar effects based on its pharmacological profile. In our study, alcohol was capable of impairing anger recognition; however, this effect was not particularly selective, nor was it independent of the type of anger expression stimuli across experimental paradigms. Fear was the only emotion for which alcohol impaired recognition in full (100%) intensity images. In general, alcohol appeared to affect the recognition of negative facial expressions (fear, sad, disgust, anger) more robustly than positive emotion (happy) or ambiguous emotion (surprise). We conclude that alcohol consistently reduces the sensitivity of detection of facial emotions and may also increase misidentification rates.

ACKNOWLEDGEMENTS

I wish to dedicate my sincere thanks to my supervisor Dr. Nicholas Coupland for his enthusiastic supervision, unrelenting patience and continual support throughout my graduate degree. Without your guidance, Dr. Coupland, completion of this thesis would not have been possible.

I also wish to thank Dr. Glen Baker and Dr. Kathryn Todd for creating the foundations of my interest in psychiatry thorough their inspirational teaching and helpful advice during my undergraduate studies in neuroscience. Additionally, I would like to acknowledge Dr. Glen Baker, Dr. Kathryn Todd, and Dr. Kathy Hegadoren for serving as members of my supervisory and examining committee.

Financial assistance in support of my graduate studies at the University of Alberta was generously provided by the Department of Psychiatry and the Alberta Heritage Foundation for Medical Research.

To John Fagnou – my best friend, to Ryan Sustrik and Emily Bell – my colleagues in graduate school – and – to all my mentors in medicine and friends from medical school – thank you for your friendship, encouragement, and strength.

To my family, thank you for your unconditional love. I could not have done this without all of you. I also wish to specially thank you, my wonderful parents, for your support and understanding in all aspects of my academic and other life endeavors – I am eternally grateful.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

%	percent
±	plus or minus
df	degrees of freedom
p-value	statistical significance
α	alpha
β	beta
γ	gamma
δ	delta
ε	epsilon
π	pi
ρ	rho
Cl^-	chloride ion
dL	decilitre
g	gram
kg	kilogram
L	litre
min	minute
ml	millilitre
mg	milligram
mmol	millimoles
ms/msec	millisecond
n	sample size
oz	ounces
ANOVA	analysis of variance
BAC	breath alcohol concentration
ERP	event-related potential
DSM-IV	Diagnostic and Statistical Manual for Mental Disorders – 4^{th} edition
fMRI	functional magnetic resonance imaging
GABA	γ-aminobutyric acid
LD	lethal dose
LD1	minimal level causing death
LD_{50}	lethal dose for half the animals tested
LHD	left hemisphere damage
M.I.N.I.	Mini International Neuropsychiatric Interview
NMDA	N-methyl-D-aspartate
PET	positron emission tomography
POMS	Profile of Mood States
RBF	regional cerebral blood flow
REM	rapid eye movement
RHD	right hemisphere damage
RMANOVA	repeated measures analysis of variance
SSAI	Spielberger State Anxiety Inventory
SSRI	selective serotonin reuptake inhibitor
SD	standard deviations
STS	superior temporal sulcus

CHAPTER 1 *INTRODUCTION*

1.1. PSYCHOACTIVE EFFECTS OF ALCOHOL

1.1.1. Definition of psychoactive drugs

A drug is defined as a natural or synthetic substance that has a psychoactive, chemical or medicinal effect when ingested; it is not a normal body constituent nor a requirement for normal body function (Ray & Ksir, 1996a). A drug of abuse is defined as any substance that alters mood, perception, behavior or brain functioning that is used in frequent amounts and interferes with an individual's physical, psychological, social or occupational functioning (Ray & Ksir, 1996a). Psychoactive or mood-altering substances are common drugs of abuse and include prescription medications, alcohol, illicit drugs and solvents.

1.1.2. Prevalence of alcohol use

Beverage alcohol (ethanol) is the product of fermented fruits and/or grains and its use dates back to 8000 BC (Dudley, 2002). Countless generations later, alcohol has become the most widely used recreational drug in most western countries for its psychoactive properties. It is estimated that 90% of adults (≥ 18 years of age) consume alcoholic beverages at some point during their lives (Devenyi & Saunders, 1986).

1.1.3. Problems associated with alcohol use

While alcohol consumption may have a role in facilitating social interactions, irresponsible and excessive alcohol consumption negatively impacts the individual and society. It is estimated that 6% of individuals encounter an alcohol-related problem (i.e. medical complication, alcohol abuse or addiction) at some point in their lives (Devenyi & Saunders, 1986; Ray & Ksir, 1996b; Ray & Ksir, 1996c). Approximately 20 – 30% of presentations at hospitals and family practice offices coincide with alcohol consumption, over 50% of traffic fatalities involve alcohol and in total, hazardous alcohol consumption is responsible for approximately 10% of premature deaths in Canada (Devenyi & Saunders, 1986; Ray & Ksir, 1996c; Single et al., 2000).

One problem that has been specifically associated with alcohol use is aggression including domestic violence, social aggression and self-aggression. Although the relationship between alcohol use and aggression is complex, there is substantial epidemiological and experimental evidence that acute alcohol intoxication itself increases aggression (Hoaken et al., 2003).

1.2. PHARMACOKINETICS OF ALCOHOL

The pharmacokinetics of alcohol are important for study design.

1.2.1. Absorption

Alcohol is absorbed through the stomach and intestine. Its absorption rate is proportional to the concentration of the alcohol (i.e. high concentrations are absorbed faster) and the type of food in the stomach (i.e. proteins and fats tend to slow down absorption). A standard drink equals 13.6 grams of absolute alcohol (Table 1.1.). Carbonation of the beverage tends to increase absorption (Ray & Ksir, 1996b). The effects of alcohol are noticed in approximately 10 min and peak between 45 to 60 min post-consumption; alcohol circulates in the blood unchanged, until it is metabolized (Ray & Ksir, 1996b; Storti, 1997b).

Table 1.1. Standard Drink Conversion Chart

Drink	% alcohol	Volume (ounces, oz.)
Beer	5%	12 oz.
Wine	12%	5 oz.
Fortified wine	18%	3 oz.
Hard liquor	40%	1.5 oz.

Note: one standard drink represents 13.6 grams of absolute alcohol.

1.2.2. Metabolism

Liver and stomach enzymes are responsible for over 90% of alcohol metabolism, via a three-step process (Quertemont, 2004): alcohol is converted to acetylaldehyde (a toxic intermediate) by the enzyme alcohol dehydrogenase, acetylaldehyde is converted to acetic acid by the enzyme aldehyde dehydrogenase, and finally, acetic acid spontaneously dissociates into the final end products of carbon dioxide and water, which are eliminated by the lungs and kidneys. Genetic polymorphism is partially accountable for the variance in alcohol metabolism across different ethnicities (Quertemont, 2004).

1.2.3. Elimination

Alcohol is eliminated from the body at approximately 10 ml per hour; however, this is dependent on the weight, age and gender of the individual (Storti, 1997b). In general, males tend to tolerate alcohol better than women due to their larger body size, body water and fat distribution (Ray & Ksir, 1996b). Tolerance from chronic alcohol use, genetics and ethnicity also play a role (Quertemont, 2004).

1.2.4. Measurement of alcohol concentration in the body

Breath alcohol concentration (BAC), a measurement of the concentration of alcohol in the breath, is proportional to amount of alcohol in the blood (Ray & Ksir, 1996b). The concentration of alcohol in the body can be quantified by either a sample of blood or deeply exhaled air using a BAC meter (CMI, 1998). Results from both methods correlate well and are considered equally accurate.

To obtain a breath sample, individuals orally exhale into a machine that automatically measures the alcohol content in the exhaled air. This method has advantages for clinical studies because it is non-invasive, produces results within seconds, and does not require a laboratory. BAC is expressed in milligrams of alcohol per deciliter of blood (mg/dL) or divided by 1000 for a decimal form without metric units (e.g. 85 mg/dL or 0.085). The latter represents the unit-less BAC meter readouts.

1.3. THE EFFECTS OF ALCOHOL ON BEHAVIOR AND COGNITION

1.3.1. Psychoactive and neurochemical properties of alcohol

Alcohol has effects on perception, cognition and mood, which are influenced by the blood alcohol concentration. These psychoactive properties correspond to the direction of change, referred to as the ascending or descending limbs of the blood alcohol curve, and the rate of change. It is thought that the effects of alcohol are mediated via a number of neurotransmitter systems (see Chapter 2).

1.3.2. Acute effects of alcohol consumption

Most acute effects of alcohol consumption correlate with the BAC (Table 1.2.). At low (BAC <0.050) and moderate (BAC 0.050 to 0.090) doses, alcohol induces cognitive and behavioral changes by compromising the regulatory and inhibitory behavioral control mechanisms in the brain. These may manifest as an impairment of attention, judgment, planning and short-term memory (Eckardt et al., 1998; Mulvihill et al., 1997; Ray & Ksir, 1996b).

Table 1.2. Breath Alcohol Concentration and its associated behavioral effects

% BAC	Behavioral effects
0.05	Lowered alertness, relaxation, release of social inhibitions, impaired judgment
0.10	Slower reaction times, impaired motor function, double vision, slurred speech
0.15	Large, consistent increases in reaction time
0.20	Marked depression in sensory and motor capability, intoxicated
0.25	Severe motor disturbance, staggering, sensory perceptions greatly impaired
0.30	Stuporous but conscious – no comprehension of surroundings
0.35	Surgical anesthesia; about LD1
0.40	About LD_{50}

Source: Adapted from Table 10-2 Blood Concentration and Behavioral Effects (p.221). Ray O & Ksir C (1996b). Drugs, society and human behavior (7^{th} ed.). St. Louis, MO: Mosby-Year Book.

Abbreviations: LD, lethal dose; LD1, minimal level causing death; LD_{50}, lethal dose for half the animals tested.

One of the most notable effects of alcohol is its ability to cause loss of regulatory behavioral control, attributed to a disinhibition of behavior (Eckardt et al., 1998; Mulvihill et al., 1997; Pihl & Peterson, 1995; Ray & Ksir, 1996b). This phenomenon cannot be adequately explained by theories of tension reduction, motivational, reward and punishment (Mulvihill et al., 1997). Moderate doses of alcohol can lead to positive (i.e. pleasurable) or negative (i.e. anxiolytic) reinforcement mechanisms (Eckardt et al., 1998). The anxiolytic properties of alcohol often result in disruption of normal critical thinking, concern and judgment (Sayette et al., 1992; Storti, 1997b). The result of these changes includes impaired risk assessment and inhibition of behavioral and physiological expressions of fear. Aggression may occur as a manifestation of the latter.

Alcohol has been shown to exert different effects on cognition, physiology and behavior according to whether these are studied on the ascending or descending limb of the blood alcohol curve (Pihl et al., 2003). Psychostimulant properties (i.e. dopamine release, heightened autonomic response, and aggression) are associated with the ascending limb (Hoaken et al., 2003), whereas sedation, γ-aminobutyric acid-like (GABA-like) and N-methyl-D-aspartate (NMDA) antagonist-like effects are associated with the descending limb (Krystal et al., 1998). Also the cognitive effects of low-moderate alcohol doses may be greater on more controlled effortful processing, including executive functions and responses to complex social stimuli, than on more automatic responses to simple stimuli (Herzog, 1999; Kirchner & Sayette, 2003; Steele & Josephs, 1990). This may lead to responding to prepotent stimuli, e.g. short term rewards, irrespective of longer term consequences, so-called "alcohol myopia" (Herzog, 1999).

Moderate to high doses (BAC above 0.050) of alcohol may also induce deficits in performance (response accuracy), reaction time and motor coordination (Ross & Pihl, 1988). Alcohol consumption leads to decreased accuracy and significant increases in reaction time (Ray & Ksir, 1996b; Rohrbaugh et al., 1987; Storti, 1997a). It is thought that performance deficits are caused by nonspecific sedative properties of alcohol and reaction time deficits are caused by a specific loss in cognitive processing (Rohrbaugh et al., 1987). Alcohol interferes with motor control mechanisms in the brain (Storti, 1997a). Simple observation suggests that alcohol causes performance and motor deficits, particularly dangerous when combined with activities requiring high levels of concentration and motor coordination (i.e. driving, operating heavy machinery).

Alcohol is primarily a central nervous system depressant (Ray & Ksir, 1996b). It makes neurons less excitable, slows repolarization after excitation and decreases spontaneous electrical activity, thereby impairing synaptic transmission (Storti, 1997a). High levels of alcohol consumption can cause respiratory depression, which may result in stupor, coma and death (Ray & Ksir, 1996b).

1.3.3. Chronic effects of alcohol consumption

Adverse physiological, neurological and psychosocial consequences are associated with chronic alcohol abuse (>80 g alcohol per day) (Storti, 1997b). Physiological complications include cardiovascular disease (i.e. hypertension and ischemic heart disease), gastrointestinal problems (i.e. liver disease, gastritis and pancreatitis), hematologic abnormalities (i.e. anemia, thrombocytopenia and leukocytosis), metabolic complications (i.e. diabetes, obesity, malnutrition and sexual dysfunction) among many

others (Devenyi & Saunders, 1986; Ray & Ksir, 1996b; Storti, 1997b). Neurological complications include Wernicke-Korsakoff syndrome, cerebral atrophy, cerebellar degeneration and peripheral neuropathy. Alcohol consumption during pregnancy is responsible for fetal alcohol effects or fetal alcohol syndrome. Overall, the psychosocial complications of chronic alcohol abuse (i.e. intellectual impairment, comorbid mood disorders such as depression and anxiety), attributed to either the cause or consequence of alcohol abuse, tend to be the most difficult to treat (Helzer & Pryzbeck, 1988).

CHAPTER 2 *NEUROPHARMACOLOGY OF ALCOHOL*

2.1. EFFECTS OF ALCOHOL IN THE BRAIN

2.1.1. Neural membrane hypothesis in the 1980s

Until the mid-1980s, the neural membrane hypothesis suggested that alcohol was responsible for changing movement fluidity and altering the electrical excitability of neural cell membranes (Alling, 1983). Later studies disproved this theory and revealed that moderate and high doses of alcohol cause direct conformational changes in neurochemical receptors, which alter protein-protein interactions within the cell membrane (Tabakoff & Hoffman, 1999).

2.1.2. Neural substrates and neurotransmitters for alcohol

Alcohol is a psychoactive substance with widespread effects on brain structures, responsible for cognition, perception, memory, emotion and movement (Storti, 1997a) including the thalamus, hypothalamus, cingulate gyrus, amygdala, and hippocampus. Alcohol also acts upon dopamine reward pathways, one of them being the medial forebrain bundle, a collection of nerve fibers with cell bodies in the limbic system terminating in a non-anatomical reward center of the brain, an area thought to be responsible for the pleasure response and biological reinforcement of psychoactive drug use (Storti, 1997a). Additionally, alcohol acts directly on the brainstem, cerebellum and other brain regions that are responsible for cognition and the control of behavior and movement (Storti, 1997a). Psychoactive substances influence behavior by directly modulating limbic and brainstem structures while decreasing executive function (Eckardt

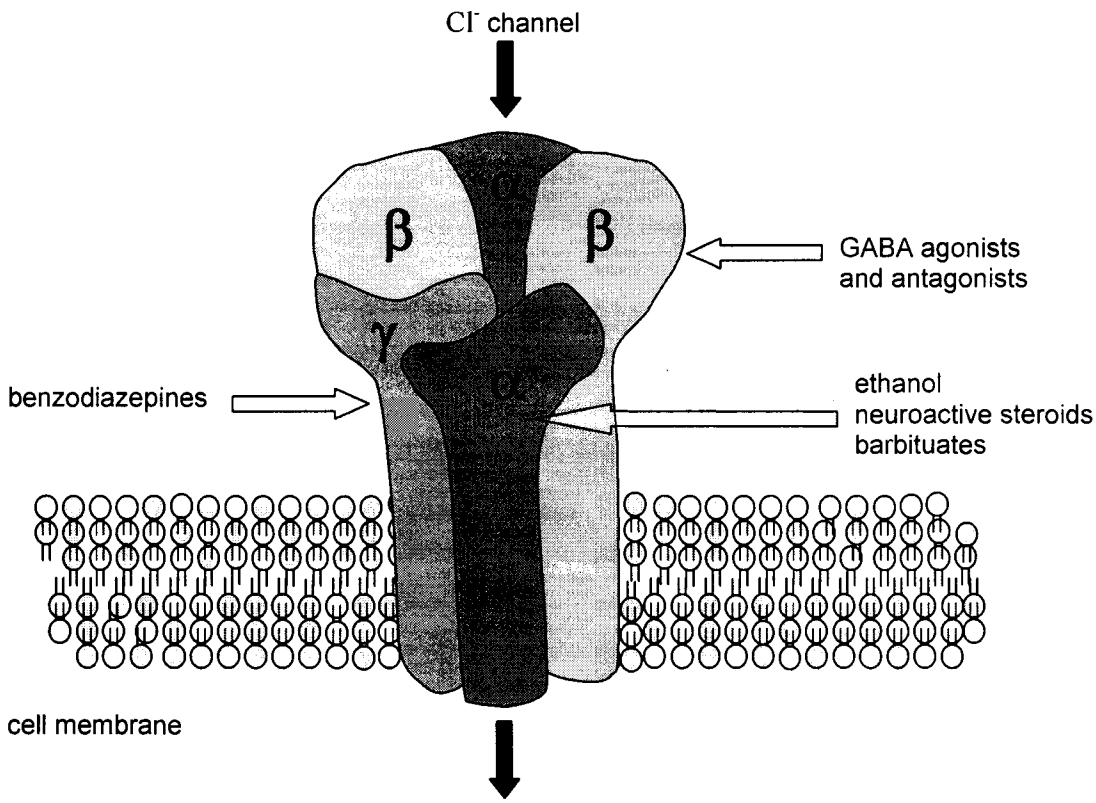
et al., 1998) via a number of neurotransmitters including GABA, glutamate, dopamine, acetylcholine, noradrenaline and serotonin (Eckardt et al., 1998; Storti, 1997a).

2.2. MAJOR NEUROTRANSMITTER SYSTEMS AFFECTED BY ALCOHOL

2.2.1. GABA and the $GABA_A$ receptor

GABA is the major inhibitory neurotransmitter in the brain and spinal cord (Cooper et al., 1996) . The $GABA_A$ receptor subtype is the best characterized of all GABA receptors. $GABA_A$ receptors belong to a superfamily of ligand-gated ion channels receptors with a chloride ion (Cl^-) channel protein (Figures 2.1. & 2.2.). These receptors are composed of approximately 20 heteropentameric isoforms that differ in various biologic and pharmacologic properties and are expressed at different times in development (Olsen & Homanics, 2000).

Figure 2. Schematic diagram of the $GABA_A$ receptor structure



At least 18 related subunits for the GABA receptor in mammals exist: α(1-6), β(1-4), γ (1-3), δ, ε, π and ρ (1-3) (Barnard, 1996; Olsen & Homanics, 2000). GABA binds all subunits of the GABA receptor with the greatest affinity for the α-subunit (Balczon et al., 1998). Like all ligand-gated ion channels, common structural arrangements contribute equally to the formation of the heteropentameric channel. There is a general consensus that the $GABA_A$ receptor subtypes consist of five subunits: two α, two β and one γ, δ or ε (Barnard, 1996; Whiting et al., 2000) surrounding the Cl^- channel (Balczon et al., 1998; Nakahiro et al., 1996). When GABA binds to the α-subunit of the receptor, a conformational change opens a Cl^- ion selective channel in the center of the receptor (Balczon et al., 1998; Nakahiro et al., 1996). Alcohols are positive allosteric modulators with a specific binding site on the $GABA_A$ receptor (Olsen & Homanics, 2000).

GABA is the primary inhibitory neurotransmitter responsible for many of the cognitive and behavioral changes observed with alcohol consumption (Eckardt et al., 1998). A review of the effects of alcohol intoxication on the disruption of memory acquisition in humans and experimental animals suggests that lower doses of alcohol (0.5 g/kg or less in animals) selectively mediate its effects by activating the GABAergic system while higher doses (0.75-2.0 g/kg) are less selective across several neurotransmitter systems (Ryabinin, 1998). The GABAergic system is not organized into discrete pathways and bundles like other neurotransmitter systems (Cooper et al., 1996) thereby making it difficult to study in isolation.

2.2.2. Glutamate and N-methyl-D-aspartate (NMDA) receptors

Glutamate, the primary excitatory neurotransmitter in the central nervous system, is an important amino acid that activates and postsynaptic NMDA receptors (Pin & Duvoisin, 1995). NMDA receptors are well known for their role in learning and memory formation. Additionally, Krystal et al (1998) found that ketamine, an NMDA receptor antagonist, produced effects similar to those of the descending limb (i.e. sedative effects) of acute alcohol ingestion, thereby suggesting alcohol may have inhibitory effects on glutamate release and/or the NMDA receptor (Krystal et al., 1998).

2.2.3. Dopamine

Dopaminergic cell bodies originate in the midbrain and project to either the basal ganglia (forming the nigrostriatal pathway), frontal cortex (forming the mesocortical dopamine pathway) or the limbic structures (forming the mesolimbic dopamine pathway) (Storti, 1997a). Although these pathways have diverse behavioral correlates, the mesocortical and mesolimbic dopamine pathways are important for reward and incentive motivation (Eckardt et al., 1998). In humans, positron emission tomography (PET) studies have reported the mesolimbic dopamine pathway to be activated by the intake of alcohol and major drugs of abuse (Boileau et al., 2003; Ray & Ksir, 1996a). Dopaminergic effects, such as arousal and heart rate acceleration, appear to be particularly associated with the ascending limb of the blood alcohol curve.

2.2.4. Acetylcholine, noradrenaline and serotonin

Cholinergic cell bodies originate in the basal ganglia and extend to the hippocampus and cerebral cortex. Acetylcholine is involved in learning, memory, attention, defense/aggression, mood and rapid eye movement (REM) during sleep (Pelham et al., 1980; Storti, 1997a). Alcohol appears to directly disrupt the aforementioned functions of this neurotransmitter; however, the findings are variable and difficult to summarize (Pelham et al., 1980).

Noradrenergic cell bodies arise in the locus ceruleus and other brainstem nuclei and project to diffuse areas of the brain. Noradrenaline and adrenaline are involved in attention, cognition, defensive, autonomic and hormonal responses (Storti, 1997a). This neurotransmitter is likely involved in the dampening of higher-level cognitive function following the acute phases of alcohol consumption.

Serotonergic cell bodies originate from the raphé nuclei and project to diffuse areas of the brain (Storti, 1997a) and are involved in mood, sleep cycles, sensation of pain and development of tolerance to alcohol and other drugs (Eckardt et al., 1998). Chronic alcohol intake has been reported to disrupt normal circadian rhythms (Devenyi & Saunders, 1986).

Of note, while it may seem simple to assign certain cognitive functions to an individual neurotransmitter system, in reality, all these systems have complex interconnections. Moreover, these monoamine effects may also be secondary consequences of $GABA_A$ receptor activation as the GABAergic system is so widely distributed in the nervous system.

2.3 PHARMACOLOGICAL SUBSTRATES THAT INTERACT WITH THE GABA RECEPTOR

Pharmacological substrates that target the $GABA_A$ receptor include alcohol, benzodiazepines, barbiturates, general anesthetics, neurosteroids, and anticonvulsants (Mascia et al., 2000; Nakahiro et al., 1996; Olsen & Homanics, 2000). The binding of these molecules make the $GABA_A$ receptor more sensitive to GABA via modifications of receptor properties (Balczon et al., 1998; Nakahiro et al., 1996; Storti, 1997a). An in depth discussion of this topic is beyond the scope of this paper.

2.3.1. General anesthetics

General anesthetics were introduced approximately 150 years ago and have become one of the most widely used therapeutic agents (Harrison et al., 2000). After more than 100 years of research, the mechanisms of action for general anesthetics continue to be elusive. Over the last several decades, ligand-gated ion channels have been studied as molecular targets that mediate the central nervous system effects for both general anesthetics and alcohol (Harrison et al., 2000).

2.3.2. Alcohol

Alcohol have an effect similar to general anesthetics at high doses (100 – 200 mmol/L ethanol); however, the effects are difficult to control and therefore are not commonly used in this manner (Harrison et al., 2000). Instead, there is an interest in the subanesthetic doses (5 – 20 mmol/L ethanol) and chronic effects of alcohol consumption.

Laboratory preparations using recombinant chimeric and mutated receptors have indicated that pure alcohol concentration of 100 mmol/L or less can acutely potentiate $GABA_A$ receptor function (Harrison et al., 2000; Nakahiro et al., 1996). Alcohol may have different effects on neurons depending on the biochemical conditions and cell type.

2.3.3. Neurosteroids, benzodiazepines and barbiturates

Neurosteroids, benzodiazepines and barbiturates are another group of allosteric modulators that exert its effects at the $GABA_A$ receptor (Nakahiro et al., 1996; Olsen & Homanics, 2000). Neurosteroids include metabolites of progesterone and other naturally occurring steroid hormones that enhance GABA action *in vitro* and *in vivo* (Paul & Purdy, 1992). Furthermore, neurosteroids are physiological mediators for bodily functions such as sleep, arousal, attention and stress (Paul & Purdy, 1992).

There is also specific binding sites for benzodiazepines and barbiturates on the $GABA_A$ receptor (Balczon et al., 1998). Both these compounds potentiate the $GABA_A$ receptor function and elicit anxiolytic and hypnotic effects (Cooper et al., 1996). It has been demonstrated that alcohol has a similar mechanism of action to benzodiazepines and barbiturates (Nakahiro et al., 1996). Alcohol may also have indirect effects on GABA function secondary to neurosteroid release (Belelli & Lambert, 2005).

CHAPTER 3 *FACIAL EMOTION RECOGNITION*

3.1. THE IMPORTANCE OF STUDYING FACIAL EXPRESSIONS

Everyday human interaction involves the interpretation of human emotion, whether it may be from tone of voice, facial expression or body language. The ability to perceive, interpret and respond appropriately to facial expressions is required for the nonverbal exchange of thoughts and emotions in interpersonal interactions and for social information processing (Singh & Ellis, 1998). Interpretation of facial expressions begins in the newborn and the development of this skill is important for guiding our behaviors. People are not explicitly taught how to read faces, but it is thought that there may be innate components to this ability that develop further with experience.

Cross-cultural studies have identified six basic facial expressions of emotions – anger, disgust, fear, happiness, sadness and surprise (Eckman et al., 1987; Matsumoto, 1992). Many studies on facial emotion recognition use standardized pictures of facial affect, such as the Pictures of Facial Affect series, prepared by Eckman and Friesen (1976), who were pioneers of facial emotion recognition research. Each picture in the series depicts one of the six basic emotions, or a neutral face, which are produced by actors either posing the intended expression, or following instructions to move their facial muscles into the appropriate position, as guided by the Facial Action Coding System, a system for recording muscle positions associated with facial expressions (Eckman & Friesen, 1976).

The principle behind such studies on facial emotion recognition is that facial expressions represent a display that can be "read out." Research has shown that most people tend to interpret facial emotions from photographs quite accurately and are correct more than 80% of the time (Gerhards, 1998; Singh & Ellis, 1998). Nevertheless, how well an individual interprets facial emotion expression may be dependent on the individual, the specific face (i.e. some faces are more difficult to interpret than others), the context of the interaction and the type of task. That is, responses tend to be more consistent when the subjects have to make a forced choice from a limited list of labels than when they are given freedom to assign any adjective that they choose (Eckman & Friesen, 1976). This consistent observation with forced choice method makes it suitable for drug studies and repeated measures designs.

3.2. NEURAL SUBSTRATES FOR FACIAL EMOTION RECOGNITION

Face perception is a complex perceptual skill that is important for social interactions. A distributed neural system of multiple brain regions mediates facial perception. One of the most widely accepted models of organization for this system involves a distinction between the invariant aspects of the face required for recognition and the changeable aspects of the face (gaze, expression, movement) responsible for social communication.

3.2.1. Neural substrates

Converging evidence indicates that facial emotion recognition is predominantly dependent on the right hemisphere and involves the amygdala, prefrontal cortex and the superior temporal sulcus (STS) (Adolphs, 2002; Haxby et al., 2000). Basic requirements of this process are the ability to perceive geometric components of facial features (visual object and motion pathways and their association areas) and to understand the emotional meaning of these configurations (limbic and association areas) (Adolphs, 2002).

The neural substrates for facial emotion recognition are currently being investigated using a variety of techniques such as single unit recording and neuroanatomical lesion (e.g. amygdala, cortical, hemispheric, etc.) studies in animals (e.g. chimpanzees), and electrophysiological, imaging and pharmacological studies in humans. A series of research studies have also reported alterations in facial emotion processing associated with brain injury, substance dependence/abuse, psychiatric disorders and mental retardation.

3.2.2. Neuropsychology and neuroimaging

The valence hypothesis suggests that the left and right hemispheres selectively interpret positive and negative emotions respectively (Leventhal & Tomarken, 1986); however, the data have been inconsistent across different studies and other theories have begun to emerge. Asthana & Mandal (1998) used hemifacial composite photographs, left-left and right-right and asked subjects to rate the intensity of the happy and sad expressions. It was observed that left-left composites were judged to have a more intense expression than the right-right composites, thereby implicating a more dominant role of the right hemisphere in the recognition of happy and sad facial emotions (Asthana & Mandal, 1998). It is unknown whether the findings can be generalized to other emotions.

Neuroimaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and regional cerebral blood flow (RBF) have been used by many research groups to identify specific areas of the brain involved in facial emotion recognition and the literature in this area is rapidly proliferating. Converging evidence from fMRI and RBF studies has implicated the amygdala (Gur et al., 2002; Hariri et al., 2002; Streit et al., 2003), as well as the anterior cingulate gyrus (George et al., 1993; Kringelbach & Rolls, 2003), right superior temporal sulcus (Winston et al., 2003), prefrontal and temporal cortex (Iidaka et al., 2001), orbitofrontal and insular cortex (Phillips et al., 1997) as being involved in the recognition of facial expressions.

Neuroimaging studies are powerful in their ability to map various functions to specific brain regions and to provide neural correlates of real-life behavioral deficits. Nevertheless, several caveats should be also noted with such studies. First, it has been easier to demonstrate whether specific regions may be involved in processing facial

emotion than to distinguish whether there are specific regions that respond selectively to specific emotions. Furthermore, activations may differ whether the task involves passive viewing (no response required), implicit judgment (differences in response to emotional expressions, when the experimental task is to respond explicitly to another characteristic e.g. gender, spatial orientation), explicit verbal judgment (to match an emotion label or explicit non-verbal judgment (to match an expression on another face). Technical limitations include limited spatial-temporal resolution and the use of subtraction designs that compare extremes of posed expression. The experimental paradigm of morphing (as described in Chapter 3.3. & 5.5.) may be useful to measure neuronal changes that correlate to an intensity of an emotion, rather than simple subtraction of images (Blair et al., 1999). However, caution is necessary in extrapolating findings to real-world social functions, in which facial expressions are dynamic, interactive, often associated with other cues, such as gesture and vocalization, and occurs within various behavioral contexts.

3.2.3. Brain injury

Brain trauma can induce deficits in facial emotion recognition, particularly when lesions involve the right hemisphere and amygdala (Adolphs, 2002; Adolphs & Tranel, 2003; Adolphs et al., 1994; Ahern et al., 1991; Mandal et al., 1998).

Compared with nonpatient controls and patients with left hemisphere damage (LHD), patients with right hemisphere damage (RHD) performed significantly more poorly on unusual (i.e. emphasis on specific facial features, schematic face or strange face of different anthropological origin than observer) and usual (normal) representations of facial emotion expressions (Mandal et al., 1998). Additionally, Kucharska-Pietura et al. (2003) found marked impairment of facial processing in RHD, but not LHD patients (Kucharska-Pietura et al., 2003). Using intracarotid injections of sodium amytal, Ahern et al. (1991) were able to discriminately anesthetize each brain hemisphere and reported an advantage of the right hemisphere in the recognition of facial expressions (Ahern et al., 1991). It appears that the right hemisphere is dominantly involved in facial emotion recognition, irrespective of a general deficit in visuo-spatial abilities after right hemisphere damage (Mandal et al., 1998).

3.2.4. Pharmacological studies

Lesion and imaging studies can show structures or systems that are involved in face processing, but do not show how these are regulated at the neurotransmitter level. Recent studies have attempted to use pharmacological methods to identify and modulate neurochemical pathways involved in facial emotion processing. These studies have modified neurotransmission by monoamines and by amino acid neurotransmitters. Given that alcohol affects both monoamine release and amino acid receptor function, the main findings of these studies will be outlined below.

Serotonergic manipulations have been reported particularly to modify recognition of fearful and happy expressions. The acute administration of citalopram, a serotonin reuptake inhibitor antidepressant, increased sensitivity to detect happy and fear expressions in healthy volunteers (Harmer et al., 2003a). The oral administration of the serotonin precursor, L-tryptophan, was not reported to increase accuracy *per se*, but did improve a measure of cognitive efficiency for happy and fear expressions that included a speed-accuracy trade-off (Attenburrow et al., 2003). Finally, acute tryptophan depletion reduced the accuracy of fear recognition, although this effect was shown only in females (Harmer et al., 2003b). Although the results above were not fully consistent, some specificity for serotonin effects on fear recognition is suggested by the bi-directional nature of serotonin manipulations.

Manipulation of noradrenergic function has also shown some effects. Propranolol, a beta-adrenergic blocker, slowed responses to sad facial expressions, without reducing recognition accuracy (Harmer et al., 2001). This finding could not be replicated in two other studies, using propranolol 80mg (Sustrik 2003, unpublished data), or metoprolol

50mg (Zangara et al., 2002). However, there was a bi-directional effect of alpha2-adrenergic drugs on recognition accuracy for facial sadness (Sustrik 2003, unpublished data). Clonidine, an alpha2-adrenergic agonist, impaired the recognition of sadness, whereas sadness recognition was increased following the antagonist yohimbine. These findings suggest that the recognition of sad expressions may be secondary to either alterations in central noradrenaline release, or post-synaptic alpha-adrenoceptor function. However, acute administration of reboxetine, a selective noradrenaline reuptake inhibitor, increased the recognition of happy expressions, rather than altering perception of sadness. Further investigation of these changes is therefore required. Dopamine function has also been investigated in one study that showed that the selective D2-antagonist sulpiride impaired recognition of facial anger (Lawrence et al., 2002).

With regard to amino acid neurotransmitters, diazepam, a benzodiazepine agonist that increases GABA-A receptor function, has been found to impair the processing of angry expressions (Blair & Curran, 1999; Zangara et al., 2002), although it also affected fear recognition, and emotion recognition more generally when using a more sensitive test (Coupland et al., 2003). Our recent study on the effects of diazepam on facial emotion recognition with the multimorph and hexagon experimental paradigms (as described in Chapter 5), only replicated the findings of Blair & Curran (1999) for a selective effect of diazepam on impairing the recognition of angry faces. A recent neuroimaging study of the effects of the NMDA receptor antagonist, ketamine, in healthy men, showed a failure to activate limbic structures following administration of the drug and a blunted fMRI signal to fearful faces (Abel et al., 2003). Studies involving alcohol will be discussed in more detail below (see Chapter 3.4.).

3.3. FACIAL STIMULI USED IN THE STUDY OF FACIAL EMOTION RECOGNITION

A wide variety of stimuli have been utilized in facial emotion studies, including live actors, drawings, still photographs, chimeric faces, morphed faces, videos and animations. Neurobiological studies have generally focused on still photographs, in order to study the processing of simple stimuli before moving on to more complex ones.

3.3.1. Chimeric face task and inverted faces

Several methods are used to study different aspects of facial emotion recognition. The chimeric face tasks consist of a set of faces with two halves that differ in various parameters (i.e. identity, gender, emotion, etc.). This method has been used for many years to assess hemispheric preferences involved in facial recognition. Consistent with neuropsychological and neuroimaging studies, chimeric faces indicate that faces are predominantly processed in the right hemisphere (Burton & Levy, 1991). Chimeric face tasks may also allow us to learn about the lateralization of specific aspects of facial emotion processing (Indersmitten & Gur, 2003). Inverted faces are sometimes used to contrast the ability to recognize upright faces and identities compared to inverted ones; this method has shown that upright faces tend to be processed as a whole (Farah et al., 1998).

3.3.2. Computer morphing – new experimental paradigms

Computer morphing is a technique described in detail by Calder et al. (2000). It is used to study facial emotion recognition by synthesizing continuous tone caricatures where two expressions have been morphed from one to the next over a series of stages (Benson & Perrett, 1991). To produce these continuous-tone caricatures, the prototype of each emotion image is assigned appropriate feature points based on a Cartesian coordinate (determined from an average of many faces) and via a cut and paste method, these points are stretched in specific increments across aligned images (Benson & Perrett, 1991; Calder et al., 2000). This is a useful tool to study facial emotion recognition because it creates photorealisitic images, examines intensity and categorical judgments and relates judgment accuracy and reaction time to a percentage of the full emotion.

Computer morphing was used to create the faces for the facial recognition tasks used in this study including the 10% increments, modified emotional hexagon and multimorph paradigms (see Chapter 5). In the 10% increments task, neutral faces were morphed into the full emotional expression over a series of 10 stages, which created 10 different emotion increments for each particular emotion. In the modified hexagon task, neutral faces were morphed between the full expressions of different emotions over a series of five stages. This was achieved by taking two prototypes of each emotion and superimposing them so that all the same feature points were aligned across images to create 10/90%, 30/70%, 50/50%, 70/30% and 90/10% blends between six pairs of emotions (angry-happy, angry-disgust, disgust-sad, fear-sad, fear-surprise and happy-surprise). In the multimorph task, neutral faces were continuously morphed into the full expression over a series of 40 stages with 2.5% increments for each emotion.

3.4. EFFECTS OF ALCOHOL ON FACIAL EMOTION RECOGNITION

Although the neurochemical and physiological effects of alcohol have been studied in detail, there is no comprehensive explanation for alcohol's effect on social behavior. Studies have investigated acute effects of alcohol, alcoholic-dependent subjects and alcoholic-dependent subjects after long-term abstinence, using a variety of experimental paradigms.

3.4.1. Electrophysiology measures

Electrophysiological measurements of alcohol-dependent subjects and healthy subjects following alcohol have been used to investigate the neural basis for the recognition of facial emotions (Glautier et al., 2001; Orozco et al., 1999). Orozco et al. (1999) conducted a within subjects study of 15 Asian American males following oral administration of 0.56 g/kg alcohol and placebo in a randomized order, using facial stimuli of male and female faces with neutral, happy and sad facial expressions. They measured event-related potentials (ERPs) following the stimuli presentation. They reported that subjects given alcohol had decreased P450 amplitudes to male happy faces compared to female happy faces and therefore concluded that the ERP paradigm may be sensitive to gender-related affective stimuli (Orozco et al., 1999). Previous studies have reported that positive component brain waves occur 300 and 600 ms after the presentation of affective stimuli and they are respectively labeled P300 or P450 late components (Lang et al., 1990). The results from such electrophysiological studies may be difficult to generalize due to the small population size, exclusion of female subjects

and previous reports that have found female faces to be more expressive than male faces (Asthana & Mandal, 1998).

3.4.2. Neuropsychological measures

3.4.2.1. Non-alcohol-dependent subjects

Research into the influence of alcohol on facial emotion recognition began a few decades ago (reviewed in Borrill et al., 1987). Unpublished data comparing the ability of normal subjects to recognize facial expressions of emotion after receiving alcohol, marijuana or placebo reported that subjects receiving pretreatment with alcohol made more errors at judging negative emotions, especially those of anger and sadness (Borrill et al., 1987).

Subsequent research into the effects of alcohol on facial emotion recognition has introduced more controls and more complex measures into the studies. Tucker & Vichinich (1983) studied the influence of alcohol on facial emotion recognition in a sample of healthy subjects consisting of 24 males and 24 females. Each subject was given either alcohol (0.50 g/kg body weight) or non-alcohol placebo. Subjects were then asked to rate modified photographs from Ekman and Friesen (1976) Pictures of Facial Affect, which were unmixed (same emotion for the entire face) or mixed (different emotions for the upper and lower half of the face). It was reported that alcohol somewhat impaired affect recognition, but this effect was more pronounced in subjects that "believed" they had consumed alcohol (Tucker & Vuchinich, 1983).

Borrill et al. (1987) studied the influence of alcohol on facial emotion recognition using normal social drinkers randomly allocated into three conditions: high alcohol (1.975 g/kg body weight), low alcohol (0.79 g/kg) and placebo. Subjects rated faces from Ekman & Friesen (1976) for the six basic emotions and neutral. Borrill and colleagues (1987) reported that subjects in the high alcohol condition made more errors than the low alcohol condition and subjects in the low alcohol condition made fewer errors than with placebo. Subjects in the high alcohol condition made more errors on negative emotions such as anger and fear. An incidental finding revealed that females decoded facial expressions better than males; this gender difference was not evident with the higher dose of alcohol (Borrill et al., 1987). Limitations of this study were the use of full intensity expressions, which are easier to decode and therefore perhaps less sensitive to drug effects, and the lack of adjustment of alcohol dose by gender. Interestingly, Baribeau et al (1986) studied non-alcohol dependent subjects who were at high or low risk for alcoholism based on family history. Acute alcohol administration led to increased recognition of facial anger in the high-risk subjects on the ascending limb of the blood alcohol curve (Baribeau et al., 1986). Overall, there has been little study of the acute effects of alcohol on this aspect of social cognition.

3.4.2.2. Alcohol-dependent subjects

A subsequent study by Philippot et al. (1999) using standardized Ekman and Friesen (1976) and Matsumoto (1992) faces compared the ability of alcohol-dependent subjects and healthy volunteers to recognize facial expressions (happy, anger, sad, disgust and fear) with different emotional intensities: neutral (0%), mild (30%), moderate (70%) and strong (100%). These researchers reported that alcohol-dependent subjects made more errors in decoding the negative emotion of anger (but not fear) and were more likely to interpret a negative facial expression as a happy face. In addition, alcohol-dependent subjects tended to overestimate the intensity of emotional expressions compared to healthy controls, without insight into their deficit in facial emotion recognition (Philippot et al., 1999). Even after a period of abstinence, alcohol-dependent subjects may continue to display deficits in the recognition of facial emotion expression (Kornreich et al., 2001; Kornreich et al., 2003). Kornreich and colleagues (2001) compared non-medicated alcohol-dependent subjects abstinent for 2 to 3 weeks, 2 to 6 months, between 1 and 9 years and a healthy volunteer control group. These researchers reported that mid- to long-term abstinent alcohol-dependent subjects continued to have deficits in decoding anger and disgust, similar to findings in a previous study (Philippot et al., 1999). The mid-term abstinent group tended to overestimate the intensity of angry, disgust and sad emotional expressions (Kornreich et al., 2001; Philippot et al., 1999). Together, these studies suggest lasting alterations in social judgment that could contribute to some of the psychosocial and social adjustment difficulties encountered by alcohol-dependent subjects, even after years of abstinence. Kornreich et al. (2001) proposed that right

frontotemporal regions and cingulate cortex are involved in the deficits in facial emotion recognition from alcohol abuse.

3.4.3. Summary

Overall, it appears that alcohol may have acute effects on how healthy individuals selectively perceive negative emotions, in particular, anger, disgust and/or fear (Borrill et al., 1987; Philippot et al., 1999; Tucker & Vuchinich, 1983). Persistent changes in facial emotion recognition are seen in chronically alcohol-dependent subjects (Kornreich et al., 2001; Kornreich et al., 2003).

CHAPTER 4 *THESIS OBJECTIVE & RATIONALE*

The purpose of the study is to examine if the acute administration of alcohol affects the explicit recognition of emotions from facial expressions using a within-subjects study design and measures of reaction time, accuracy, and detection thresholds across three experimental paradigms (10% increments, modified emotional hexagon, multimorph) with a range of facial expression intensities (0 –100%). If alcohol does affect facial emotion recognition, it could be important for several reasons. First, it may increase our understanding of how the brain recognizes specific social signals. Second, it would demonstrate how alcohol might contribute to difficulties with facial emotion recognition in substance abuse disorders and other mental disorders. Third, it may implicate some potentially unwanted effects of alcohol on psychosocial functioning.

The hypotheses were that alcohol would impair emotion recognition and that this impairment would be at least partly selective for impairment of anger recognition. The predicted specificity for anger was based on the GABAergic effects of alcohol on the descending limb of the blood alcohol curve (see Chapter 2.3.), which impaired anger recognition following alcohol in the study of Borrill et al (1987) and the GABAergic effects of benzodiazepines on anger recognition (Blair & Curran, 1999; Zangara et al., 2002), which appeared to be relatively selective.

CHAPTER 5 *METHODS & MATERIALS*

5.1 SUBJECTS

The study was approved by the University of Alberta Research Ethics Committee. Written informed consent was obtained from all subjects before participation in the study. Healthy volunteers between the ages of 18-45 years of age were recruited via notice boards. The inclusion and exclusion criteria were as follows.

Inclusion criteria:

(1) Males with a usual alcohol intake of less than 14 standard drinks per week.

(2) Females with a usual alcohol intake of less than 7 standard drinks per week.

(3) Subjects were raised in North America.

Exclusion criteria:

(1) Previous or current history of Diagnostic and Statistical Manual for Mental Disorders (DSM)-IV axis I psychiatric disorders, including mood disorders, schizophrenia, anxiety or substance dependence/abuse disorders.

(2) Family history of depression, bipolar illness or schizophrenia in first-degree relatives.

(3) Allergy to alcohol.

(4) Pregnant or lactating women.

In total, 32 individuals participated in the study, 12 males and 20 females. The average age of males and females was 24.0 years and 25.8 years respectively. The combined average age of all research participants was 25.1 years. 29/32 subjects were Caucasian and 3/32 were Asian. All members of the latter group were raised in Canada and had frequent and long-term experience of Caucasian facial expressions.

Significant medical and DSM-IV axis I psychiatric disorders, including substance dependence and abuse, were excluded by a structured medical history and structured psychiatric interview, the Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998).

A negative urine pregnancy test prior to each session excluded the possibility that female subjects were pregnant.

For confidentiality purposes, each subject was assigned a code number (for instance C01, C02, CO3, etc.) and records were kept in a locked office.

5.2. DRUGS

The study used a randomized, placebo-controlled, single-blind, within-subjects design. Subjects performed the tests in a specified order (1st control, 10% increments task, 2nd control, modified emotional hexagon task, multimorph task) on two separate occasions, once after alcohol and once after placebo. The order of alcohol and placebo administration was randomized. The test order was fixed so that each test would be performed at relatively consistent breath alcohol concentrations (BACs) across subjects. The sessions were scheduled at least 48 hours apart and subjects were asked to undertake a two-hour fast prior to each test session in order to prevent effects of food on alcohol absorption (see Chapter 1). Each session lasted approximately three hours.

The investigator measuring the BAC was non-blind, but did not perform any other observer ratings. The only communication between the investigator and subjects was to provide instructions before each test commenced. While subjects were not told the order of their beverages, it is unlikely that they remained blinded, as the effects of alcohol are recognizable at the target BAC used for our study.

The two beverages used were the following:

(1) Alcohol: 40% ethanol (vodka) – males: 0.8 g/kg body weight vs. females: 0.7 g/kg body weight. The alcohol was mixed with tonic and limejuice.

(2) Placebo: tonic/limejuice, which was masked by an alcohol spray on the surface.

The doses differed between males and females to control for sex differences in alcohol absorption and distribution and to achieve a target peak BAC of 85 mg/dL at 45 minutes after ingestion.

5.3. BREATH ALCOHOL CONCENTRATION (BAC)

The tasks commenced 60 min after alcohol/placebo administration (i.e. after the peak BAC was predicted) (Pihl et al., 2003). A breath sample from the subject was obtained and tested using a BAC meter (Intoxilyzer®, CMI Inc., Owensboro, KY) prior to testing in order to determine the peak BACs. The doses of alcohol were selected to produce a predicted average BAC of ~85 mg/dL (0.085 BAC meter readout) in both males and females. This target BAC was chosen as being likely to produce behavioral and affective changes, without marked decrements in motor function or reaction times (see Chapter 1 & Table 1.2).

Sixteen subjects received alcohol in the first session and placebo in the second session. The other 16 subjects received the reverse order of alcohol and placebo. Mean BAC for the alcohol session was 81.7 mg/dL (0.082±0.090 standard deviations). Mean BAC for the placebo session was 1.3 mg/dL (0.001±0.001). This nonzero figure reflects traces of alcohol that may be found in some foods, non-alcoholic drinks, and in the alcohol masking spray. BAC values below 0.002 are considered normal for individuals that have not consumed alcohol (Intoxilyzer®, CMI Inc., Owensboro, KY). Those subjects achieving a mean BAC meter read out ± 2 standard deviations from the mean

were to be excluded from the data analysis. However, none of the 32 subjects had a BAC out of the accepted range.

5.4. MOOD AND ANXIETY RATINGS

5.4.1. Profile of Mood State (POMS)

Before and 45 min after alcohol/placebo administration, each subject was required to complete the Profile of Mood States (POMS) (Lorr et al., 1982). The POMS is a self-rating scale that consists of 72 mood adjectives scored on a four-point scale (0 = unlike mood adjective to 3 = very much like mood adjective). Scores on five bipolar mood states (composed versus anxious, agreeable versus hostile, energetic versus fatigued, elated versus depressed and clearheaded versus confused) are calculated from the adjective scores. Half of the mood items make a positive contribution and the other half make a negative contribution to the scale.

The purpose of the POMS was to measure the current mood of the subject before and after alcohol/placebo administration, as a control for possible mood effects on the facial emotion recognition tasks. Studies have demonstrated that the POMS is a reliable and internally consistency measure (Salinsky et al., 2001; Terry et al., 1999). In addition, the POMS has shown construct validity against other psychological measures, including the Beck Depression Inventory, Visual Analogue Scale for Fatigue and Stanford Sleepiness Scale (Fillion & Gagnon, 1999; Jacobs & Boze, 1993; Lee et al., 1991). Furthermore, the POMS has been shown to be sensitive to the acute effects of alcohol on mood (Conrod et al., 2001).

5.4.2. Spielberger State Anxiety Inventory (SSAI)

Immediately following the POMS, each subject was required to complete the Spielberger State Anxiety Inventory (SSAI) (Spielberger et al., 1970). The SSAI is a 20-item self-rating questionnaire in which the items are scored on a five-point scale (0 = not at all to 4 = very much so). Half of the anxiety items make a positive contribution and the other half makes a negative contribution to the scale.

The purpose of the SSAI is to measure the current state anxiety of the subject before and after alcohol/placebo administration. These measurements are used to control for possible effects of anxiety on the facial emotion recognition tasks. Previous studies have demonstrated that the SSAI is a reliable measure for test-retest reliability and internal consistency (Spielberger, 1983; van Widenfelt et al., 2002). Moreover, the SSAI has shown construct validity against the Diagnostic and Statistical Manual for Mental Disorders IV (DSM-IV) diagnosis of generalized anxiety disorder (Okun et al., 1996) and against other psychological measures of anxiety, including Childhood Anxiety Sensitivity Index, Fear Survey Schedule for Children-Revised and the Visual Analogue Scale for Affective State (Maruff et al., 1994; Okun et al., 1996; van Widenfelt et al., 2002).

5.5. EXPERIMENTAL PARADIGMS

Three facial emotion recognition tasks were used in a specified order (1st control, 10% increment task, 2nd control, modified emotional hexagon task, multimorph task). The 10% increment and modified emotional hexagon tasks involved a reaction-time component while the multimorph task did not. Prior to each of the two tasks that involved a reaction-time component, a control task required subjects to match emotion labels to the emotion words that were presented. This task was used to test for non-specific effects of alcohol on reaction time. The facial emotion recognition tasks used face stimuli that featured six basic emotions – anger, disgust, fear, happy, sad and surprise. Face stimuli were produced by a computer morphing technique (see Chapter 3.3.). All testing was done with custom software programmed for Windows 98 on a Pentium PC. Face stimuli were viewed on a 19" color monitor with a screen resolution of 600x800 pixels.

5.5.1. Control Reaction Time Task

The instructions on the computer screen were as follows:

(1) You will be shown a series of emotion words on the screen.

(2) Immediately after each word, a list of emotion words will appear.

(3) Please click as quickly and accurately as you can on the word in the list that matches the word that was shown.

The control was a simple word-matching task. After a 300 msec fixation cross, one of six basic emotion words was presented on a screen. At the offset of the emotion word, a

list of six emotion words was presented and subjects were asked to click as quickly as possible with the left mouse button on the corresponding emotion word from the list. Due to a programming error, all stimulus emotion words except disgust were presented; this factor did not interfere with assessments of reaction time. Reaction times were assessed in each test session prior to the 10% increment and modified emotional hexagon tasks. Reaction time data were logarithmically transformed to reduce positive skew. The stimulus duration and interstimulus interval for the control task were set to the same duration as for the succeeding facial emotion recognition tasks (i.e. 10% increment task, modified hexagon task). The purpose of the control task was to account for the general effect of alcohol on reaction time.

5.5.2. 10% Increment Task

The instructions on the computer screen were as follows:

(1) You will be shown a series of faces on the screen. Each face will show an emotional or neutral expression.

(2) Immediately after each face, you will be shown a list of emotion words or neutral.

(3) Please click as quickly and accurately as you can on the correct word for the expression on each face.

The 10% increment task adapted a test design reported by Harmer et al. (2001) involving 366 facial stimuli derived from six face identities for each of the six basic emotions (Harmer et al., 2001). The stimuli were 640x480 pixel gray scale JPEG images

from the Ekman and Friesen (1976) Pictures of Facial Affect series (Eckman & Friesen, 1976). For each identity and emotion, an image series was produced in which the face morphed from a neutral (0%) expression to the full (100%) expression in 10% stages. For each identity, the neutral (0%) face was presented only once. The images were masked to exclude hair, neck and shoulders.

All the facial stimuli were randomized. After a 300 msec fixation cross, each face was presented for 750 msec. At the offset of the image, subjects were asked to identify the facial emotion as quickly as possible by clicking on the correct label from a list of seven emotion words (six basic emotions and neutral). The interstimulus interval was 1500 msec. Three rest periods of a few minutes were incorporated into the test at regular intervals to minimize fatigue. For each test session, the subject's choice and response time for each stimulus was recorded. Prior to this task, a practice run of 24 similar examples was completed.

Several task variables were subsequently analyzed.

(1) Reaction times: these were analyzed for all emotions combined and for individual emotions. Reaction time data were logarithmically transformed to reduce positive skew.

(2) Accuracy (the frequency of correct answers was analyzed):

(a) For the expressions shown at 100% intensities, which most resembles prior studies in which full intensity expressions only were used.

(b) Across emotions, with all intensities combined.

(c) Where (b) showed significant drug x emotion effects, for each emotion across intensity levels.

(3) Error types were analyzed, where there were significant changes in accuracy:

(a) "Non-detection": where the subject did not detect the depicted emotion and thereby labelled it as neutral.

(b) "Misidentification": where the subject detected an emotion that was not depicted.

(4) Detection threshold: which was defined as the intensity level at above which subjects consistently recognized $\geq$4/6 expressions correctly for that emotion.

The purpose of this task was to determine if alcohol has effects on accuracy, detection thresholds and speed of facial emotion judgments, using a range of expression intensities, rather than simply full expressions, as in most previous studies.

5.5.3. Modified Emotional Hexagon Task

The instructions on the computer screen were as follows:

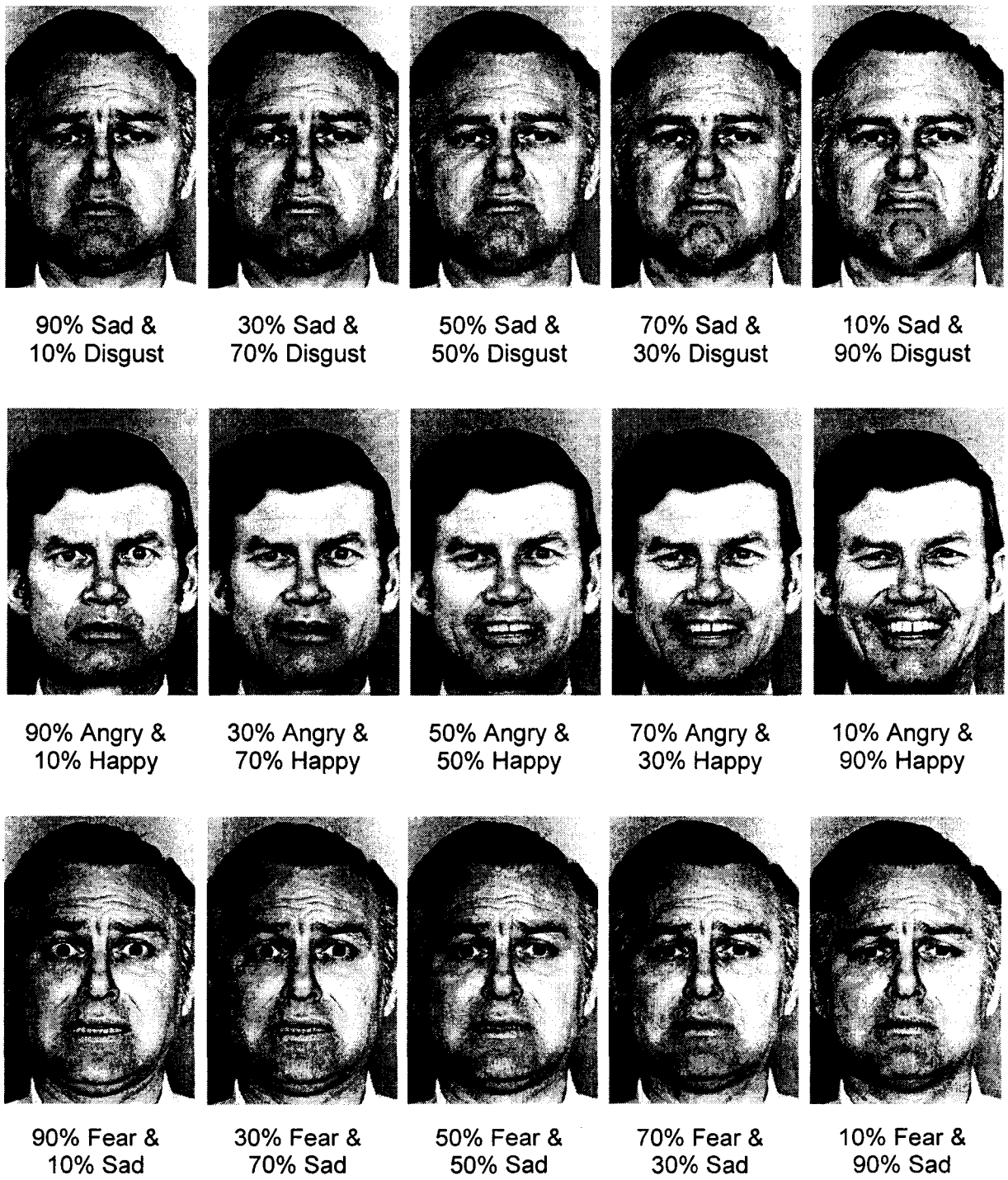
(1) You will be shown a series of faces on the screen. Each face will show an emotional or neutral expression.

(2) Immediately after each face, you will be shown a list of emotion words or neutral.

(3) Please click as quickly and accurately as you can on the correct word for each face.

The modified emotional hexagon task is a variation of a test design previously reported by Blair & Curran (1999). The stimuli were 640x480 pixel grayscale JPEG images (Figure 5.1.) comprised of 150 facial stimuli derived from five identities from the Ekman & Friesen (1976) Pictures of Facial Affect series. The images were morphed to 10/90%, 30/70%, 50/50%, 70/30% and 90/10% blends between six pairs of emotions (angry-happy, angry-disgust, disgust-sad, fear-sad, fear-surprise and happy-surprise) (Calder et al., 1996; Coupland et al., 2003). Neutral faces were not used in this task.

Figure 5.1. Examples of facial emotion blends used in the hexagon paradigm



After a 300 msec fixation cross, each face was presented for 500 msec. The stimulus presentation time was shorter than compared to the 10% increment task to increase task difficulty, because ceiling effects (subjects scored correctly on nearly all facial stimuli) occurred with long stimulus presentations in pilot studies and previously published papers. At the offset of the image, subjects were asked to identify the facial emotion as quickly as possible by clicking on the correct label from a list of seven emotion words (six basic emotions and neutral). The interstimulus interval was 1500 msec. Since this task was shorter than the 10% increment task, one rest period of a few minutes was incorporated into the test to minimize fatigue. For each test session, the subject's choice and response time for each stimulus was recorded. None of the stimuli were repeated. All facial stimuli were randomized.

The two major modifications from previous studies were the use of five different facial identities, since prior studies used five repetitions of a single face for each emotional blend, and the use of short stimulus presentations. In addition, a "neutral" response was allowed by mistake, although no neutral expressions were shown. A further limitation was that detailed validation of these modifications was not carried out before the study, although pilot studies indicated that accuracy for the 70% and 90% expressions decreased to approximately 60%, meeting the goal of avoiding ceiling effects.

Several task variables were subsequently analyzed:

(1) Reaction times: these were analyzed for the 70% and 90% intensities.

(2) Accuracy was analyzed:

(a) For the combined 70% and 90% intensity expressions

(b) For the ambiguous 50% intensity expressions

The purpose of this task was to determine whether alcohol has effects on the accuracy and speed of facial emotion judgments that are dependent on the intensity of the expression, but this time using blends with other emotions rather than a neutral expression to vary the intensity of emotion. A second aim was to determine whether alcohol affects facial emotion judgment when the expressions are ambiguous, i.e. involving 50%/50% blends. Prior studies have shown that subjects tend to identify blends containing 70% or 90% of an emotion categorically, based on the predominant emotion and that the 50%/50% blends are ambiguous, being identified as either emotion (Blair & Curran, 1999; Calder et al., 1996; Coupland et al., 2003). Furthermore, diazepam, which shares the property with alcohol of being a positive allosteric modulator of GABA-A receptors, produced relatively selective effects on the recognition of anger expressions in the original version of this task (Blair & Curran, 1999; Zangara et al., 2002).

5.5.4. Multimorph Task

This task has been published in a recent study (Coupland et al., 2003). No instruction screen was used for the Multimorph Task, which comprised of 54 (9x6) facial stimuli derived from nine identities and the six basic emotions (Figure 5.2.). The images were 640x480 pixel grayscale JPEG images from the Ekman & Friesen's Pictures of Facial Affect (1976) series (Eckman & Friesen, 1976). Each stimulus is presented as a continuous series of "morphed" images, where the intensity of emotion gradually increases in 40 stages from neutral (0%) to full expression (100%) in 2.5% increments. Each stage is presented for 500msec with the total duration of the stimulus lasting 20 sec. All faces were randomized.

A list of six emotion labels was presented alongside the face stimulus. Prior to starting the task, subjects were given the instructions to make a left mouse-click on the appropriate emotion label as soon as they thought they recognized the emotion. They were allowed to change their choice during the 40 stages by clicking on a different word. They were then required to confirm their final choice at stage 40 with another left mouse-click. Prior to this task, a practice run of 12 similar examples was completed.

For each test session, the subject's final choice was recorded. If the final choice was correct, the stage at which they made the correct choice was recorded. Correct choices were given the score of the intensity of the corresponding stage (e.g. 77.5%) and incorrect choices were scored 102.5%. Scores for both correct and incorrect choices were

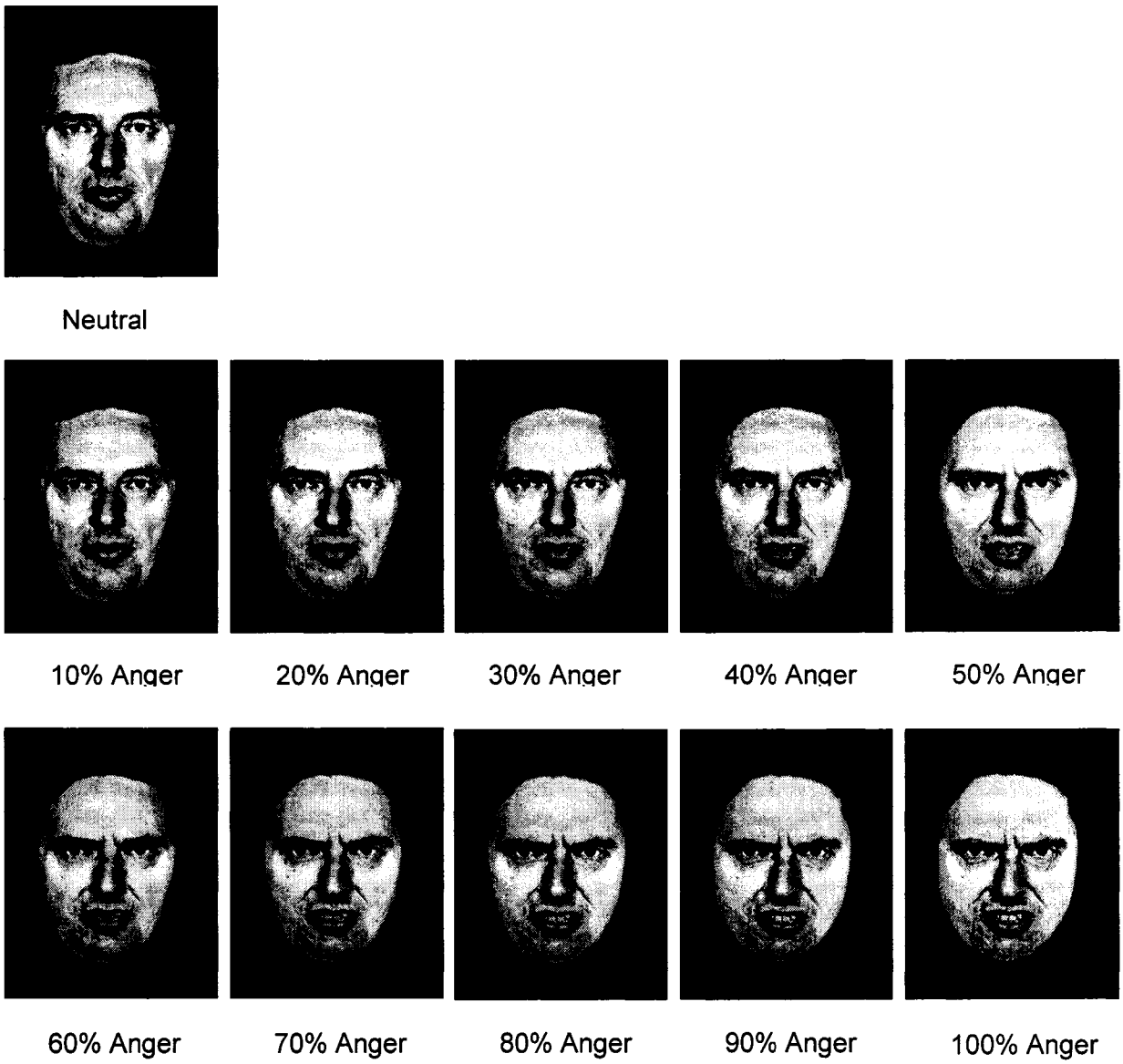
combined to determine a score for the average stage of emotion recognition. In pilot studies, this scoring mainly reflected the intensity of expression for correct choices, but allowed the scores to include a negative weighting for incorrect choices. Scoring only correct responses could give low scores for fast, but inaccurate guessing. The purpose of this task was to determine whether alcohol has effects on the accuracy of judgments and on the threshold intensity at which subjects can first accurately judge each facial emotion.

The task variables subsequently analyzed were:

(1) Accuracy for the final response.

(2) Threshold intensity of recognition.

Figure 5.2. Example of faces used in the 10% increment and multimorph paradigm.



5.6. STATISTICAL ANALYSES

Within the test data, the following test factors were present: Drug (alcohol vs. placebo), Emotion (anger vs. disgust vs. fear vs. happy vs. sad vs. surprise vs. neutral), Intensity and Order (alcohol first vs. placebo first). Drug, Emotion and Intensity were within-subjects factors, and Order was a between-subjects factor.

Data analyses mainly used repeated measures analysis of variance (RMANOVA) with the within-subject factors of emotion, intensity and drug. In order to simplify analyses of the 10% increment tasks, which used a large number of intensities of expression, we made three sets of comparisons for accuracy. In one set, only the full intensity (100%) expressions were used. In the second set, accuracies for each emotion at all intensity levels were combined. If these analyses were significant, then the third set of comparisons examined at which intensities the changes in accuracy occurred. For repeated measures analyses, Mauchley's test for sphericity was used and, where indicated, Greenshouse-Geisser adjustments were made to the degrees of freedom (df) and significance (p) values. However, in order to simplify the data presentation, the unadjusted degrees of freedom are reported with the adjusted significance values.

For significant findings, the types of error were examined. Furthermore, the effect of BAC and mood were tested as possible covariates for alcohol-placebo differences in emotion recognition. In all analyses, reaction times were logarithmically transformed to correct for positive skew.

Given the specific hypothesis that alcohol would impair anger recognition, planned comparisons were made with placebo using paired *t* tests at 1-tailed $p<0.05$. For other comparisons Bonferroni-adjusted two-tailed p values for specific emotions ($p<0.008$ or 0.05/6) or morphed expression intensities ($p<0.005$ or 0.05/10) were used. A possible problem with this approach is that alcohol might appear to have more selective effects on anger recognition than is the case, simply because a less stringent statistical threshold is being applied to anger than to other emotional expressions. Therefore, in addition to Bonferroni-corrected significance, the uncorrected significance is also reported.

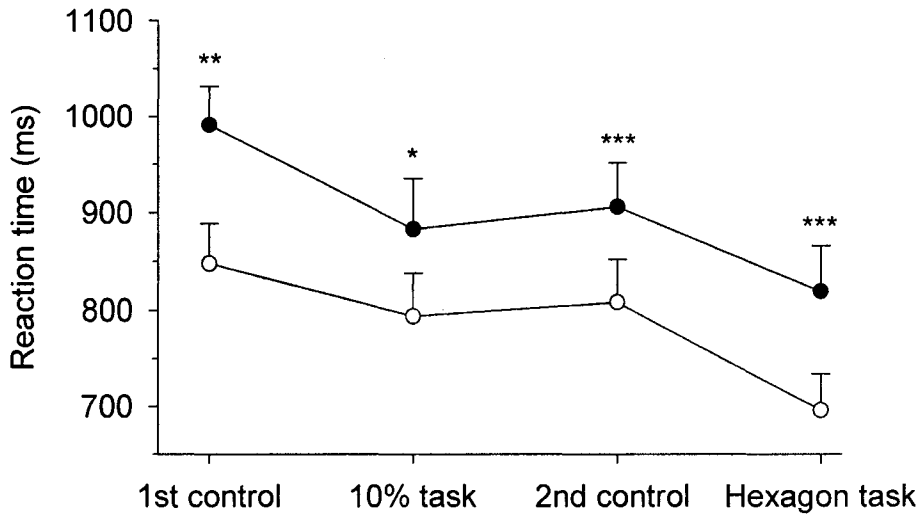
CHAPTER 6 *RESULTS*

6.1. REACTION TIMES

Alcohol caused a general increase in reaction times in the 10% increment and modified emotional hexagon tasks. This was indicated by drug effects, but no drug x emotion interactions for the 10% increment task: drug $F(1,31) = 6.0$, $p = 0.02$; drug x emotion $F(5,155) = 0.9$, $p = 0.5$; and the emotional hexagon task: drug $F(1,29) = 13.6$, $p = 0.001$; drug x emotion $F(5,145) = 0.9$, $p = 0.5$.

Since the reaction time increases following alcohol were not specific to particular emotions in the emotion recognition tasks, we averaged the reaction times from these tasks and from the 10% and emotional hexagon tasks across all emotions. The alcohol and placebo sessions were compared using repeated measures ANOVA for drug (alcohol and placebo) and for task (1^{st} control, 10% increment task, 2^{nd} control, emotional hexagon). The results indicated a significant drug effect from alcohol: drug $F(1,29) = 18.1$, $p < 0.0001$ and a task effect : $F(3,87) = 6.4$, $p = 0.002$; but no drug x task interaction $F(3,87) = 0.3$, $p = 0.8$. The reaction times gradually decreased over the tasks (Figure 6.1.), but alcohol affected reaction times for all the tasks to a similar degree ($ts < 1.0$; $ps > 0.3$). The decreases in reaction times across tasks might be due to practice effects, or to a more speeded response for the emotional hexagon task and control task, because these used shorter stimulus presentations (500 msec) than the 10% increments task (750 msec).

Figure 6.1. Reaction times (logarithmic mean ± standard deviation SD) across tasks. Key: Alcohol (closed circles); placebo (open circles); *significant at uncorrected $p<0.05$; **significant at Bonferroni corrected $p<0.008$; ***significant at Bonferroni corrected $p<0.005$.



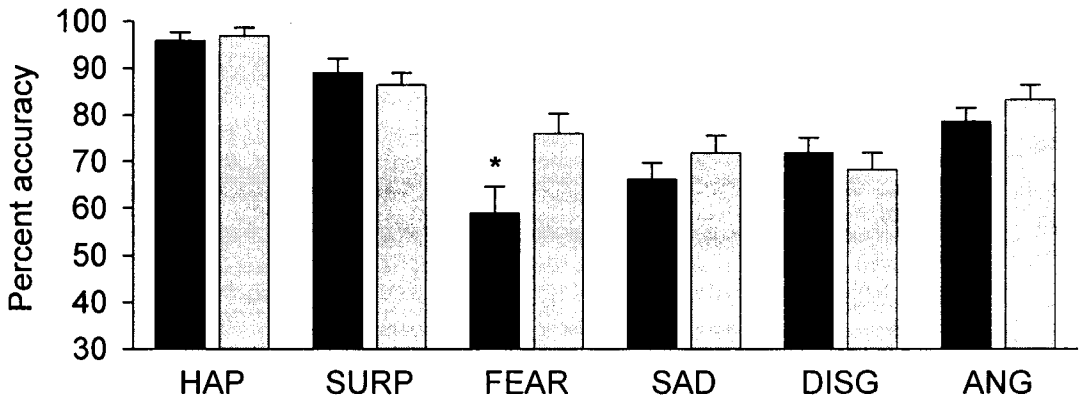
6.2. 10% INCREMENT TASK

6.2.1. Accuracy

Full intensity expressions: alcohol had a selective effect on the accuracy of emotion recognition for full intensity expressions (100%): drug $F(1,31) = 7.0$, $p = 0.013$ and drug x emotion $F(5,155) = 17.4$, $p < 0.0001$ (Figure 6.2.1.1.). Post hoc tests showed a significant decrease in fear recognition, $t(1,31) = 3.5$; $p = 0.001$. The planned analysis showed a trend only to decreased anger recognition $t(1,31) = 1.5$; $p = 0.08$.

Figure 6.2.1.1. Recognition accuracy (mean ± SD) for the 100% intensity expressions in the 10% increment task.

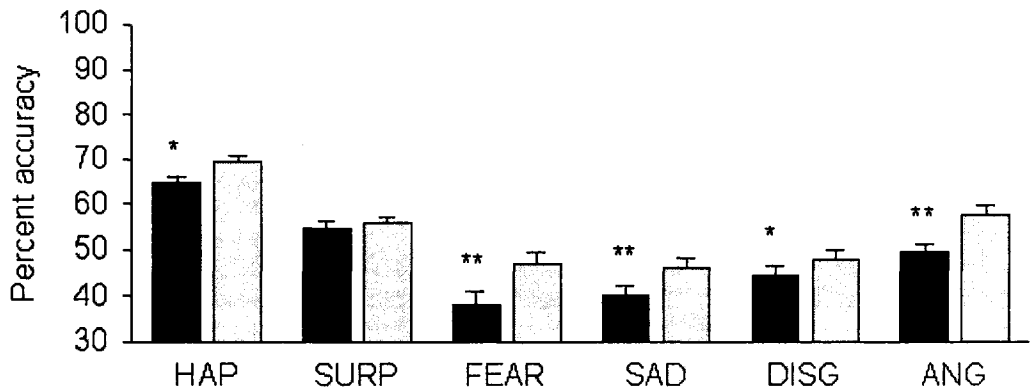
Key: Alcohol (black bars), placebo (grey bars); *significant at Bonferroni corrected $p<0.008$; HAP = happy, SURP = surprise, DISG = disgust, ANG = anger.



Combined morphed intensities: alcohol also decreased recognition accuracy when all morphed intensities were combined, compared with placebo: drug $F(1,31) = 32.8$, $p < 0.0001$; drug x emotion $F(5,155) = 2.9$, $p = 0.017$ (Figure 6.2.1.2.). The effects were significant for fearful, sad and angry expressions following Bonferroni correction. Effects were also significant for happy and disgust expressions at an uncorrected $p < 0.05$.

Figure 6.2.1.2. Recognition accuracy (mean ± SD) for all morphed intensities of expression in the 10% increment task.

Key: Alcohol (black bars), placebo (grey bars); *significant at uncorrected $p<0.05$; **significant at Bonferroni corrected $p<0.008$; HAP = happy, SURP = surprise, DISG = disgust, ANG = anger.

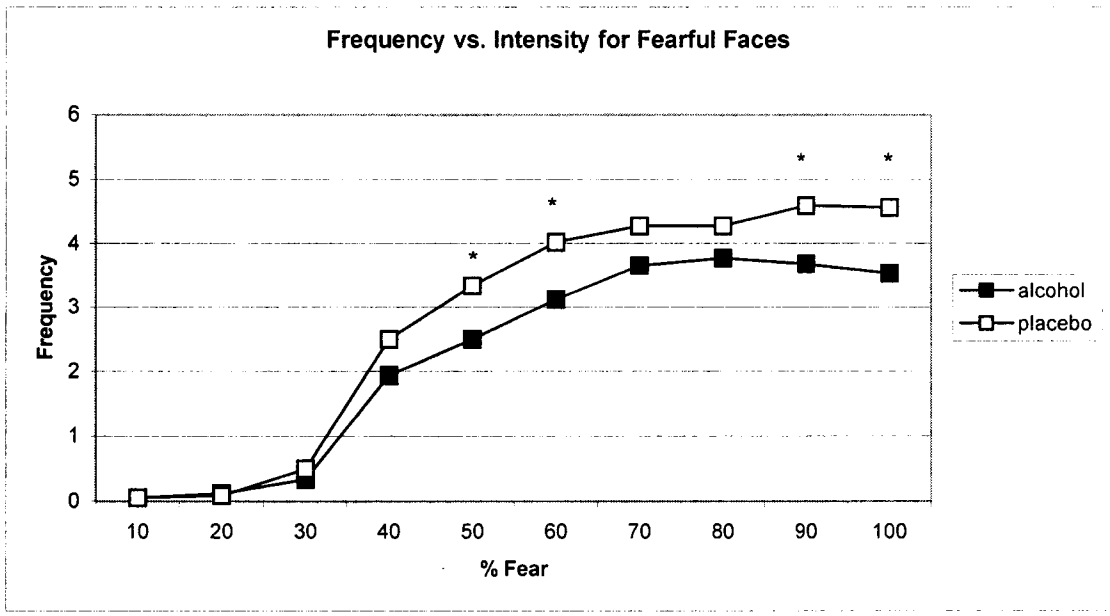


The alcohol minus placebo difference in recognition accuracy was significantly larger for anger recognition than for happy $t(1,31) = 1.9$, $p = 0.037$; surprise $t(1,31) = 2.9$, $p = 0.004$; or disgust $t(1,31) = 1.9$, $p = 0.03$ expressions. Alcohol also had greater effects on fear expressions than surprise $t(1,31) = 2.8$, $p = 0.008$; or disgust $t(1,31) = 2.4$, $p = 0.025$ expressions.

Effects of expression intensity: there was a significant drug × intensity interaction for recognition of fear expressions $F(1,9) = 3.3$; $p = 0.004$ (Figure 6.2.1.3.).

Figure 6.2.1.3. Recognition accuracy for fear expressions across different morphed intensities in the 10% increment task.

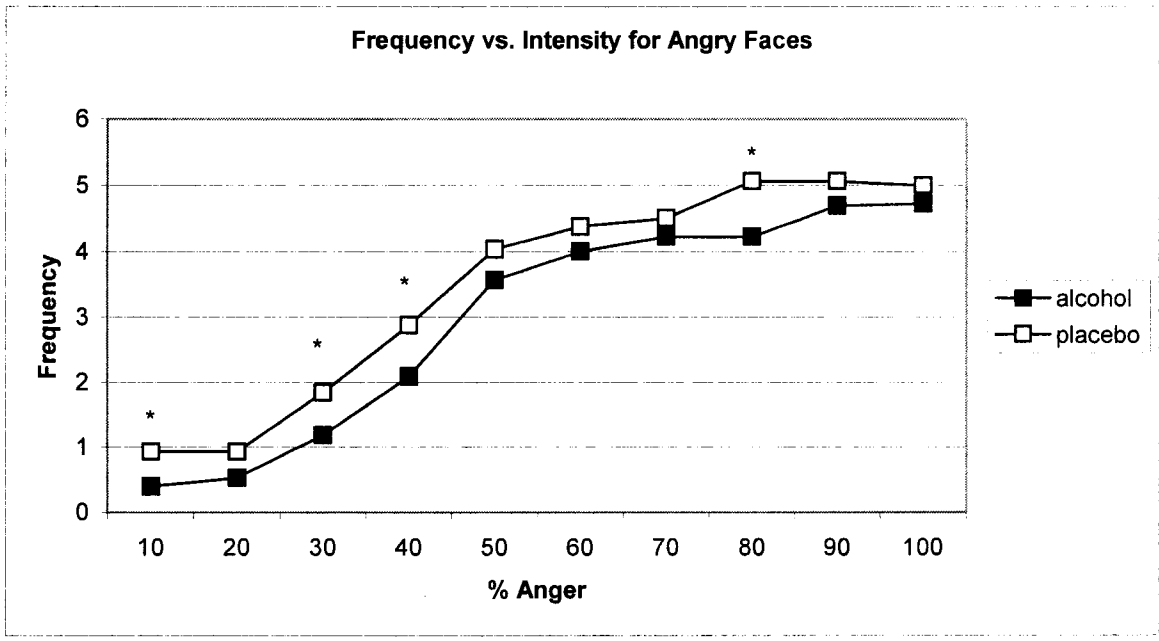
Key: Alcohol (black squares), placebo (open squares); *significant at Bonferroni corrected $p<0.005$.



Similar drug x intensity interactions were not present for other emotions (Fs < 1.0; ps > 0.4). As predicted and consistent with our analysis of all morphed intensities, alcohol significantly reduced anger recognition at several intensities (Figure 6.2.1.4.).

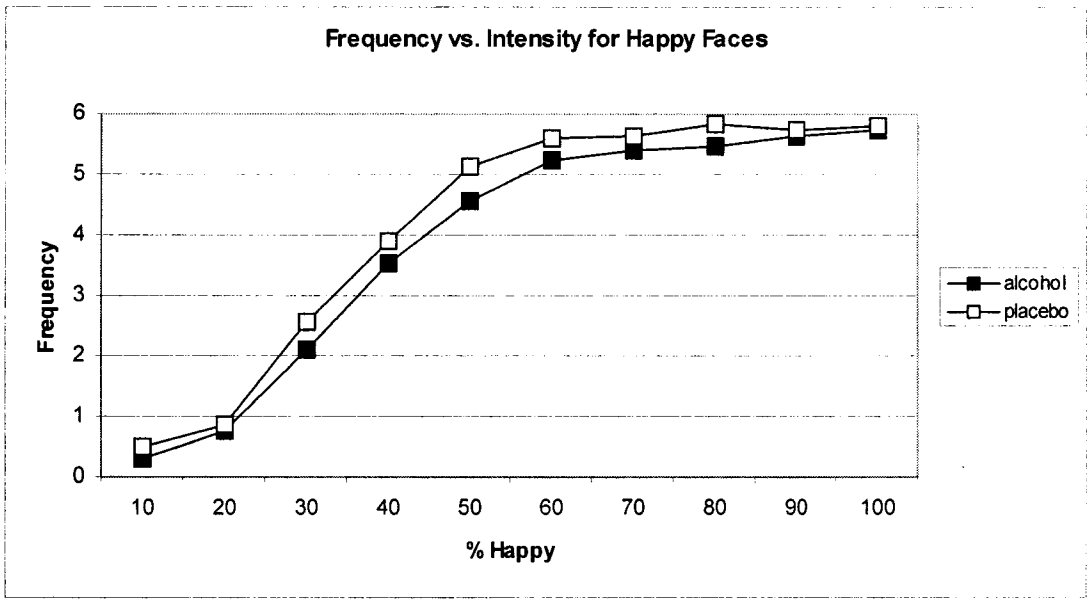
Figure 6.2.1.4. Recognition accuracy for anger expressions across different morphed intensities in the 10% increment task.

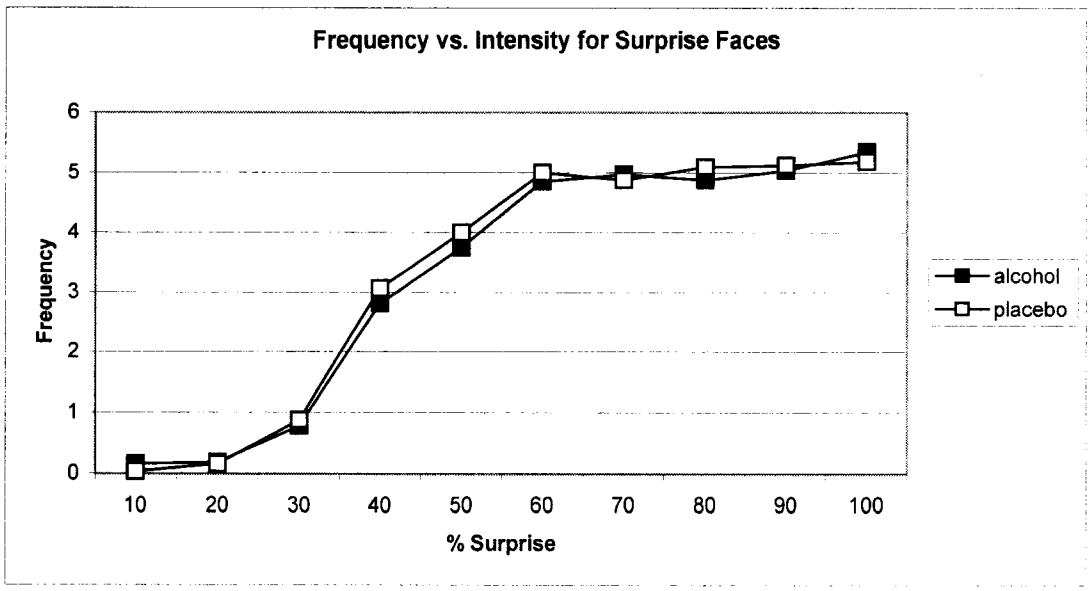
Key: Alcohol (black squares), placebo (open squares); *significant at Bonferroni corrected p<0.005.

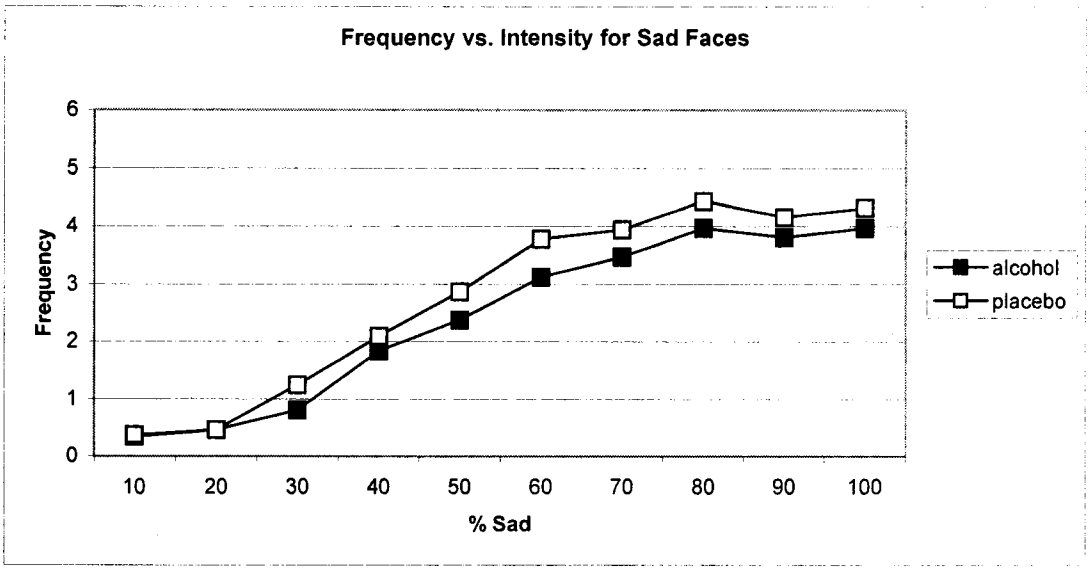


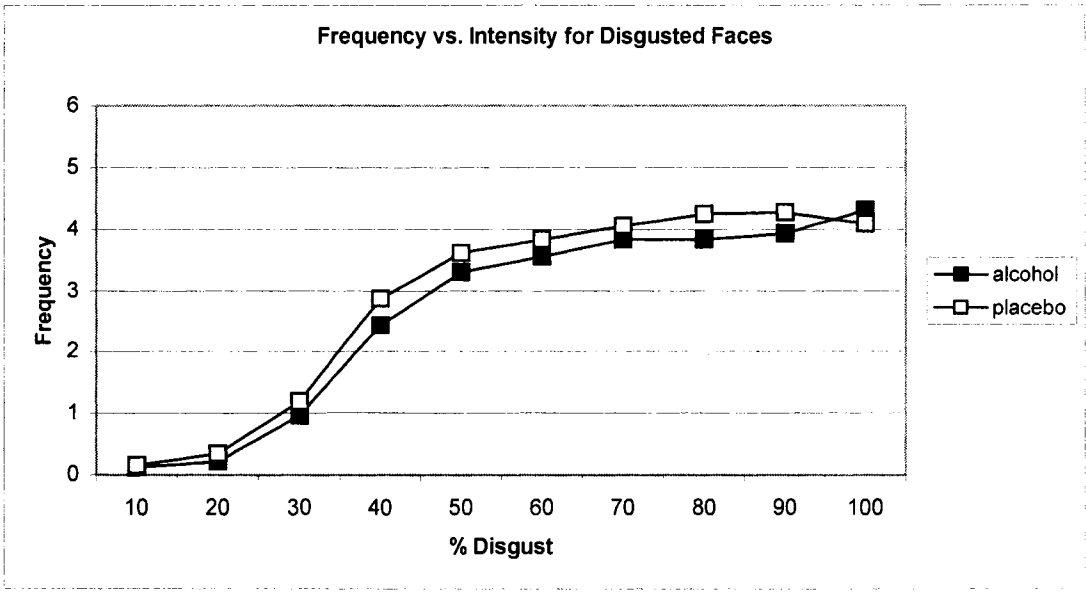
For other emotions, there were no significant effects of alcohol at specific intensities of expression (Figure 6.2.1.5-8.).

Figure 6.2.1.5-8. Recognition accuracy for happy, surprise, sad and disgust expressions across different morphed intensities in the 10% increment task. Key: Alcohol (black squares), placebo (open squares).









6.2.2. Errors

Errors in emotion recognition can be attributed to non-detection (i.e. did not perceive an emotion and thereby labelling it as neutral) or misidentification (i.e. detected the wrong emotion). An analysis was also performed of these two types of error.

For non-detection, alcohol affected all facial expressions: drug $F(1,31) = 22.5$, $p < 0.0001$, drug x intensity $F(9,279) = 5.2$, $p < 0.0001$. However, there was no drug x emotion interaction $F(5,155) = 0.6$, $p = 0.7$. In general, alcohol decreased the detection of all emotions, particularly at lower morphed intensities (Figures 6.2.2.1. and 6.2.2.2.).

Figure 6.2.2.1. Frequency of non-detection (mean ± SD) of emotional expressions in the 10% increment task.

Key: Alcohol (black bars), placebo (grey bars). *significant at uncorrected $p < 0.05$; **significant at Bonferroni-corrected $p < 0.005$; HAP = happy, SURP = surprise, DISG = disgust, ANG = anger.

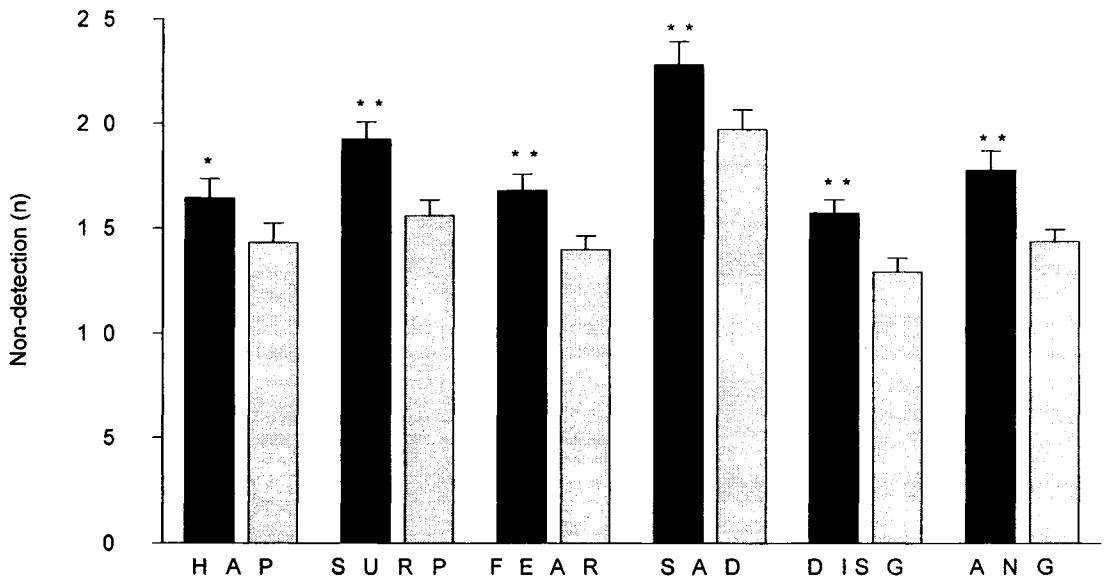
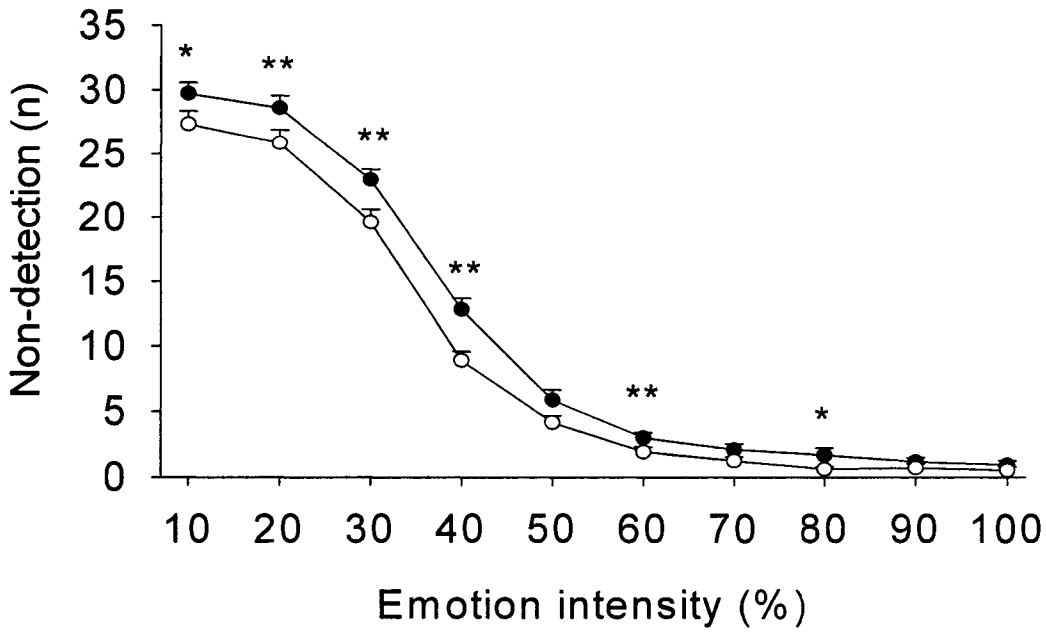


Figure 6.2.2.2. Frequency of non-detection (mean ± SD) of emotional expressions in the 10% increment task.

Key: Alcohol (black circles), placebo (open circles). *significant at uncorrected p <0.05; **significant at Bonferroni-corrected p<0.005.



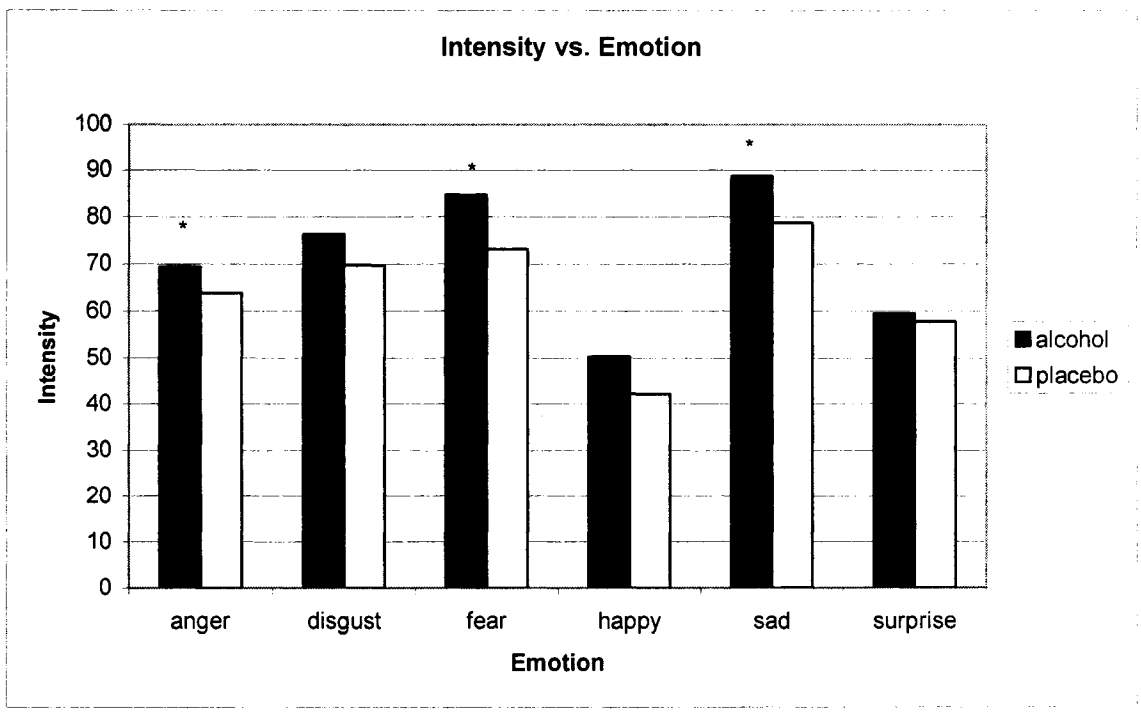
For misidentification, there was no main effect of alcohol: drug $F(1,31) = 0.2$, $p = 0.6$; although a drug x emotion interaction was present: $F(5,155) = 4.1$, $p = 0.002$. Alcohol increased misidentifications of fear $t(1,31) = 2.2$, $p = 0.04$. For comparison, alcohol did not significantly increase misidentifications of anger or other emotions ($ts < 1.2$; $ps > 0.22$) and there was a decrease in misidentifications of surprise $t(1,31) = 3.1$, $p = 0.004$.

6.2.3. Detection Threshold

This was defined as the intensity level at above which subjects consistently recognized ≥4/6 expressions correctly for that emotion (Figure 6.2.3.). There was a significant emotion effect: $F=20.3_{(5,155)}$; $p<0.0001$, indicating that the threshold differed across emotions, and a significant drug effect: $F=13.3_{(1,31)}$; $p<0.0001$, indicating an effect of alcohol. There was no significant emotion x drug interaction: $F=0.63_{(5,31)}$; $p=0.64$, indicating that alcohol effects were not specific for a particular emotion.

Figure 6.2.3. Mean intensity threshold for correct recognition of facial expressions (≥4/6 correct).

Key: Alcohol (black bars), placebo (open bars). *significant at uncorrected $p<0.05$.



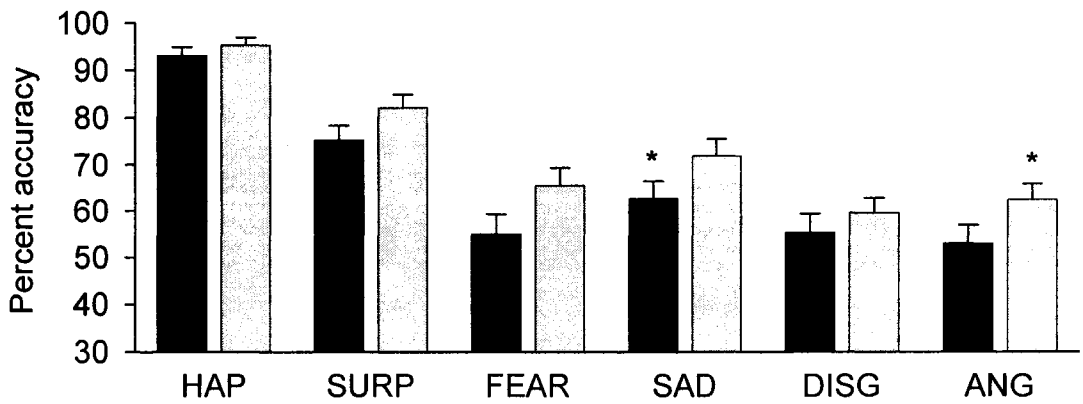
6.3. MODIFIED EMOTIONAL HEXAGON TASK

6.3.1. Accuracy

Alcohol reduced recognition accuracy for the combined 70-90% intensity expressions, drug $F(1,31) = 41.3$; $p < 0.0001$, drug × emotion $F(5,155) = 0.7$; $p = 0.5$ (Figure 6.3.1.). Recognition of sad, $t(1,31) = 2.2$; $p = 0.04$, and angry expressions, $t(1,31) = 2.2$; $p = 0.02$, showed significant decreases compared with placebo, at an uncorrected $p < 0.05$, and there was a trend effect for fear, $t = 1.8$; $p = 0.08$. However, the alcohol minus placebo differences for sad and angry expressions were not significantly greater than for other emotions (ts <2.0; ps > 0.06).

Figure 6.3.1. Recognition accuracy (mean ± SD) for the combined 70% & 90% expressions in the modified emotional hexagon task.

Key: Alcohol (black bars), placebo (grey bars); *significant at uncorrected $p<0.05$. HAP = happy, SURP = surprise, DISG = disgust, ANG = anger.



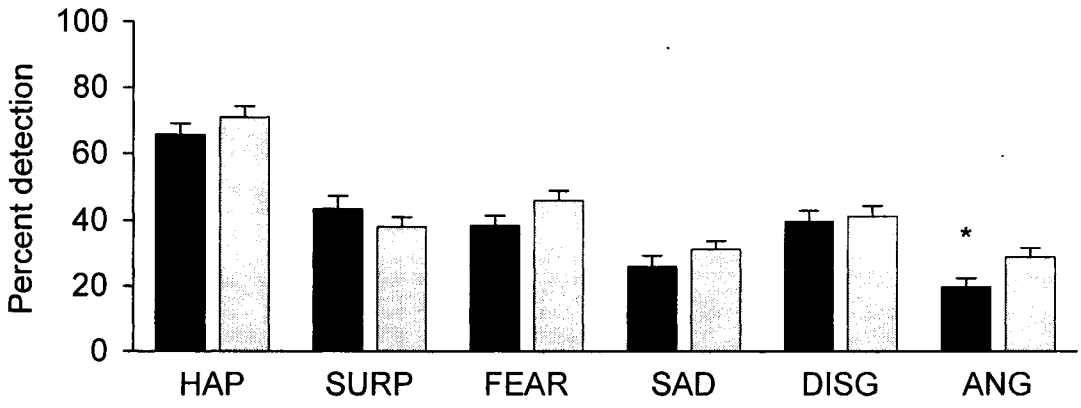
Individual analysis of the 90% and 70% faces revealed differences in the frequency of correct responses. Consistent with our expectations, there was an overall trend towards more correct responses with the 90% faces versus the 70% faces: emotion x intensity $F(5,25) = 4.3$, $p = 0.006$. Alcohol, however, did not appear to affect the frequency of correct responses with respect to emotion intensity: drug x intensity $F(1,29) = 0.1$, $p = 0.3$. Compared with placebo, alcohol had a significant effect on the frequency of correct responses for the 90% faces across all emotions: drug $F(1,29) = 8.4$, $p = 0.007$; drug x emotion $F(5,145) = 0.6$, $p = 0.6$. The same effect on the frequency of correct responses occurred with the 70% faces: drug $F(1,29) = 7.1$, $p = 0.01$; drug x emotion $F(5,145) = 0.8$, $p = 0.5$.

6.3.2. 50% intensity expressions

For the ambiguous 50%-50% blends, there was a significant drug effect, $F(1,31) = 13.1$; $p = 0.001$, and a trend to a drug × emotion effect, $F(5,155) = 2.0$; $p = 0.077$. Alcohol significantly reduced the detection of angry expressions, $t(1,31) = 2.8$; $p = 0.0045$ (Figure 6.3.2.).

Figure 6.3.2. Percent detection (mean ± SD) of emotional expressions in the 50% intensity blends in the modified emotional hexagon task.

Key: Alcohol (black bars), placebo (grey bars); *significant at Bonferroni corrected $p<0.008$; HAP = happy, SURP = surprise, DISG = disgust, ANG = anger.



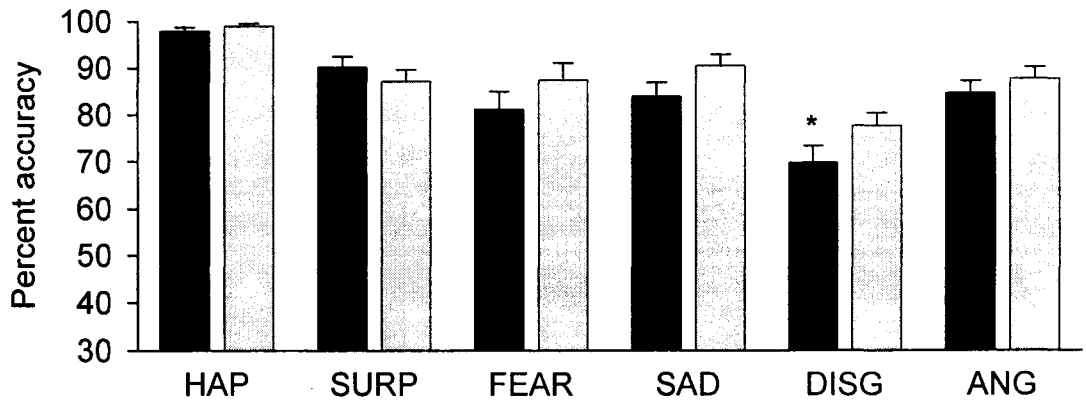
6.4. MULTIMORPH TASK

6.4.1. Accuracy

Alcohol significantly affected recognition accuracy for emotional expressions: drug $F(1,31) = 9.6$, $p = 0.004$; drug x emotion $F(5,155) = 2.8$, $p = 0.037$. The drug x emotion effect was only significant for disgust compared with placebo $t(1,31) = 3.3$, $p = 0.003$ (Figure 6.4.1.). Disgust recognition was impaired more than recognition of happy expressions $t(1,31) = 2.7$, $p = 0.01$. Recognition of both fear $t(1,31) = 2.5$, $p = 0.02$ and disgust $t(1,31) = 3.3$, $p = 0.002$ was impaired more than for surprise, although this may have reflected a small improvement in surprise recognition. Alcohol did not significantly affect accuracy for recognition of anger $t(1,31) = 1.3$, $p = 0.11$.

Figure 6.4.1. Percent accuracy (mean ± SD) in the multimorph task.

Key: Alcohol (black bars), placebo (grey bars); *significant at Bonferroni corrected $p<0.008$; HAP = happy, SURP = surprise, DISG = disgust, ANG = anger.

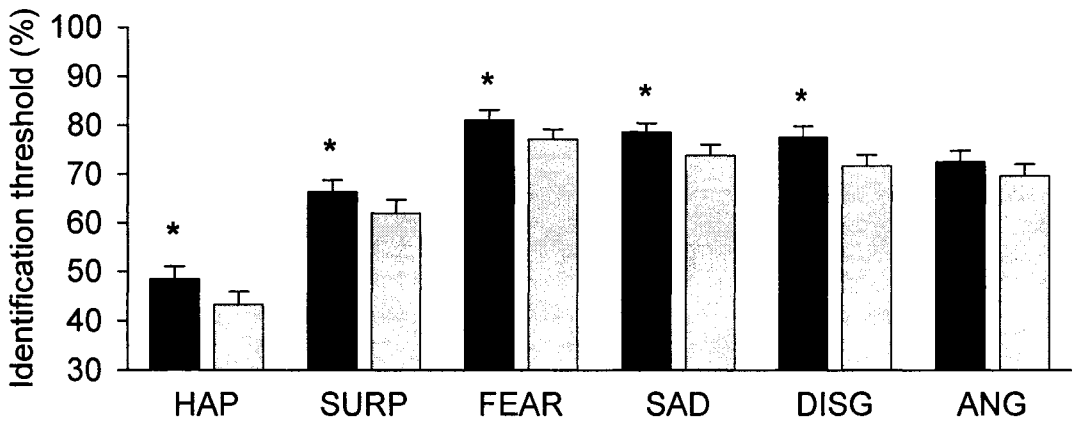


6.4.2. Detection Threshold

We also examined the effect of alcohol on the threshold of recognition (i.e. the percent intensity at which subjects correctly recognized the emotion). There was a general drug effect across all emotions $F(1,31) = 11.4$, $p = 0.002$ (Figure 6.4.2.), but no drug x emotion interaction $F(5,155) = 0.4$, $p = 0.8$. Alcohol increased the threshold for identification non-selectively across all emotions, although this was only significant when uncorrected p values were used, and not after Bonferroni correction. The effect was not significant for anger, $t(1,31) = 1.4$, $p = 0.08$. None of the alcohol-placebo differences in identification threshold differed significantly between emotions $ts < 1.6$; $ps > 0.12$.

The lack of selectivity for alcohol on this measure was not simply due to impaired accuracy (and the inclusion of incorrect responses that were scored at 102.5%), because the effect was not selective even when thresholds were analyzed using only correct responses: drug x emotion: $F(5,155) = 0.8$, $p = 0.6$. Furthermore, alcohol did not increase errors as a result of impulsive responding. The intensity at which subjects made their first response was compared and showed that after alcohol, subjects only made their first responses at higher intensities, alcohol: 61.5±12.3%, placebo: 57.3±14.0%; $t = 2.7$; df 31; $p = 0.012$.

Figure 6.4.2. Threshold intensities (mean ± SD) of recognition in the multimorph task. Key: Alcohol (black bars), placebo (grey bars); *significant at uncorrected $p<0.05$. HAP = happy, SURP = surprise, DISG = disgust, ANG = anger.



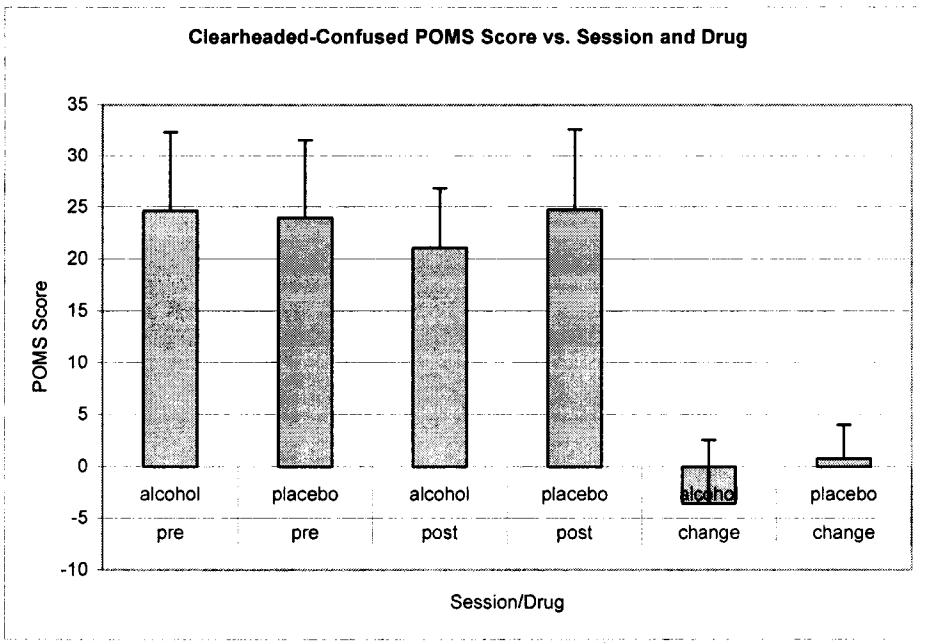
6.5. MOOD RATINGS

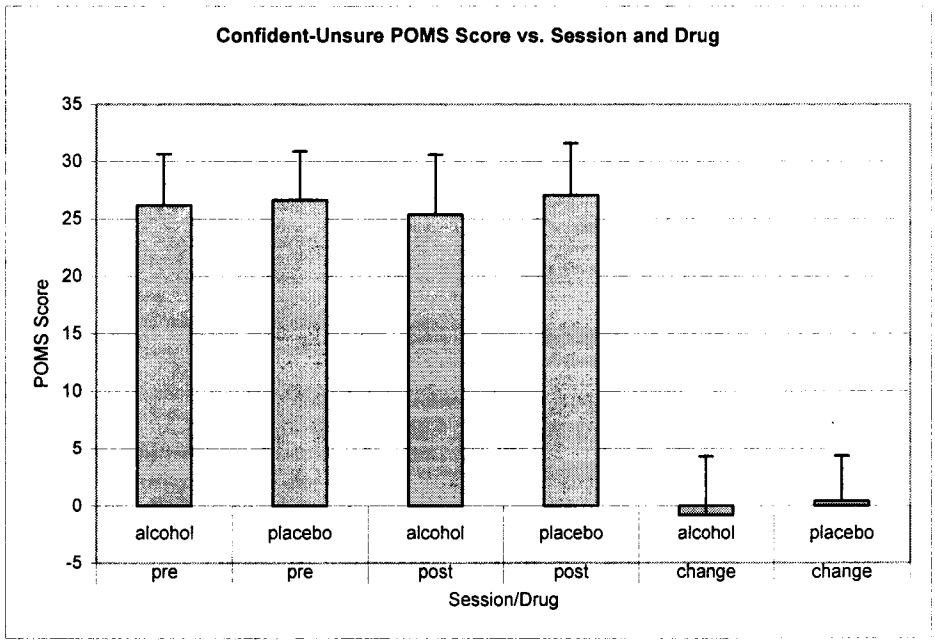
No baseline mood differences were detected between sessions ($ts < 1.1$; $ps > 0.25$). Alcohol caused a decrease in clear-headedness, but did not significantly affect other POMS measurements (Table 6.5. & Figure 6.5.). Changes in clear-headed ratings were not correlated with alcohol minus placebo changes in emotion recognition accuracy for any of the tasks.

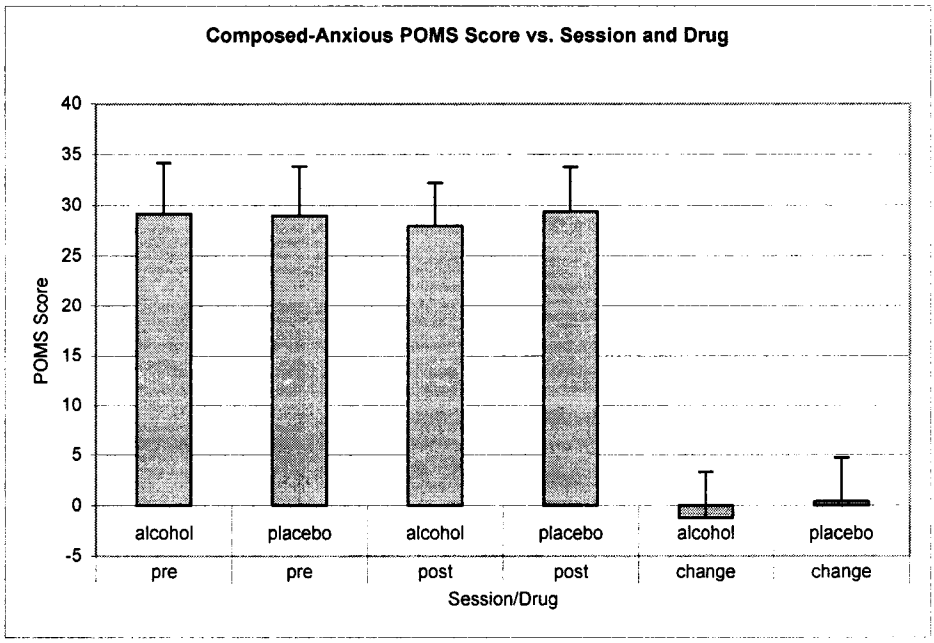
Table 6.5. Changes in Profile of Mood States (POMS) mood ratings (mean ± SD) according to session. Key: * statistically significant difference, paired t test.

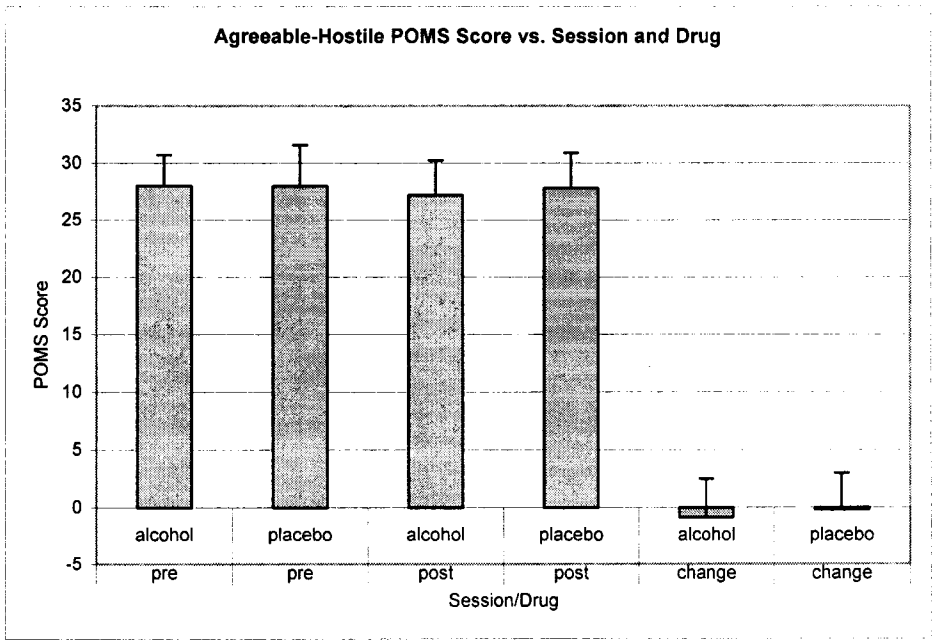
	alcohol	placebo	F(1,31)	p-value
clearheaded-confused	-3.6±6.1*	0.8±3.2	12.8	0.001
agreeable-hostile	-0.8±3.3	-0.2±3.2	0.7	0.40
composed-anxious	-1.2±4.5	0.4±4.3	2.0	0.16
confident-unsure	-0.8±5.1	0.4±3.9	1.4	0.25
elated-depressed	-0.3±5.5	-1.0±3.6	0.3	0.56
energetic-tired	0.8±9.1	1.0±6.1	0.01	0.92

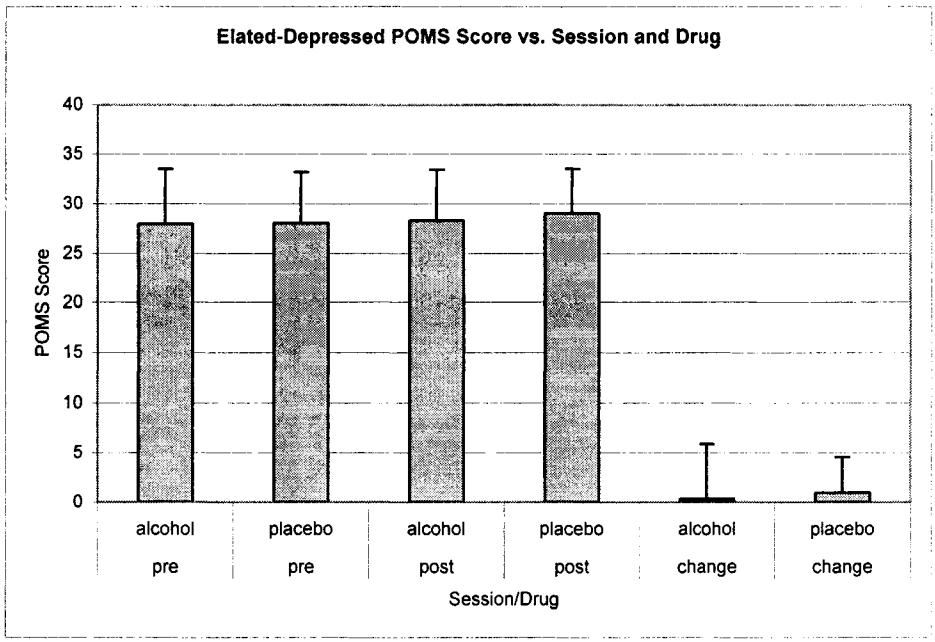
Figure 6.5. Profile of Mood States (POMS) mood ratings and changes (mean ± SD) from pre- to post-drug administration.

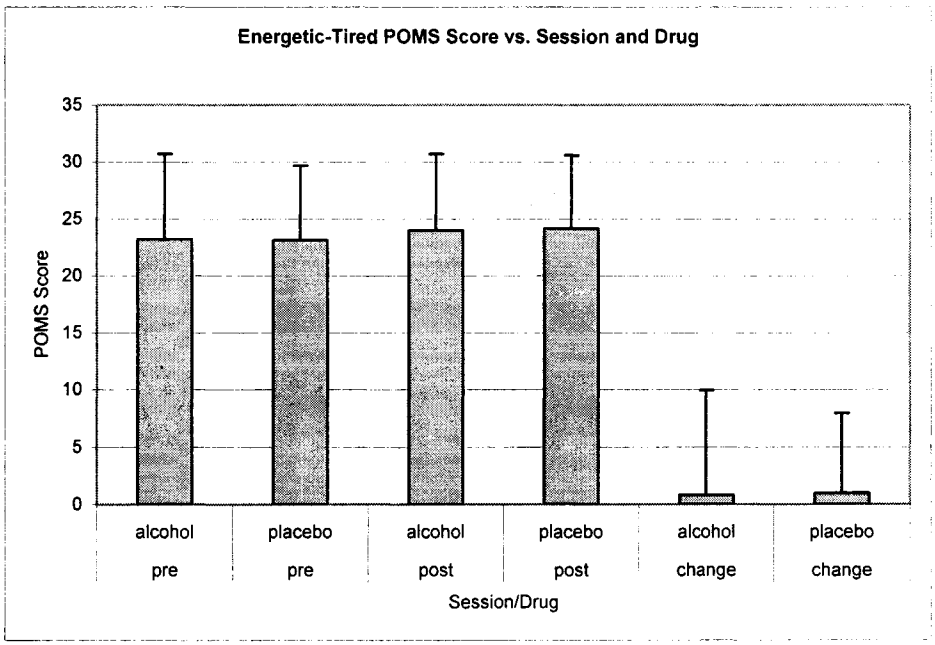












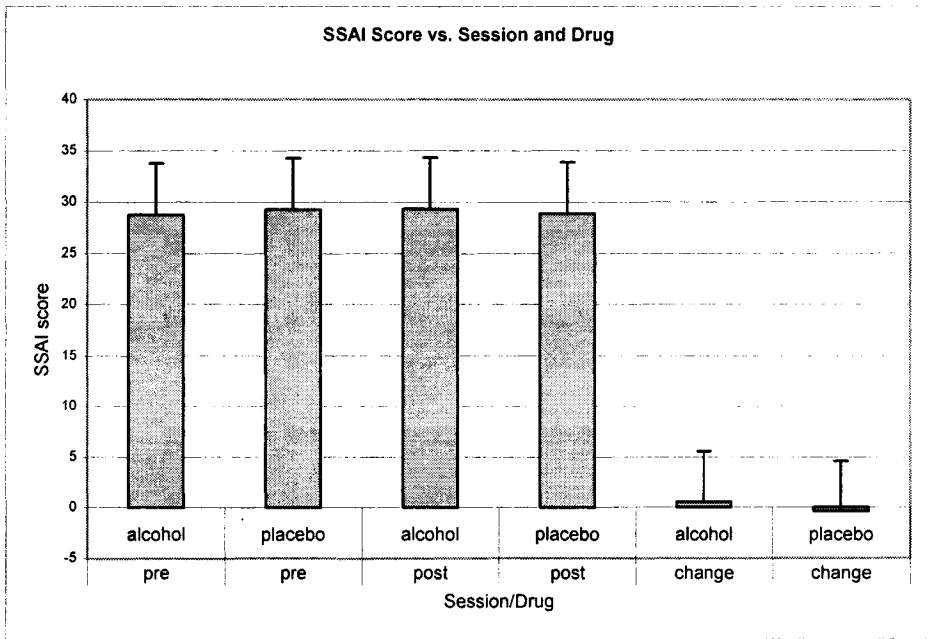
6.6. ANXIETY RATINGS

SSAI scores were equivocal in both alcohol and placebo sessions (Table 6.6. & Figure 6.6.). No baseline anxiety differences were detected between sessions (t = 1.0; p = 0.31).

Table 6.6. Changes in Spielberger State Anxiety Inventory (SSAI) anxiety ratings (mean ± SD) according to session.

	alcohol	placebo	F(1,31)	p-value
anxiety score	0.6 ± 5.3	-1.2 ± 5.0	2.0	0.16

Figure 6.6. Spielberger State Anxiety Inventory (SSAI) anxiety ratings and changes (mean ± SD) from pre- to post-drug administration.



6.7. BREATH ALCOHOL CONCENTRATION (BAC) AND OTHER FACTORS

BAC: BAC did not differ between the sexes: males: 0.082 ± 0.014, females: 0.082 ± 0.010; t = 0.09; df 30; p = 0.92. Weak and statistically non-significant correlations between increasing BAC and decreasing accuracy were observed in the hexagon task for the combined 70% & 90% stimuli (r = -3.3, p = 0.073) and in the multimorph task (r = -3.4, p = 0.054).

Subject Sex: Twelve subjects were males and 20 were females. We therefore reanalyzed the main variables for recognition accuracy with a mixed ANOVA, including sex as a between-subjects factor. However, there were no significant effects of sex in these analyses, suggesting that alcohol may produce similar impairments in emotion recognition in both sexes.

CHAPTER 7 *DISCUSSION*

7.1. SPECIFICITY OF ALCOHOL EFFECTS ON FACIAL EMOTION RECOGNITION

The main study finding was that alcohol produced impairments in the accuracy of emotion recognition, but that the degree of impairment and its specificity were dependent on the particular task that was used, as summarized in Table 7.1.

Table 7.1. Summary of significant effects of alcohol on measures of emotion recognition compared with placebo. Key: *effects significant at uncorrected $p < 0.05$; **effects significant at Bonferroni corrected $p < 0.008$.

	Happy	**Surprise**	**Fear**	**Sad**	**Disgust**	**Anger**
10% increment						
100% intensity			**			
All intensity	*		**	**	*	**
Threshold			*	*		*
Hexagon						
70/90%				*		*
50%						*
Multimorph						
Accuracy					*	
Threshold	*	*	*	*	*	

From Table 7.1., it can be seen that alcohol appeared to affect the recognition of negative facial expressions (fear, sad, disgust, anger) more robustly than positive emotion (happy) or ambiguous emotion (surprise). In this context, surprise is suggested to be ambiguous because recent research has shown clear individual differences in whether healthy subjects rate surprised expressions as being pleasant or unpleasant (Kim et al., 2003). In the current study, it is not known whether subjects would have interpreted surprised faces as positive or negative. Impaired recognition of happy or surprised faces was shown only when the task variable that was analyzed reflected a wide range of expression intensities, i.e. the 10% increment task across all intensities and the multimorph task threshold for recognition.

Even for the negative emotional expressions, the results did not fully support the prediction that alcohol would produce particular impairment of recognition for angry expressions. In the 10% task, alcohol had a broad effect on the recognition of negative emotions. Although on the combined intensity measure, alcohol affected anger recognition significantly more than several other expressions, fear recognition was also strongly affected. Fear was the only emotion for which alcohol impaired recognition in full (100%) intensity images. Anger recognition was affected in the emotional hexagon task, in both the 70/90% images and in the 50% images. However, recognition of sad expressions was also altered in the 70/90% images. Furthermore, it cannot be said that alcohol produced a selective effect, because it did not produce *significantly greater* impairments for anger than for other expressions. In the multimorph task, anger was the only emotional expression for which there was *no* significant impairment following

alcohol. Thus although alcohol was capable of impairing anger recognition, this effect was not particularly selective, nor was it independent of the type of anger expression stimuli and their mode of presentation.

In the task measures that included a full range of intensities of expression, from neutral to 100%, alcohol appeared to show its broadest effects on recognition accuracy. The analysis of errors in the 10% increment task showed that an effect of alcohol, that was not specific to any one emotion, was to increase the frequency of non-detections, i.e. the rating of low intensity emotional expressions as being neutral (Figure 6.2.2.1.). This was also consistent with the multimorph task, where the threshold intensities for recognition were increased non-specifically (Figure 6.4.1.). This finding on the multimorph task could not simply be explained by the threshold measures being inflated by impulsive errors, since subjects took significantly longer to make their first response after alcohol. *Taken together, these findings suggest that alcohol consistently reduces the sensitivity of detection of facial emotions.*

This finding raises further questions. The first is why, on simple accuracy measures, alcohol appears to produce at least some partly selective impairments. The second is what are the possible mechanisms for this general reduction in sensitivity.

7.2. APPARENT SELECTIVITY OF ALCOHOL EFFECTS ON EMOTION RECOGNITION ACCURACY

One reason for partial selectivity may be that in addition to decreased sensitivity to emotional expressions, alcohol also increased misidentification rates for some emotions. However, the patterns of misidentification did not transfer consistently across tasks. For example, in the 10% task, alcohol increased the frequency with which fear was misidentified as surprise, but in the multimorph task, alcohol increased the frequency with which disgust was misidentified as anger. These two patterns of misidentification are the most common in healthy subjects (Eckman & Friesen, 1976). Misidentification did not appear to explain why anger recognition was particularly impaired in the 10% increment task, however, because misidentifications of anger expressions were not significantly increased. One possibility relates to the effect of alcohol on recognition of low intensity angry faces (Figure 6.2.1.4.). This appeared to present a special case, since following placebo, there was some tendency to rate the low intensity faces as being angry and this was decreased by alcohol. For other emotions, there was a floor effect, since the low intensity faces were identified as neutral following placebo. An explanation for the anger ratings is that there is a normal bias to interpret a lack of positive facial expressions as mildly hostile, since social interactions are customarily facilitated by positive expressions (Phillips et al., 1997).

Another explanation for apparently selective effects on accuracy involves task difficulty effects. It is known that emotion recognition can be impaired, even in healthy

subjects, by factors such as the use of short stimulus durations, faces from a less familiar racial background, and degraded stimuli, for stimuli with a low spatial frequency that show only coarse features and no fine detail (Johnston et al., 2001; Rapcsak et al., 2000). The use of such stimuli tends to impair the recognition of negative emotions (fear, sadness, disgust, anger) to a greater extent than for happy or surprise expressions. This has been interpreted as a task difficulty effect, because normally full negative expressions are recognized less accurately than full positive expressions (Johnston et al., 2001). In the present data, it can be seen following placebo that happy and surprised expressions are recognized more readily than the other expressions. In this case, reducing the sensitivity to detect all expressions with alcohol might cause apparently less effect on happy and surprise expressions, since for these a higher proportion of the stimuli are in an "easy" range of intensities for recognition.

Another possible factor in apparent selectivity, specifically for the emotional hexagon task, is that the emotional "blends" that have been used in this task are not balanced across all emotions, but contain only blends between specific pairs of emotions. The original idea behind this is that there is greater similarity of features between some pairs of emotions than others, e.g. widened eyes in fear and surprise (Calder et al., 1996). The original stimuli were therefore produced going across such pairs from happy-surprise-fear-sad-disgust-anger. However, in order to have a paired emotional blend for anger, the pairing was then looped back to happy expressions, despite the lack of similarity for angry and happy expressions. We have previously shown that this blended pair is associated with the longest reaction times of any of the emotional hexagon stimuli

(Coupland et al., 2003). In the present study, it can also be seen that recognition rates for anger in the placebo condition tend to be low, particularly in the 50% blends (Figure 6.3.2.). In contrast, the happy expression component is recognized at high rates, probably also because happy expressions are well recognized even at low intensity. This might help to explain why anger faces are particularly affected by alcohol-induced decrements in this task.

7.3. IMPLICATIONS FOR ALCOHOL EFFECTS ON VISUAL PROCESSING OF AFFECTIVE EXPRESSIONS

Given research on impairments of emotion recognition using degraded visual stimuli (Johnston et al., 2001; Rapcsak et al., 2000), it is possible that alcohol might impair emotion recognition because it impairs lower level visual perception, or because it impairs affective processing of those perceptions. Whilst this cannot be determined from the present data, prior research has shown that the effects of alcohol on visual acuity are relatively modest at BACs achieved in the present study (Pearson & Timney, 1998; Watten & Lie, 1996). Furthermore, while measurements with evoked response potentials of alcohol effects on facial emotion discrimination showed no effects on early, more perceptual components of visual processing, alcohol did affect impaired late components, which reflect cognitive and affective elaboration (Orozco et al., 1999).

7.4. POSSIBLE THEORIES FOR THE GENERALIZED PATTERN OF ALCOHOL-INDUCED COGNITIVE DEFICITS

Given that alcohol affects several neurotransmitter systems that might impact affective and cognitive processing of visual stimuli, it cannot be determined from the present study whether alcohol affects multiple systems for emotion recognition, each of which may be relatively more influenced by particular neurotransmitters, or whether it affects a more general system through a single mechanism. Certainly, several recent articles have argued against the idea that the perception of different facial emotions can be fully dissociated at the level of neural systems (Johnston et al., 2001; Rapcsak et al., 2000; Winston et al., 2003; Yang et al., 2002). Most studies of drug effects on emotion recognition to date have used a single task. It may therefore be that apparently specific effects occurred because these were task specific. For example, although some studies have reported relatively selective effects of benzodiazepines on facial anger recognition, these studies used the emotional hexagon task, which has limitations as described as above (Blair & Curran, 1999; Zangara et al., 2002). When we re-examined the effects of diazepam using the multimorph task in addition, the effects were not specific to anger (Coupland et al., 2003). Apparently specific deficits in the recognition of a negative emotional expression in a single task may not be strong evidence of selectivity.

In contrast to these arguments, however, some recent studies of the serotonergic and noradrenergic systems have suggested that neurotransmitter modulation can have bidirectional effects on emotion recognition. For example, whereas acute depletion of

serotonin in healthy subjects, using tryptophan depletion, decreased fear recognition, augmentation of serotonin by the acute administration of tryptophan or citalopram actually enhanced recognition (Attenburrow et al., 2003; Harmer et al., 2003a; Harmer et al., 2003b). Furthermore, whereas the beta-adrenergic antagonist propranolol increases reaction times to recognize sad faces (Harmer et al., 2001) and decreasing noradrenaline release using clonidine decreases accuracy of sad face recognition, increasing noradrenaline release using yohimbine increases recognition of sad expressions (Sustrik et al., 2003). These studies provide better evidence that specific neurotransmitters may have dissociable effects on specific emotions, since they do not depend solely on impairments.

Alcohol may therefore produce a general impairment because it affects multiple systems simultaneously, particularly in the descending limb of the blood alcohol curve, when dopaminergic activation has worn off. Given that in this phase of the curve, alcohol enhances GABA function and impairs glutamatergic neurotransmission (see Chapter 2), it is interesting that a recent fMRI study showed that the NMDA antagonist, ketamine, blocked the normal activation of limbic structures to emotional expressions in healthy males (Abel et al., 2003).

Additionally, since alcohol has generalized effects on the sensitivity for emotion recognition on two measures and, an overall, minimal effect on mood ratings, it appears likely that any effects of alcohol on emotion recognition are direct and not a consequence of alterations in the subjects' mood.

7.5. LIMITATIONS AND STRENGTHS OF THE STUDY

There were both limitations and strengths of the present study. Only the descending limb of the alcohol blood concentration curve was tested, because the predominant sedative effects of alcohol on this limb fitted predictions based theoretically on GABA effects, and dopamine release on the ascending limb might possibly offset impairment of anger recognition, because dopamine receptor blockade has been suggested to impair anger recognition (Boileau et al., 2003; Lawrence et al., 2002). Selection of the descending limb was based purely on timing and we did not obtain multiple BAC and POMS measures to confirm that all subjects were in this phase. Furthermore, since the different tasks were performed in a fixed order, they would have been performed at different BACs. However, even at the end of testing significant BACs would be predicted (~0.06) and subjects showed similar slowing of reaction times across all tests, suggesting continued effects of alcohol. More BAC measures and detailed mood ratings over time might theoretically have revealed some relationships that were not present with single measures. However, this seems unlikely for mood, given the small peak effects of alcohol on the POMS ratings.

It is possible that more specific effects might have occurred on the ascending limb of the blood alcohol curve, since this is when arousal and dopamine release occur (Boileau et al., 2003), and when social provocation paradigms have typically shown release of aggression (Hoaken et al., 2003). Effects of alcohol in this period need to be tested separately.

The present study did not investigate whether the non-specific emotion recognition deficit following alcohol was primarily visual or affective in nature, in part because the target BACs were not expected to produce marked effects on visual perception (Orozco et al., 1999). This might be strengthened in future studies by including complex non-emotional visual perception control tasks. However, even this approach can present problems in equating task difficulty across tests (Johnston et al., 2001).

A final limitation is that at present, it is uncertain to what degree any changes in emotion recognition in these simplified tasks, using static photographs devoid of contextual information, transfers to real life situations, in which emotional displays are dynamic, multichannel (speech, vocal tone, expression, gesture, etc.) and presented within behavioural contexts.

The present design had several strengths relative to other recent investigations of the pharmacological manipulation of emotion recognition. The larger sample and within-subjects design gave substantially increased power. For example, typically emotion recognition studies have used between-subjects designs, with samples on the order of n=12 per group. However, given differences of the magnitude that we found in the 10% increment task in the present study, this would have given only 40% power to show differences in anger recognition and 17% power for disgust recognition. False conclusions about specificity can result from differential power to detect changes in the recognition of target and non-target emotions. The present study included a further protection against this that has not generally been employed, which is to show not only

that the target emotions are significantly affected (at a specific level of p values), but also that the drug effects on the target emotion are *significantly greater* than the effects on non-target emotions. For example, recognition accuracy for anger was significantly decreased in the hexagon task, but this was not good evidence for specificity, because the decrease was not significantly greater than that for any other emotion.

A further strength was that in the present study, every actor or model showed every type of emotional expression or blend that was used. In some studies, some faces have been shown only by specific actors, chosen to be good examples of specific emotional expressions (Harmer et al., 2001). A problem with this is that subjects might learn associations between identity of the actor and the emotional expression shown, at least implicitly.

An improvement in the analysis of the 10% increment task over previous studies was that we dissociated error types into non-detection and misidentification, rather than simply describing overall accuracy. This allowed us to show that alcohol non-selectively reduced detection, but more selectively increased misidentification.

Finally, a main strength of the study was the use of multiple tasks, since for any drug that produces a major selective effect for a specific emotion, this should be expected to transfer with a reasonable degree of robustness across different task parameters.

CHAPTER 8 *CONCLUSION*

Alcohol produced a general deficit in facial emotion recognition specifically on the descending limb of the blood alcohol curve.

The specific nature of this deficit needs further clarification and it remains to be determined whether such a deficit is predictive of social behaviour.

The use of multiple emotion recognition tasks can substantially clarify the interpretation of drug effects in comparison with data from a single test.

Larger sample sizes and future studies involving functional neuroimaging techniques may be useful in more detailed mapping of the effects of alcohol-induced deficits in cognitive function and facial emotion processing.

CHAPTER 9 *REFERENCES*

Abel KM, Allin MP, Kucharska-Pietura K, David A, Andrew C, Williams S, Brammer MJ, Phillips ML (2003). Ketamine alters neural processing of facial emotion recognition in healthy men: an fMRI study. *Neuroreport* 14 (3):387-391.

Adolphs R (2002). Neural systems for recognizing emotion. *Curr Opin Neurobiol* 12 (2):169-177.

Adolphs R, Tranel D (2003). Amygdala damage impairs emotion recognition from scenes only when they contain facial expressions. *Neuropsychologia* 41 (10):1281-1289.

Adolphs R, Tranel D, Damasio H, Damasio A (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature* 372 (6507):669-672.

Ahern GL, Schomer DL, Kleefield J, Blume H, Cosgrove GR, Weintraub S, Mesulam MM (1991). Right hemisphere advantage for evaluating emotional facial expressions. *Cortex* 27 (2):193-202.

Alling C (1983). Alcohol effects on cell membranes. *Subst Alcohol Actions Misuse* 4 (2-3):67-72.

Asthana HS, Mandal MK (1998). Hemifacial asymmetry in emotion expressions. *Behav Modif* 22 (2):177-183.

Attenburrow MJ, Williams C, Odontiadis J, Reed A, Powell J, Cowen PJ, Harmer CJ (2003). Acute administration of nutritionally sourced tryptophan increases fear recognition. *Psychopharmacology (Berl)* 169 (1):104-107.

Balczon R, Gard AL, Goodman SR, Kayes SG, Zimmer WE (1998). Chapter 8: Signal transduction events in: Medical Cell Biology, 2nd ed (Goodman SR, editor. p. 249-280. Philadelphia, PA: Lippincott-Raven Publishers.

Baribeau JM, Braun CM, Dube R (1986). Effects of alcohol intoxication on visuospatial and verbal-contextual tests of emotion discrimination in familial risk for alcoholism. *Alcohol Clin Exp Res* 10 (5):496-499.

Barnard EA (1996). The molecular biology of GABAA recpetors and its applications in: GABA: Receptors, Transporters and Metabolism, (Tanaka C, Bowery NG, editors). p. 129-143. Basel, Switzerland: Birkhauser Verlag.

Belelli D, Lambert JJ (2005). Neurosteroids: endogenous regulators of the GABA(A) receptor. *Nat Rev Neurosci* 6 (7):565-575.

Benson PJ, Perrett DI (1991). Synthesising continuous-tone caricatures. *Image and Vision Computing* 9:123-129.

Blair RJ, Curran HV (1999). Selective impairment in the recognition of anger induced by diazepam. *Psychopharmacology (Berl)* 147 (3):335-338.

Blair RJ, Morris JS, Frith CD, Perrett DI, Dolan RJ (1999). Dissociable neural responses to facial expressions of sadness and anger. *Brain* 122 (Pt 5):883-893.

Boileau I, Assaad JM, Pihl RO, Benkelfat C, Leyton M, Diksic M, Tremblay RE, Dagher A (2003). Alcohol promotes dopamine release in the human nucleus accumbens. *Synapse* 49 (4):226-231.

Borrill JA, Rosen BK, Summerfield AB (1987). The influence of alcohol on judgement of facial expression of emotion. *Br J Med Psychol* 60 (Pt 1):71-77.

Burton LA, Levy J (1991). Effects of processing speed on cerebral asymmetry for left- and right-oriented faces. *Brain Cogn* 15 (1):95-105.

Calder A, Young A, Perrett D, Etcoff N, Rowland D (1996). Categorical perception of morphed facial expressions. *Visual Cognition* 3:81-117.

Calder AJ, Rowland D, Young AW, Nimmo-Smith I, Keane J, Perrett DI (2000). Caricaturing facial expressions. *Cognition* 76 (2):105-146.

CMI (1998). Intoxilyzer S-D2 Operator's Manual. Owensboro, KY: CMI Inc.

Conrod PJ, Peterson JB, Pihl RO (2001). Reliability and validity of alcohol-induced heart rate increase as a measure of sensitivity to the stimulant properties of alcohol. *Psychopharmacology (Berl)* 157 (1):20-30.

Cooper JR, Bloom FE, Roth RH (1996). Chapter 6: Amino acid transmitters in: Biochemical Basis of Neuropharmacology, 7th ed. p. 126-193. New York, NY: Oxford University Press.

Coupland NC, Singh AJ, Sustrik RA, Ting P, Blair RJ (2003). Effects of diazepam on facial emotion recognition. *J Psychiatry Neurosci* 28 (6):452-463.

Devenyi P, Saunders SJ (1986). Physicians' handbook for medical management of alcohol- and drug-related problems. Toronto, ON: Alcoholism and Drug Addiction Research Foundation.

Dudley R (2002). Fermenting fruit and the historical ecology of ethanol ingestion: is alcoholism in modern humans an evolutionary hangover? *Addiction* 97 (4):381-388.

Eckardt MJ, File SE, Gessa GL, Grant KA, Guerri C, Hoffman PL, Kalant H, Koob GF, Li TK, Tabakoff B (1998). Effects of moderate alcohol consumption on the central nervous system. *Alcohol Clin Exp Res* 22 (5):998-1040.

Eckman P, Friesen WV (1976). Pictures of Facial Affect. San Francisco, CA: University of California Medical Center.

Eckman P, Friesen WV, O'Sullivan M, Chan A, Diacoyanni-Tarlatzis I, Heider K, Krause R, LeCompte WA, Pitcairn T, Ricci-Bitti PE, et al. (1987). Universals and cultural differences in the judgments of facial expressions of emotion. *J Pers Soc Psychol* 53 (4):712-717.

Farah MJ, Wilson KD, Drain M, Tanaka JN (1998). What is "special" about face perception? *Psychol Rev* 105 (3):482-498.

Fillion L, Gagnon P (1999). French adaptation of the shortened version of the Profile of Mood States. *Psychol Rep* 84 (1):188-190.

George MS, Ketter TA, Gill DS, Haxby JV, Ungerleider LG, Herscovitch P, Post RM (1993). Brain regions involved in recognizing facial emotion or identity: an oxygen-15 PET study. *J Neuropsychiatry Clin Neurosci* 5 (4):384-394.

Gerhards F (1998). Decoding of facially expressed emotions in patients with psychosomatic gastrointestinal disorders. *Behav Modif* 22 (2):184-191.

Glautier S, O'Brien J, Dixon J (2001). Facial electromyographic (EMG) responses to emotionally significant visual images: differences between light and heavy drinkers. *Drug Alcohol Depend* 64 (3):337-345.

Gur RC, Schroeder L, Turner T, McGrath C, Chan RM, Turetsky BI, Alsop D, Maldjian J, Gur RE (2002). Brain activation during facial emotion processing. *Neuroimage* 16 (3 Pt 1):651-662.

Hariri AR, Tessitore A, Mattay VS, Fera F, Weinberger DR (2002). The amygdala response to emotional stimuli: a comparison of faces and scenes. *Neuroimage* 17 (1):317-323.

Harmer CJ, Bhagwagar Z, Perrett DI, Vollm BA, Cowen PJ, Goodwin GM (2003a). Acute SSRI administration affects the processing of social cues in healthy volunteers. *Neuropsychopharmacology* 28 (1):148-152.

Harmer CJ, Perrett DI, Cowen PJ, Goodwin GM (2001). Administration of the beta-adrenoceptor blocker propranolol impairs the processing of facial expressions of sadness. *Psychopharmacology (Berl)* 154 (4):383-389.

Harmer CJ, Rogers RD, Tunbridge E, Cowen PJ, Goodwin GM (2003b). Tryptophan depletion decreases the recognition of fear in female volunteers. *Psychopharmacology (Berl)* 167 (4):411-417.

Harrison NL, Krasowski MD, Harris RA (2000). Chapter 11: Alcohol and general anesthetic actions on the GABAA receptor in: Nervous System: The View at Fifty Years, (Martin DL, Olsen RW, editors). p. 167-189. Philadelphia, PA: Lippincott Williams & Wilkins.

Haxby JV, Hoffman EA, Gobbini MI (2000). The distributed human neural system for face perception. *Trends Cogn Sci* 4 (6):223-233.

Helzer JE, Pryzbeck TR (1988). The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. *J Stud Alcohol* 49 (3):219-224.

Herzog TA (1999). Effects of alcohol intoxication on social inferences. *Exp Clin Psychopharmacol* 7 (4):448-453.

Hoaken PN, Campbell T, Stewart SH, Pihl RO (2003). Effects of alcohol on cardiovascular reactivity and the mediation of aggressive behaviour in adult men and women. *Alcohol Alcohol* 38 (1):84-92.

Iidaka T, Omori M, Murata T, Kosaka H, Yonekura Y, Okada T, Sadato N (2001). Neural interaction of the amygdala with the prefrontal and temporal cortices in the processing of facial expressions as revealed by fMRI. *J Cogn Neurosci* 13 (8):1035-1047.

Indersmitten T, Gur RC (2003). Emotion processing in chimeric faces: hemispheric asymmetries in expression and recognition of emotions. *J Neurosci* 23 (9):3820-3825.

Jacobs KW, Boze MM (1993). Correlations among scales of the Beck Depression Inventory and the profile of mood states. *Psychol Rep* 73 (2):431-434.

Johnston PJ, Katsikitis M, Carr VJ (2001). A generalised deficit can account for problems in facial emotion recognition in schizophrenia. *Biol Psychol* 58 (3):203-227.

Kim H, Somerville LH, Johnstone T, Alexander AL, Whalen PJ (2003). Inverse amygdala and medial prefrontal cortex responses to surprised faces. *Neuroreport* 14 (18):2317-2322.

Kirchner TR, Sayette MA (2003). Effects of alcohol on controlled and automatic memory processes. *Exp Clin Psychopharmacol* 11 (2):167-175.

Kornreich C, Blairy S, Philippot P, Hess U, Noel X, Streel E, Le Bon O, Dan B, Pelc I, Verbanck P (2001). Deficits in recognition of emotional facial expression are still present in alcoholics after mid- to long-term abstinence. *J Stud Alcohol* 62 (4):533-542.

Kornreich C, Foisy ML, Philippot P, Dan B, Tecco J, Noel X, Hess U, Pelc I, Verbanck P (2003). Impaired emotional facial expression recognition in alcoholics, opiate dependence subjects, methadone maintained subjects and mixed alcohol-opiate antecedents subjects compared with normal controls. *Psychiatry Res* 119 (3):251-260.

Kringelbach ML, Rolls ET (2003). Neural correlates of rapid reversal learning in a simple model of human social interaction. *Neuroimage* 20 (2):1371-1383.

Krystal JH, Petrakis IL, Webb E, Cooney NL, Karper LP, Namanworth S, Stetson P, Trevisan LA, Charney DS (1998). Dose-related ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. *Arch Gen Psychiatry* 55 (4):354-360.

Kucharska-Pietura K, Phillips ML, Gernand W, David AS (2003). Perception of emotions from faces and voices following unilateral brain damage. *Neuropsychologia* 41 (8):1082-1090.

Lang SF, Nelson CA, Collins PF (1990). Event-related potentials to emotional and neutral stimuli. *J Clin Exp Neuropsychol* 12 (6):946-958.

Lawrence AD, Calder AJ, McGowan SW, Grasby PM (2002). Selective disruption of the recognition of facial expressions of anger. *Neuroreport* 13 (6):881-884.

Lee KA, Hicks G, Nino-Murcia G (1991). Validity and reliability of a scale to assess fatigue. *Psychiatry Res* 36 (3):291-298.

Leventhal H, Tomarken AJ (1986). Emotion: Today's problems. *Annu Rev Psychol* 37:565-610.

Lorr M, McNair DM, Fisher SU (1982). Evidence for bipolar mood states. *J Pers Assess* 46 (4):432-436.

Mandal MK, Asthana HS, Maitra S (1998). Right hemisphere damage impairs the ability to process emotional expressions of unusual faces. *Behav Modif* 22 (2):167-176.

Maruff P, Wood S, Currie J, McArthur-Jackson C, Malone V, Benson E (1994). Computer-administered visual analogue mood scales: rapid and valid assessment of mood in HIV positive individuals. *Psychol Rep* 74 (1):39-42.

Mascia MP, Trudell JR, Harris RA (2000). Specific binding sites for alcohols and anesthetics on ligand-gated ion channels. *Proc Natl Acad Sci U S A* 97 (16):9305-9310.

Matsumoto D (1992). American-Japanese cultural differences in recognition of universal facial expressions. *J Cross-Cultural Psychol* 27:616-643.

Mulvihill LE, Skilling TA, Vogel-Sprott M (1997). Alcohol and the ability to inhibit behavior in men and women. *J Stud Alcohol* 58 (6):600-605.

Nakahiro M, Arakawa O, Narahashi T, Nishimura T (1996). GABA receptor-chloride channel complex as a target site of alcohol in: GABA: Receptors, Transporters and Metabolism, (Tanaka C, Bowery NG, editors). p. 221-235. Basel, Switzerland: Birkhauser Verlag.

Okun A, Stein RE, Bauman LJ, Silver EJ (1996). Content validity of the Psychiatric Symptom Index, CES-depression Scale, and State-Trait Anxiety Inventory from the perspective of DSM-IV. *Psychol Rep* 79 (3 Pt 1):1059-1069.

Olsen RW, Homanics GE (2000). Chapter 6: Function of GABAA receptors: insights from mutant and knockout mice in: GABA in the Nervous System: The View at Fifty Years, 1st ed (Martin DL, Olsen RW, editors). p. 81-96. Philadelphia, PA: Lippincott Williams & Wilkins.

Orozco S, Wall TL, Ehlers CL (1999). Influence of alcohol on electrophysiological responses to facial stimuli. *Alcohol* 18 (1):11-16.

Paul SM, Purdy RH (1992). Neuroactive steroids. *Faseb J* 6 (6):2311-2322.

Pearson P, Timney B (1998). Effects of moderate blood alcohol concentrations on spatial and temporal contrast sensitivity. *J Stud Alcohol* 59 (2):163-173.

Pelham RW, Marquis JK, Kugelmann K, Munsat TL (1980). Prolonged ethanol consumption produces persistent alterations of cholinergic function in rat brain. *Alcohol Clin Exp Res* 4 (3):282-287.

Philippot P, Kornreich C, Blairy S, Baert I, Den Dulk A, Le Bon O, Streel E, Hess U, Pelc I, Verbanck P (1999). Alcoholics' deficits in the decoding of emotional facial expression. *Alcohol Clin Exp Res* 23 (6):1031-1038.

Phillips ML, Young AW, Senior C, Brammer M, Andrew C, Calder AJ, Bullmore ET, Perrett DI, Rowland D, Williams SC, Gray JA, David AS (1997). A specific neural substrate for perceiving facial expressions of disgust. *Nature* 389 (6650):495-498.

Pihl RO, Paylan SS, Gentes-Hawn A, Hoaken PN (2003). Alcohol affects executive cognitive functioning differentially on the ascending versus descending limb of the blood alcohol concentration curve. *Alcohol Clin Exp Res* 27 (5):773-779.

Pihl RO, Peterson J (1995). Drugs and aggression: correlations, crime and human manipulative studies and some proposed mechanisms. *J Psychiatry Neurosci* 20 (2):141-149.

Pin JP, Duvoisin R (1995). The metabotropic glutamate receptors: structure and functions. *Neuropharmacology* 34 (1):1-26.

Quertemont E (2004). Genetic polymorphism in ethanol metabolism: acetaldehyde contribution to alcohol abuse and alcoholism. *Mol Psychiatry* 9 (6):570-581.

Rapcsak SZ, Galper SR, Comer JF, Reminger SL, Nielsen L, Kaszniak AW, Verfaellie M, Laguna JF, Labiner DM, Cohen RA (2000). Fear recognition deficits after focal brain damage: a cautionary note. *Neurology* 54 (3):575-581.

Ray O, Ksir C (1996a). Chapter 1: Drug use in modern society in: Drugs, Society and Human Behavior, 7th ed. p. 1-22. St. Louis, MO: Mosby-Year Book.

Ray O, Ksir C (1996b). Chapter 10: Alcohol in: Drugs, Society and Human Behavior, 7th ed. p. 600-605. St. Louis, MO: Mosby-Year Book.

Ray O, Ksir C (1996c). Chapter 11: Alcohol and society in: Drugs, Society and Human Behavior, 7th ed. p. 236-263. St. Louis, MO: Mosby-Year Book.

Rohrbaugh J, Stapleton JM, Parasuraman R, Frowein H, Eckardt MJ, Linnoila M (1987). Alcohol intoxication in humans: effects on vigilance performance. *Alcohol Alcohol* Suppl 1:97-102.

Ross DF, Pihl RO (1988). Alcohol, self-focus and complex reaction-time performance. *J Stud Alcohol* 49 (2):115-125.

Ryabinin AE (1998). Role of hippocampus in alcohol-induced memory impairment: implications from behavioral and immediate early gene studies. *Psychopharmacology (Berl)* 139 (1-2):34-43.

Salinsky MC, Storzbach D, Dodrill CB, Binder LM (2001). Test-retest bias, reliability, and regression equations for neuropsychological measures repeated over a 12-16-week period. *J Int Neuropsychol Soc* 7 (5):597-605.

Sayette MA, Smith DW, Breiner MJ, Wilson GT (1992). The effect of alcohol on emotional response to a social stressor. *J Stud Alcohol* 53 (6):541-545.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 59 Suppl 20:22-33;quiz 34-57.

Singh NN, Ellis CR (1998). Facial expressions of emotion. *Behav Modif* 22:123-127.

Single E, Rehm J, Robson L, Truong MV (2000). The relative risks and etiologic fractions of different causes of death and disease attributable to alcohol, tobacco and illicit drug use in Canada. *Cmaj* 162 (12):1669-1675.

Spielberger C, Gorsuch RL, Lushene RE (1970). Manual for the State-Trait Anxiety Inventory. Palo Alto: Consulting Psychologist Press.

Spielberger CD (1983). State-Trait Anxiety Inventory. Palo Alto: Consulting Psychologists' Press.

Steele CM, Josephs RA (1990). Alcohol myopia. Its prized and dangerous effects. *Am Psychol* 45 (8):921-933.

Storti SA (1997a). Chapter 3: Alcohol and the brain in: Alcohol, Disabilities, and Rehabilitation. p. 19-29. San Diego, CA: Singular Publishing Group, Inc.

Storti SA (1997b). Chapter 5: Consequences of alcohol use and abuse in: Alcohol, Disabilities, and Rehabilitation. p. 39-58. San Diego, CA: Singular Publishing Group, Inc.

Streit M, Dammers J, Simsek-Kraues S, Brinkmeyer J, Wolwer W, Ioannides A (2003). Time course of regional brain activations during facial emotion recognition in humans. *Neurosci Lett* 342 (1-2):101-104.

Sustrik RA, Coupland NJ, Blair RJR. Noradrenergic drug effects on facial emotion recognition. In: Proceedings of the ACNP annual meeting; 2003 December 7-11; Puerto Rico; 2003.

Tabakoff B, Hoffman PL (1999). Chapter 1: Neurobiology of alcohol in: Textbook of Substance Abuse and Treatment, 2nd ed (Galanter M, Kleber HD, editors). p. 3-9. Washington, DC: American Psychiatric Press.

Terry PC, Lane AM, Lane HJ, Keohane L (1999). Development and validation of a mood measure for adolescents. *J Sports Sci* 17 (11):861-872.

Tucker JA, Vuchinich RE (1983). An information processing analysis of the effects of alcohol on perceptions of facial emotions. *Psychopharmacology (Berl)* 79 (2-3):215-219.

van Widenfelt BM, Siebelink BM, Goedhart AW, Treffers PD (2002). The Dutch Childhood Anxiety Sensitivity Index: psychometric properties and factor structure. *J Clin Child Adolesc Psychol* 31 (1):90-100.

Watten RG, Lie I (1996). Visual functions and acute ingestion of alcohol. *Ophthalmic Physiol Opt* 16 (6):460-466.

Whiting PJ, Wafford KA, McKernan RM (2000). Chapter 8: Pharmacologic subtypes of GABAA receptors based on subunit composition in: GABA in the Nervous System: The View at Fifty Years, 1st ed (Martin DL, Olsen RW, editors). p. 113-126. Philadelphia, PA: Lippincott Williams & Wilkins.

Winston JS, O'Doherty J, Dolan RJ (2003). Common and distinct neural responses during direct and incidental processing of multiple facial emotions. *Neuroimage* 20 (1):84-97.

Yang T, Menon V, Eliez S (2002). Amygdalar activation associated with positive and negative facial expressions. *Neuroreport* 13 (1737-41).

Zangara A, Blair RJ, Curran HV (2002). A comparison of the effects of a beta-adrenergic blocker and a benzodiazepine upon the recognition of human facial expressions. *Psychopharmacology (Berl)* 163 (1):36-41.